ELSEVIER

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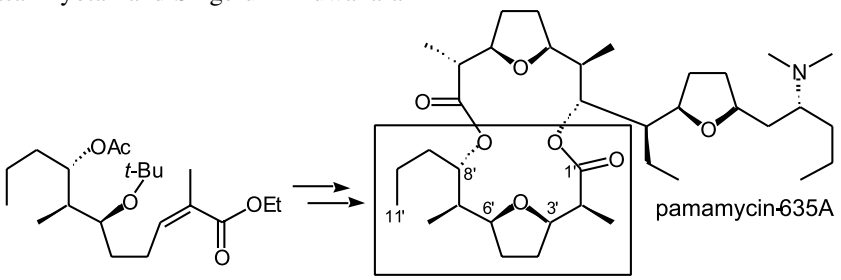
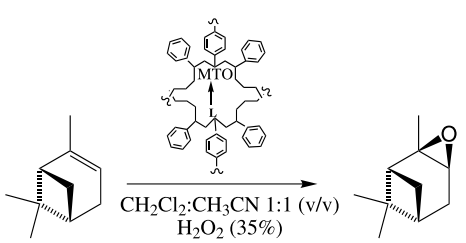
Contents

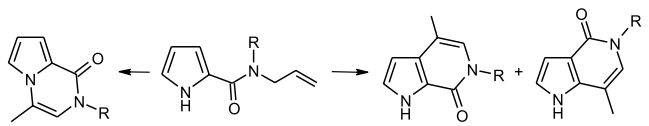
REPORT

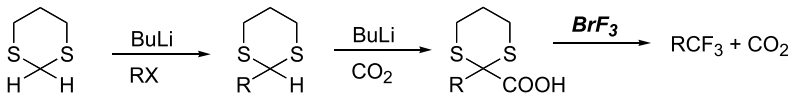
ARTICLES



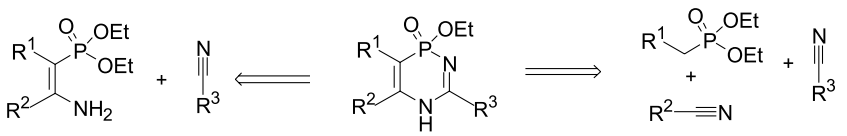
The synthesis of the southern (C1′–C11′) fragment of pamamycin-635A, isolated from *Streptomyces alboniger*, was achieved via an Evans aldol reaction, a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps.

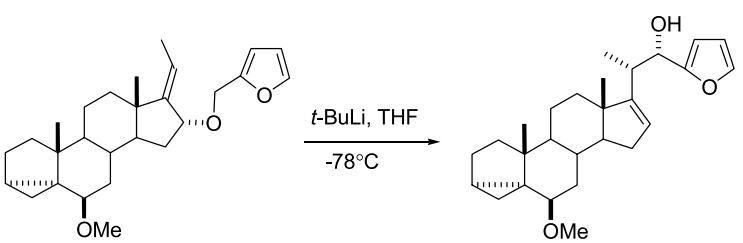


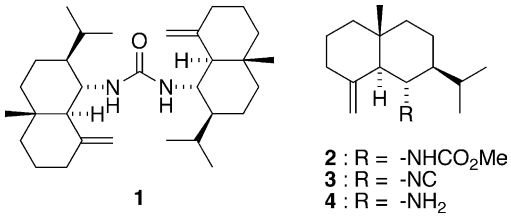




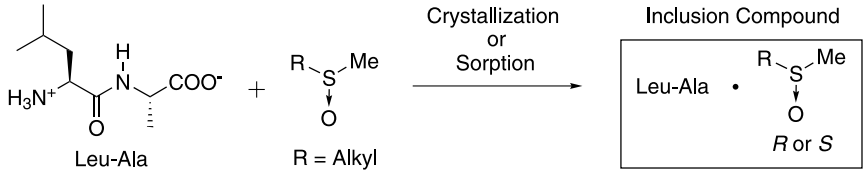
From alkyl halides to the respective trifluoromethylalkanes

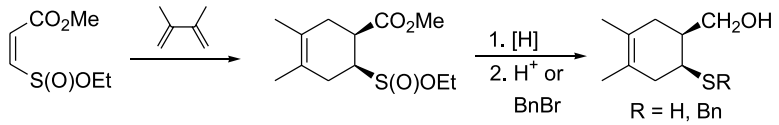


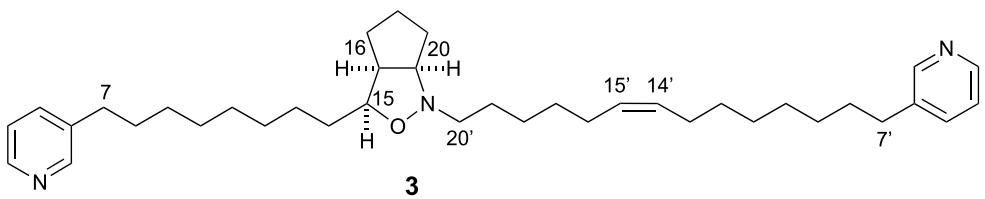




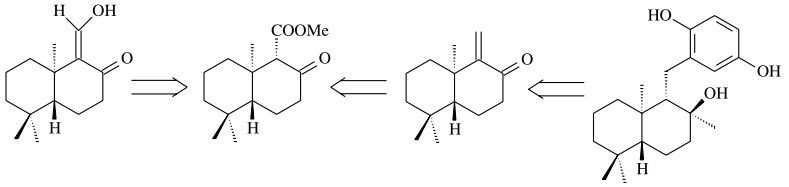
A new dimeric sesquiterpenoid with two eudesmane skeletons through a urea linkage, halichonadin A (**1**), as well as new eudesmane sesquiterpenoids having a carbamate, an isonitrile, or an amino functionality, halichonadins B (**2**), C (**3**), and D (**4**), respectively, have been isolated from a marine sponge *Halichondria* sp.





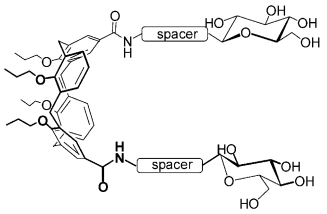


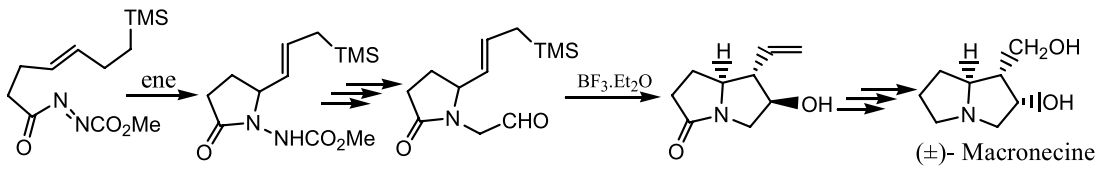
The structure of the cytotoxic marine sponge alkaloid pyrinodemin A is best represented as **3**.



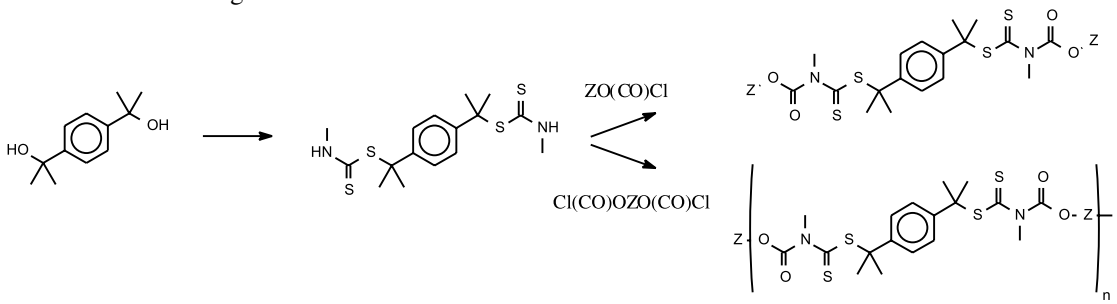
11-hydroxy-12-nordrim-9-en-8-one | 8-oxo-12-nor-drimanic acid methyl ester | 12-nordrim-9-en-8-one | yahazunol

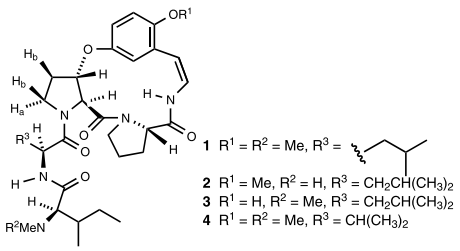
The total synthesis of two 12-nordrimanes and yahazunol was achieved via 8-oxo-12-nordrimanic acid methyl ester.

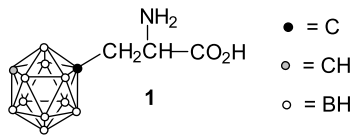




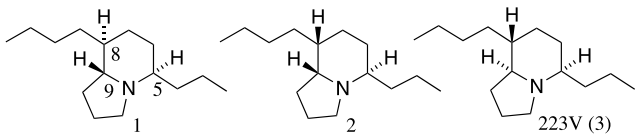
(±)- Macronecine

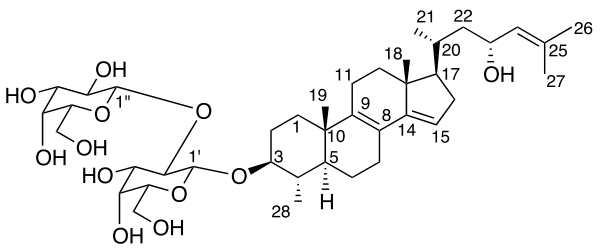






Both enantiomers of the new, highly lipophilic carborane-containing amino acid **1** have been prepared.





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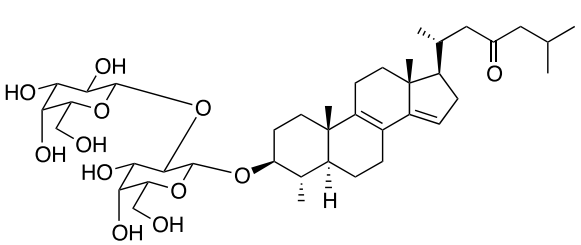
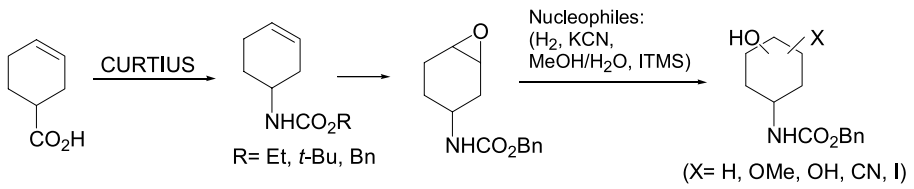
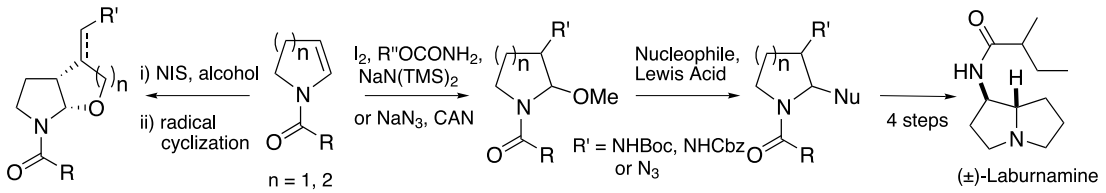
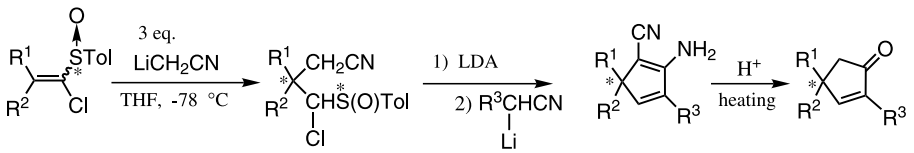
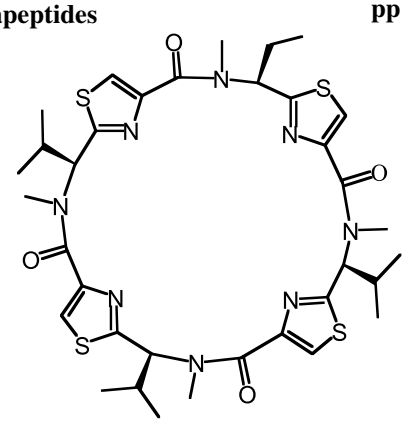


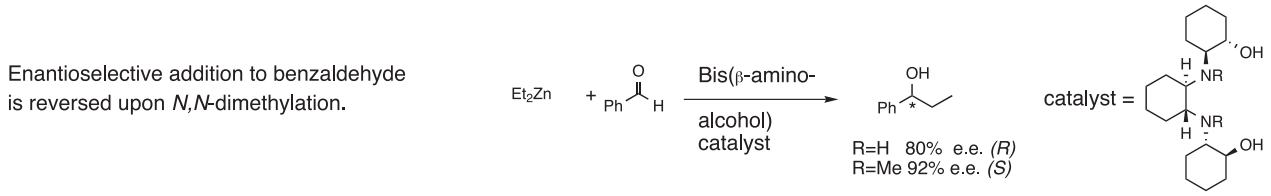
Eryloside L (**3**)

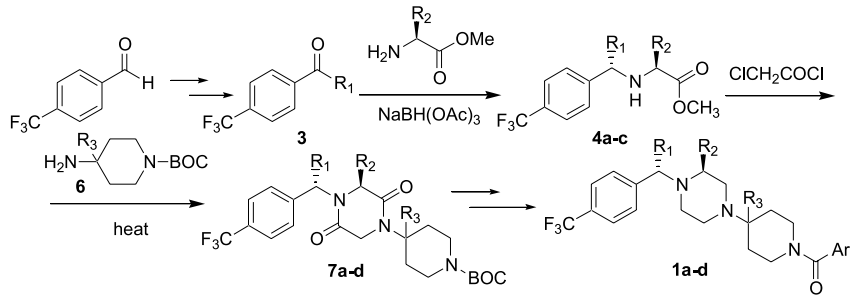


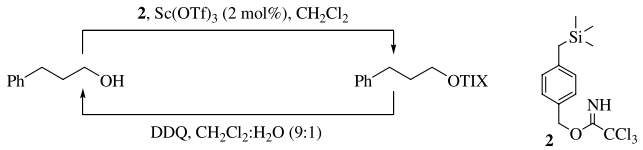


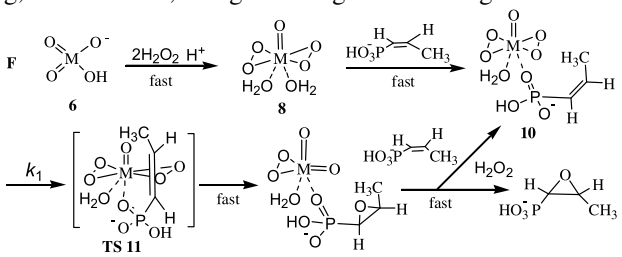




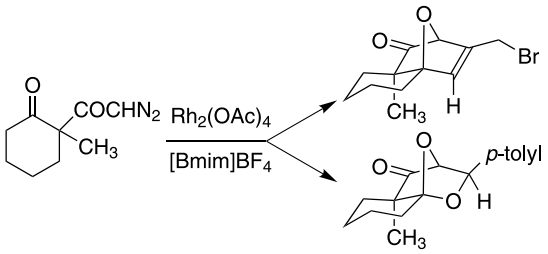


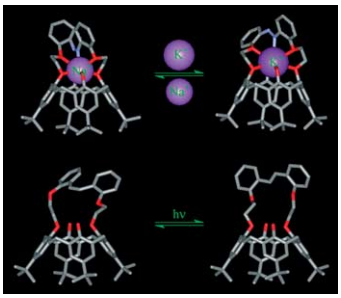


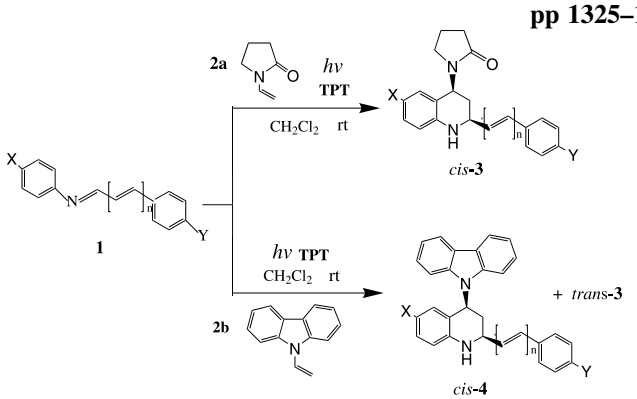


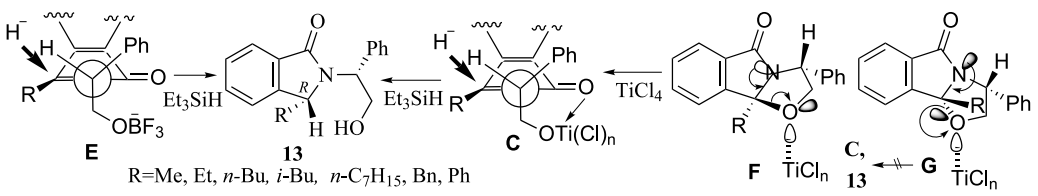


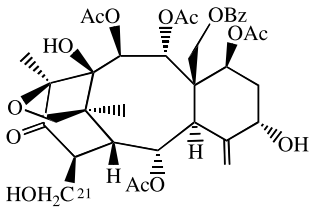
A specific direct transfer mechanism on epoxidation of *cis*-1-propenylphosphonic acid (CPPA) catalyzed by tungstate (VI) or molybdate (VI) in aqueous solvents.



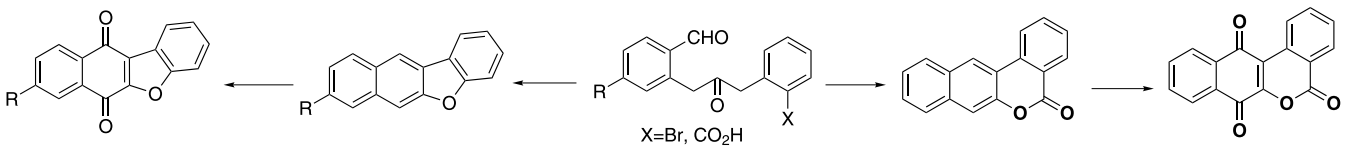


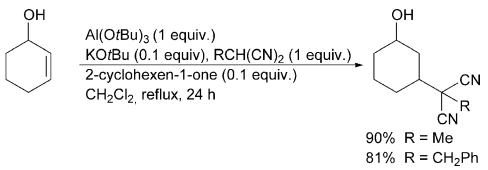






Tasumatrol L (**5**)





OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

Indexed/Abstracted in: AGRICOLA, Beilstein, BIOSIS Previews, CAB Abstracts, Chemical Abstracts, Chemical Engineering and Biotechnology Abstracts, Current Biotechnology Abstracts, Current Contents: Life Sciences, Current Contents: Physical, Chemical and Earth Sciences, Current Contents Search, Derwent Drug File, Ei Compendex, EMBASE/Excerpta Medica, Medline, PASCAL, Research Alert, Science Citation Index, SciSearch

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Chemical and biochemical transformations in ionic liquids

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Contents

Abbreviations: Hacac, Acetylacetone; [R(Rf)taz][Y], 1,4-Alkyl(polyfluoroalkyl)-1,2,4-triazolium ionic liquids; [taz][X], 1-Alkyl-4-polyfluoroalkyl-1,2,4-triazolium halides; $(DHQ)_2PHAL$, 1,4-Bis(9-*O*-dihydroquininyl)phthalazine; $(DHQD)_2PHAL$, 1,4-Bis(9-*O*-dihydroquinidinyl)phthalazine; $(DHQD)_2PYR$, 1,4-Bis(9-*O*-dihydroquinidinyl)biphenyl-pyrimidine; $(QN)_2PHAL$, 1,4-Bis(9-*O*-quininyl)phthalazine; [tfsa], Bis(trifluoromethanesulphonyl)amide; TFSI, $N(Tf)_2$, Bis(trifluoromethanesulphonyl)imide; bm_2im, 1-Butyl-2,3-dimethylimidazolium; [bdmim][BF_4], 1-Butyl-2,3-dimethylimidazolium tetrafluoroborate; [bhim][BF_4], 1-Butyl-3-hexylimidazolium tetrafluoroborate; bmim, 1-Butyl-3-methylimidazolium; [bmim][$(CF_3SO_2)_2N$], 1-Butyl-3-methylimidazolium bis(trifluoromethyl)sulphonamide; [bmim][BF_4], 1-Butyl-3-methylimidazolium tetrafluoroborate; [bmim][Tf_2N], 1-Butyl-3-methylimidazolium bis-triflimide; [bmim]Cl·$AlCl_3$, 1-Butyl-3-methylimidazolium chloroaluminate; bmpy, 1-Butyl-1-methylpyrrolidinium; BPC, 1-Butylpyridinium chloride; [bpy][BF_4], *N*-Butylpyridinium tetrafluoroborate; [bpy]Cl·$AlCl_3$, 1-Butylpyridinium chloroaluminate; CAL B, *Candida antarctica* lipase type B; CRL, *Candida rugosa* lipase; Selectfluor™, 1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); cyt-c, Cytochrome-c; DABCO, 1,4-Diazabicyclo[2.2.2]octane; dba, Dibenzylidineacetone; dca, Dicyanamide anion; DHP, 3,4-Dihydro-2*H*-pyran; DMAP, 4-Dimethylaminopyridine; DMSO, Dimethylsulphoxide; dppe, Diphenylphosphinoethane; EMIC, 1-Ethyl-3-methylimidazolium chloride; [emim][BF_4], 1-Ethyl-3-methylimidazolium tetrafluoroborate; [emim][Tf_2N], 1-Ethyl-3-methylimidazolium bis-triflimide; [EtDBU][OTf], 8-Ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulphonate; Accufluor®, 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate); [6-mim]PF_6], 1-Hexyl-3-methyl imidazolium hexafluorophosphate; [HexPy][PF_6], *N*-Hexylpyridinium hexafluorophosphate; ILCE, Ionic liquid-coated-enzyme; MALDI, Matrix-assisted laser desorption/ionisation; MA, Methyl acrylate; [MeDBU][OTf], 8-Methyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulphonate; dpRe, Methyldiperoxorhenium; NMO, 4-Methylmorpholine-*N*-oxide; MTBE, Methyl *t*-butyl ether; MTO, Methyltrioxorhenium; [moemim][OMs], 1-Methoxyethyl-3-methylimidazolium methanesulphonate; mpRe, Monoperoxorhenium; NMDPP, Neomenthyldiphenylphosphine; [omim][PF_6], 1-Octyl-3-methylimidazolium hexafluorophosphate; [ppmim], 1-(3′-Phenylpropyl)-methylimidazolium; PDI, Polydispersity index; PEG, Poly(ethylene glycol); PEO, Polyethylene oxide; PCL, *Pseudomonas cepacia* lipase; PsL, *Pseudomonas lipase*; RCM, Ring-closing metathesis; TBAA, Tetrabutylammonium acetate; TBAB, Tetrabutylammonium bromide; NHB_3-CHCA, Tributylammonium α-cyano-4-hydroxycinnamate; NHB_3-SA, Tributylammonium sinapinate acid; TPPTS, Triphenylphosphine trisulphonate, sodium salt; TRIPHOS, 1,1,1-Tris(diphenylphosphonium-ethyl)ethane; TSAC, 2,2,2-Trifluoro-*N*-(trifluoromethylsulphonyl)acetamide; TsOH, *p*-Toluenesulphonic acid; TON, Turnover number; sEH, Soluble epoxide hydrolase; UHP, Urea hydrogen peroxide.

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1. Introduction

Ionic liquids have gained wide popularity in recent years[1–8] for their increasing use in the two important fields of chemistry—synthetic and biochemical—and their concept and history has been well documented.[9–17] Ionic liquids were primarily explored for their applications in electrochemical technologies and as solvents in electronic

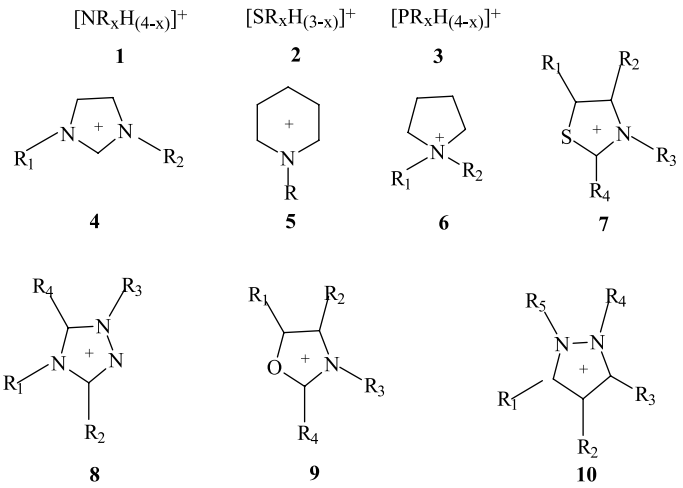


Figure 1. Different types of organic cations in ionic liquids.

absorption spectroscopy for highly charged complex ions. They have been used for liquid–liquid extraction processes,[18] as recyclable alternatives to aprotic solvents in organometallic reactions,[19] in biocatalysis,[20] for catalytic cracking of polyethylene[21] and for radical polymerisation.[22] There is an urgent need to develop alternative solvents and technologies due to pressure from the government organisations and other regulatory bodies to protect the environment. Ionic liquids are salts that are generally liquid at room temperature. Reactions in ionic liquids have different thermodynamic and kinetic behaviour, which often leads to improved process performance. They are 'designer solvents',[23] as their physical properties such as melting point, viscosity, density and hydrophobicity can be modified according to the nature of the desired reactions by altering the nature of their cations and anions.[24] They enjoy a variety of special properties (see below) and, for this reason, they outperform other solvents in many organic reactions.

1 They have essentially no vapour pressure and thus serve as potential replacements for volatile organic compounds in the chemical industry.
2 They possess good thermal stability and do not decompose over a large temperature range, thereby making it feasible to carry out reactions requiring high temperature conveniently in ionic liquids.
3 They are able to dissolve a wide range of organic, inorganic and organometallic compounds.
4 They serve as a good medium to solubilise gases such as H_2, CO, O_2 and CO_2 and many reactions are now being performed using ionic liquids and supercritical CO_2.
5 The solubility of ionic liquids depends upon the nature of the cations and counteranions.
6 They generally do not co-ordinate to metal complexes, enzymes and different organic substrates.
7 Their ionic character enhances the reaction rates to a great extent in many reactions including microwave-assisted organic synthesis.[25]
8 Most of the ionic liquids can be stored without decomposition for a long period of time.
9 They show a high degree of potential for enantioselective reactions as a significant impact on the reactivities and selectivities due to their polar and non-coordinating properties can be achieved. In addition, chiral ionic liquids have been used to control the stereoselectivity.
10 The viscosity of 1-alkyl-3-methyl imidazolium salts can be decreased by using highly branched and compact alkyl chain, as well as by changing the nature of anion.[26] The viscosity decreases in the order: $Cl^- > PF_6^- > BF_4^- \approx NO_3^- > NTF_2$.

An attempt has been made to present a detailed and comprehensive review of the versatility of ionic liquids as environmentally friendly green solvents, as well as reagents for various chemical and biochemical transformations.

2. Synthesis of ionic liquids

Ionic liquids mainly comprise organic cations such as tetraalkylammonium (**1**),[27] trialkylsulphonium (**2**),[28] tetraalkylphoshonium (**3**),[29] 1,3-dialkylimidazolium (**4**),[30] *N*-alkylpyridinium (**5**),[31] *N*,*N*-dialkylpyrrolidinium (**6**),[32] *N*-alkylthiazolium (**7**),[33] *N*,*N*-dialkyltriazolium (**8**),[34] *N*,*N*-dialkyloxazolium (**9**)[35] and *N*,*N*-dialkylpyrazolium (**10**)[36] (Fig. 1).

The common anions which lead to neutral and stoichiometric ionic liquids are: BF_4^-, PF_6^-, SbF_6^-, $ZnCl_3^-$, $CuCl_2^-$, $SnCl_3^-$, $N(CF_3SO_2)_2^-$, $N(C_2F_5SO_2)_2^-$, $N(FSO_2)_2^-$, $C(CF_3SO_2)_3^-$, $CF_3CO_2^-$, $CF_3SO_3^-$ and $MeSO_3^-$. There is another class of polynuclear anions, which are air and water sensitive such as $Al_2Cl_7^-$, $Al_3Cl_{10}^-$, $Au_2Cl_7^-$, $Fe_2Cl_7^-$, and $Sb_2F_{11}^-$.

The cation shows a remarkable effect on the halide nucleophilicity in a series of bis(trifluoromethylsulphonyl)-imide ionic liquids. The nucleophilicity of chloride, bromide and iodide have been determined in the ionic liquids, [bmim][$N(Tf)_2$], [bm_2im][$N(Tf)_2$] and [bmpy]-[$N(Tf)_2$], where bmim = 1-butyl-3-methylimidazolium, bm_2im = 1-butyl-2,3-dimethylimidazolium, bmpy = 1-butyl-1-methylpyrrolidinium and $N(Tf)_2$ = bis(trifluoromethanesulphonyl)imide.

It was found that chloride is the least and iodide the most

nucleophilic in [bmim][$N(Tf)_2$], whereas chloride is the most and iodide the least nucleophilic in a [bmpy][$N(Tf)_2$] ionic liquid. Among the different ionic liquids that were studied, the bromide nucleophilicities were approximately constant, while iodide showed a little variation and chloride showed more. In view of these results, it is apparent that all ionic liquids are not the same and it is not possible to take a conventional organic reaction and replace the solvent with a simple ionic liquid and then expect this outcome to be achieved in all other ionic liquids.

The nucleophilicities of the halides are therefore ionic liquid specific, just as nucleophilicity is solvent specific in molecular solvents, with the ability of the cation to act as hydrogen-bond donor being a key feature of this dependence in the reaction. The relative nucleophilicities of the halides in 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF_4] were examined[37] and found to be Cl^- (1.06): Br^- (1): I^- (1.41).

The trend of halide nucleophilicities in [bmim][$N(Tf)_2$] is not the same as that in [bmim][BF_4] and shows that the nucleophilicity is determined by a combination of cation and anion properties.

2.1. Synthesis of ammonium cation-based ionic liquids

The aliphatic quaternary ammonium (AQA) cation is a useful cationic component of room temperature ionic liquids (Fig. 2), since the salts containing AQA cations and appropriate oxidation resistant anions such as ClO_4^-, BF_4^- or PF_6^- are electrochemically stable and may be used as a supporting electrolyte. The asymmetric amide anion $(CF_3SO_2\text{-}N\text{-}COCF_3)^-$ has an excellent ability to lower both the melting points and viscosities of room temperature ionic liquids, combining with the small aliphatic cations.[38]

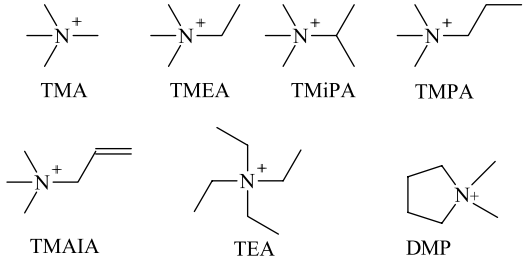


Figure 2. Different AQA cations in ionic liquids.

There is, however, a limitation on the reduction of the viscosity of the AQA-based room temperature ionic liquids, compared with the imidazolium systems since, the molecular weight of the AQA cations cannot be reduced to below a threshold value. The 2,2,2-trifluoro-*N*-(trifluoromethylsulphonyl)acetamide (TSAC) anion was prepared as its potassium salt and a series of trimethylalkylammonium cations were prepared as the halides. The TSAC salts

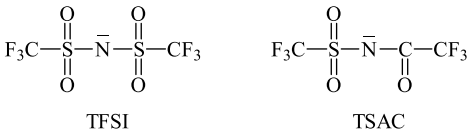


Figure 3. Structures of TFSI and TSAC anions.

containing small aliphatic ammonium cations were made by following the method of preparation of room temperature ionic liquids based on the bis(trifluoromethanesulphonyl-imide) (TFSI) anion (Fig. 3).[38]

The water-insoluble TSAC salts immediately separated out after mixing the two aqueous solutions containing equimolar amounts of K-TSAC and a quaternary alkylammonium halide. The resulting room temperature ionic liquid was washed with water, extracted with CH_2Cl_2 and dried under vacuum (100 °C) for 24 h.

2.2. Synthesis of non-functionalised imidazolium ionic liquids

Room temperature ionic liquids are prepared by direct quaternisation of the appropriate amines or phosphines.[39] Dialkylimidazolium and alkylpyridinium cation-based ionic liquids have been easily prepared by alkylation of the commercially available *N*-methylimidazole or pyridine with an alkyl halide to give the corresponding 1-alkyl-3-methylimidazolium or 1-alkylpyridinium halide. Different anions have subsequently been introduced by anion exchange, although, due to their non-volatile nature, they cannot be purified by distillation. Purification is therefore, usually carried out by dissolving the ionic liquid in acetonitrile or tetrahydrofuran (THF), treating it with activated charcoal for $\geq$24 h and, finally, removing the solvent in vacuo. A more recent method involves the microwave-assisted solvent-less synthesis of imidazolium ionic liquids.[40] The microwave heating reduces the reaction time from several hours to minutes and avoids the use of a large excess of alkyl halides/organic solvents as the reaction medium. Dialkylimidazolium tetrachloroaluminates are prepared in a few minutes by the reaction of the appropriate *N*,*N*′-dialkylimidazolium chloride and aluminium chloride under microwave irradiation. An improved synthetic method for the preparation of 1-alkyl(aralkyl)-3-methyl-(ethyl) imidazolium halides has been described.[41] A new series of salts based on the dicyanamide anion (dca), most of which are liquids at room temperature, were synthesised (Fig. 4). They have potential donor characteristics, as the anion is a powerful ligand, and possess a lower viscosity.[42]

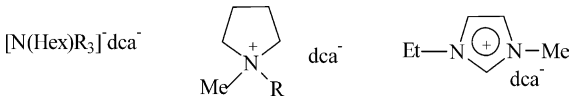
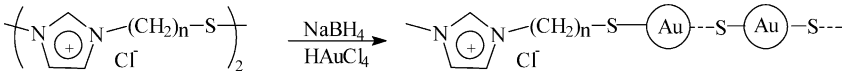


Figure 4. Dicyanamide anion based ionic liquids.

More recently, gold nanoparticles based on imidazolium cation ionic liquids were synthesised (Scheme 1).[43]

An excess amount of $NaBH_4$ was added dropwise to an aqueous solution of $HAuCl_4$ in the presence of 3,3′-[disulphanylbis(hexane-1,6-diyl)]bis(1-methyl-1*H*-imidazol-3-ium)dichloride. The colour of the solution immediately changed from yellow to dark red, indicating the formation of gold nanoparticles. These nanoparticles were further modified by reactions with various anions and it was found that the surface property of the gold nanoparticles changed from hydrophilic to hydrophobic by the anion exchange, which led to the nanoparticles aggregating in

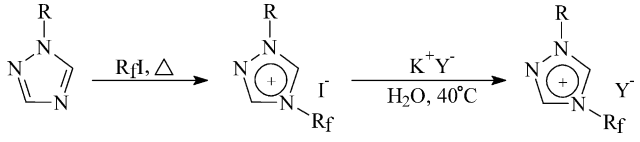


Scheme 1.

water. Gold nanoparticles containing Cl^- are soluble in water, while those containing PF_6^- are immiscible in water. Thus, by this method, gold nanoparticles can be efficiently transferred from aqueous solution to the ionic liquid containing the transferred metal nanoparticles and are potentially useful for a recyclable biphasic catalysis process. These nanoparticles can be used as exceptionally high extinction dyes for the calorimetric sensing of anions in water via a particle aggregation process.

2.3. Synthesis of functionalised imidazolium ionic liquids

Most ionic liquids are based on 1,3-dialkylimidazolium or 1-alkylpyridinium ions and there are few reports on the synthesis of ionic liquids with functionalised alkyl chains. Davis and Rogers have reported the synthesis of imidazolium salts with urea, thiourea, and thioether groups in one of the *N*-alkyl substituents.[44] These ionic liquids have been used as the PF_6^- salts to extract Hg^{2+} or Cd^{2+} ions from aqueous solutions. The synthesis of ionic liquids with a fluorous alkyl chain has also been reported.[45]



Scheme 2.

Several 1,4-alkyl(polyfluoroalkyl)-1,2,4-triazolium iodides or bromides have been prepared, followed by metathesis reactions, to form low-melting salts that are air and moisture stable and have broad liquid ranges.[46] Quaternisation of 1-alkyl-1,2,4-triazoles at *N*-4 using polyfluoroalkyl halides under neat reaction conditions at 100–120 °C gave the 1-alkyl-4-polyfluoroalkyl-1,2,4-triazolium halides [taz][X]. Metathesis of these polyfluoroalkylated triazolium halides with fluorine-containing anions led to the formation of new 1,4-alkyl(polyfluoroalkyl)-1,2,4-triazolium ionic liquids [R(Rf)taz][Y] (Scheme 2).

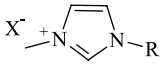
Along the same lines, there is another report discussing the synthesis of mono- and polyfluoroalkyl-substituted imidazolium quaternary salts and ionic liquids.[47]

A new series, [$C_nO_m$mim][X], of imidazolium cation-based room temperature ionic liquids with ethers and alcohols were prepared and their properties compared with those reported for the 1-alkyl-3-methylimidazolium [$C_n$mim][X] series (Table 1).[48] While the density and solid–liquid phase transition properties were similar for both series, the new room temperature ionic liquids presented a lower energy and an increased ability to dissolve $HgCl_2$ and $LaCl_3$ (up to 16-fold higher).

In general, the introduction of hydroxyl or ether functional groups in the alkyl chain considerably modifies the solubility behaviour, while modification of the anion (PF_6^-, BF_4^- or TFA^-) does not seem to have any significant influence (Table 2).

Further, from the data in Table 2, it can be concluded that both room temperature ionic liquid series (the new [$C_nO_m$mim][X] and [$C_n$mim][X]) display quantitatively similar viscosity behaviour. The viscosity of ionic liquids is essentially influenced by their hydrogen-bonding ability and by the strength of their van der Waals interaction, being

Table 1. Structures of new ionic liquids of the series [$C_nO_m$mim][X]



Ionic liquid	Cation (R)	Anion (X^-)
[C_2OHmim][Cl]	$(CH_2)_2OH$	Cl^-
[C_2OHmim][PF_6]	$(CH_2)_2OH$	PF_6^-
[C_2OHmim][BF_4]	$(CH_2)_2OH$	BF_4^-
[C_2OHmim][TFA]	$(CH_2)_2OH$	$CF_3CO_2^-$
[C_3Omim][Cl]	$(CH_2)_2OMe$	Cl^-
[C_3Omim][PF_6]	$(CH_2)_2OMe$	PF_6^-
[C_3Omim][BF_4]	$(CH_2)_2OMe$	BF_4^-
[C_4OHmim][Br]	$(CH_2)_4OH$	Br^-
[C_5O_2mim][Cl]	$(CH_2)_2O(CH_2)_2OMe$	Cl^-
[C_5O_2mim][PF_6]	$(CH_2)_2O(CH_2)_2OMe$	PF_6^-
[C_5O_2mim][BF_4]	$(CH_2)_2O(CH_2)_2OMe$	BF_4^-

Table 2. Solubility and viscosity (cP) of new room temperature ionic liquids

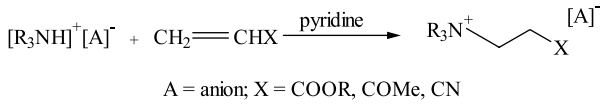
Entry	Ionic liquid	Solubility				cP (30 °C)
		H_2O [g/l]	Et_2O	EtOAc	EtOH	
1	[C_2OHmim][PF_6]	Miscible	Immiscible	Partially miscible	Miscible	82.7
2	[C_2OHmim][BF_4]	Miscible	Immiscible	Partially miscible	Miscible	70.9 (25 °C)
3	[C_3Omim][PF_6]	Miscible	Immiscible	Partially miscible	Partially miscible	148.1
4	[C_3Omim][BF_4]	Miscible	Immiscible	Partially miscible	Partially miscible	138.0
5	[C_5O_2mim][PF_6]	0.38[a]	Immiscible	Immiscible	Partially miscible	212.3
6	[C_5O_2mim][BF_4]	0.43[a]	Immiscible	Immiscible	Miscible	189.2
7	[C_4Omim][PF_6]	0.57[a]	Immiscible	Immiscible	Miscible	172.8
8	[C_4Omim][BF_4]	Miscible	Immiscible	Immiscible	Miscible	65.2
9	[C_8mim][PF_6]	0.22[a]	Immiscible	Immiscible	Miscible	425.2
10	[C_8mim][BF_4]	0.30[a]	Immiscible	Immiscible	Miscible	82.1
11	[C_{10}mim][BF_4]	0.59[a]	Immiscible	Immiscible	Miscible	223.4

[a] Determined by UV spectroscopy.

strongly dependent on the anion type. All of the room temperature ionic liquids containing a BF_4^- anion have a lower viscosity than the room temperature ionic liquids with a PF_6^- anion and this difference is even more noticeable at lower temperatures (10 °C). The significant difference in the viscosities between the PF_6^- and BF_4^- anions is less pronounced for the $[C_nO_m\text{mim}][X]$ series than for the $[C_n\text{mim}][X]$ series. The structure of the cation also influences the viscosity of the ionic liquid. The viscosity of the room temperature ionic liquid $[C_2O_n\text{mim}][PF_6]$ is less than half as large as those of the room temperature ionic liquids $[C_3\text{Omim}][PF_6]$ and $[C_4\text{mim}][PF_6]$. Ionic liquids thus display a very large range of viscosities depending on the cation/anion combinations. On the other hand, the temperature co-efficient of viscosity at room temperature is high when compared to 'normal' solvents.

The best room temperature ionic liquids in the above series with regard to viscosity are $[C_2\text{OHmim}][PF_6]$, $[C_2\text{OHmim}][BF_4]$, $[C_3\text{Omim}][BF_4]$ and $[C_4\text{mim}][BF_4]$, since they have a low viscosity which finds important usage in some applications. The new room temperature ionic liquids in the $[C_nO_m\text{mim}][X]$ series have high densities as compared to the $[C_n\text{mim}][X]$ series. The room temperature ionic liquids containing the PF_6^- anion have a higher density than those with BF_4^- or Cl^- anions. A large alkyl chain in the $[C_n\text{mim}]$ series results in a decrease in the density (butyl > hexyl > octyl > decyl).

Abbott et al.[49] described chlorozincate and chlorostannate ionic liquids based on functionalised ammonium cations of the type $[Me_3NCH_2CH_2Y]$(Y = OH, Cl, OC(O)Me and OC(O)Ph).

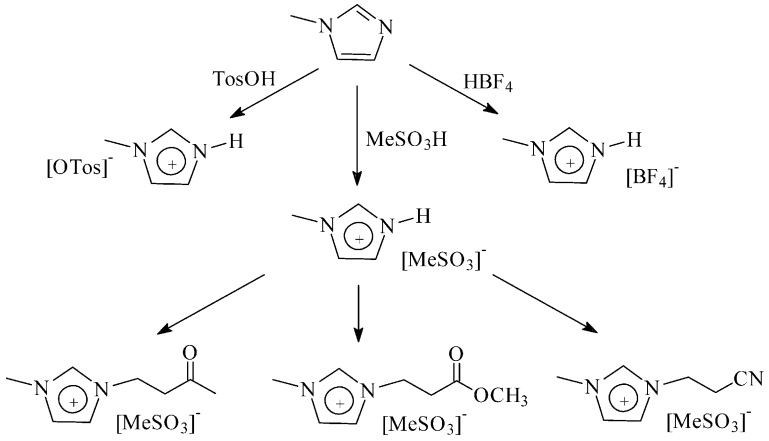


Scheme 3.

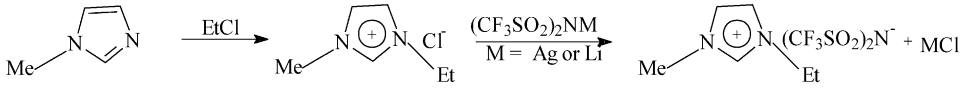
The synthesis of functionalised ionic liquids is rather complicated and multistep procedures are required. These include the synthesis of a functionalised alkylating agent, followed by alkylation of the amine. Some further modification of the obtained salt to obtain the desired functional group is required which is followed in most cases by an anion exchange reaction. There are, however, recent reports on the synthesis of new functionalised ionic liquids by a simple and straightforward method. The Michael-type addition of a protonated *tert*-amine or phosphine to α,β-unsaturated compounds has been applied to a one-pot, two-step synthesis of functionalised ionic liquids (Scheme 3).[50]

In the first step, the *tert*-amine, *N*-methylimidazole or pyridine, was protonated with an acid, giving the ammonium salt, and the anion of the final ionic liquid was introduced in this step. In the second step, the protonated amine was reacted with the α,β-unsaturated compound in the presence of weak and volatile bases such as pyridine at 70 °C for about 16 h to yield the ionic liquid (Scheme 4). The reaction went well with acrylonitrile and unsubstituted acrylates as Michael acceptors. With substituted acrylates such as methyl methacrylate and cinnamic acid esters, however, the reaction stayed incomplete or did not occur at all. The viscosity of these functionalised ionic liquids, as expected, was higher as compared to their unfunctionalised counterparts. This viscous character has been attributed to the keto functionality, which introduces a strong hydrogen-bound acceptor site into the salt. For wider industrial applications, however, the limited thermal stability of these ionic liquids may be a concern, since the Michael-type addition reaction is found to be reversible at higher temperatures. An additional functional group transformation reaction could, however, help to solve this problem.[50]

Another method for the synthesis of room temperature ionic liquids involves the direct methylation and trifluoroethylation of imidazole and pyridine derivatives using *N*-methyl bis-((perfluoroalkyl)sulphonyl)imides (**11a**,**b**) or



Scheme 4.



Scheme 5.

trifluoroethylphenyliodonium bis-((trifluoromethyl)sulphonyl)imide (**11c**) (Scheme 5). Of the many examples of both organic and inorganic anions used, bis((trifluoromethyl)sulphonyl)imide was one of the most effective anions for obtaining ionic liquids of low melting point and high thermal stability.[51] The preparation of this type of ionic liquid, however, usually required a multistep synthesis and involved the formation and removal of metal halides.[52]

An improved method for the synthesis of these compounds was carried out by using trimethyl orthoacetate. Bis((perfluoroalkyl)sulphonyl)imides were refluxed with trifluoro orthoacetate followed by removal of the less volatile co-products under vacuum to yield good yields of **11a**,**b** (Fig. 5).[53]

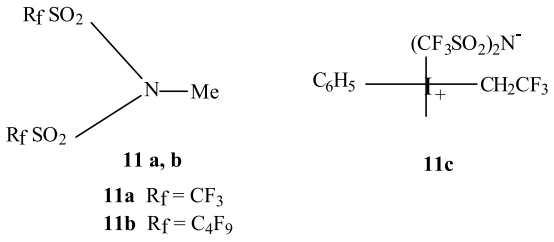
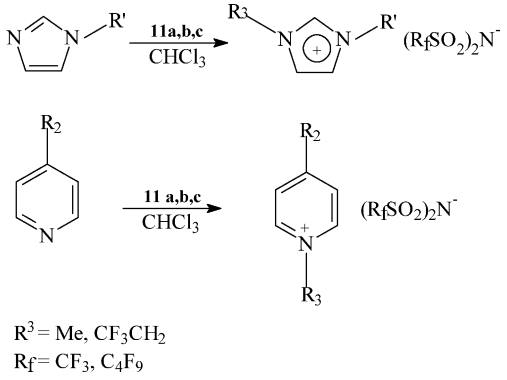


Figure 5.

The imides **11a**,**b** exhibit excellent alkylation activity and reacted readily with imidazole and pyridine compounds and formed exclusively ionic salts with melting points lower than 70 °C. Similarly, iodonium salt **11c** also acted as a good trifluoroethyl transfer agent (Scheme 6).



Scheme 6.

2.4. Synthesis of chiral ionic liquids

Chiral ionic liquids are quite attractive for their potential application to chiral discrimination including asymmetric synthesis and optical resolution of racemates. New chiral ionic liquids, directly derived from the 'chiral pool', have been synthesised and are interesting solvents for enantioselective reactions and useful in chiral separation techniques.[54] The ionic liquids prepared by this method meet the following criteria:

(a) easy preparation by direct synthesis in enantiopure form
(b) low melting points
(c) good chemical stability towards water and common organic substrates and
(d) relatively low viscosity and good thermal stability.

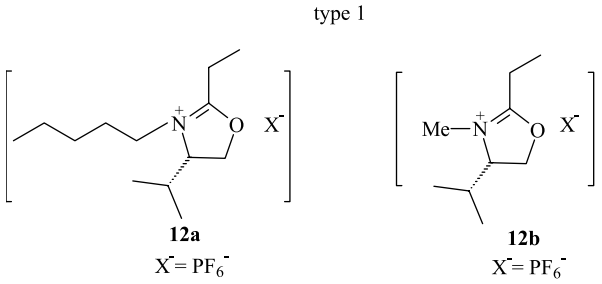


Figure 6. Oxazolinium cation based chiral ionic liquids.

Howarth and co-workers have described the use of chiral imidazolium cations in Diels–Alder reactions.[55] The synthesis of these systems, however, required an expensive chiral alkylating agent. The use of ionic liquids with chiral anions is somehow more obvious, since some of these are readily available as sodium salts.[56] Ionic liquids (**12a**,**b**) of the type 1 (Fig. 6) were prepared by alkylation of the corresponding oxazoline with an alkyl bromide followed by anion exchange. Although ionic liquids of the type 1 can be prepared on a multigram scale, the relatively low overall yield of the four-step synthesis is a concern for the practical use of type 1 ionic liquids. Moreover, the oxazolinium cation has a low stability under acidic conditions and ring opening occurs to a large extent. These considerations led to the development of a room temperature ionic liquid of the type 2 (Fig. 7), which is more readily obtained from the alkaloid ephedrine in a three-step synthesis. A Leuckart–Wallach reaction, followed by alkylation with Me_2SO_4 and ion exchange in aqueous solution, gave the ionic liquid of type 2 in 80% yield with a melting point of 54 °C.

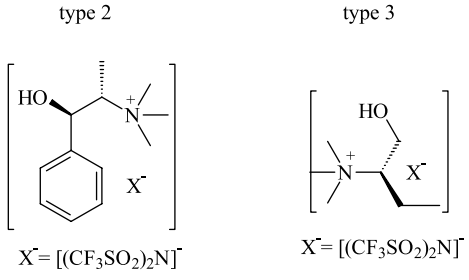
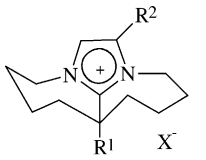


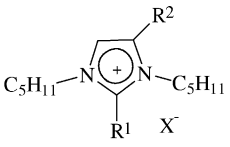
Figure 7. Chiral ionic liquids.

A further quest for room temperature ionic liquids with chiral cations resulted in the synthesis of an ionic liquid of the type 3 (Fig. 7) in a very similar manner to type 2 in an overall yield of 75%. The enantiopurity of **12a** was confirmed by ^{19}F NMR spectroscopy after basic hydrolysis of **12a** and reaction with (*S*)-Mosher's acid chloride. The enantiopurity of type 2 and type 3 was confirmed by ^{19}F NMR spectroscopy after esterification of type 2 and type 3 with (*S*)-Mosher's acid chloride.

Imidazolium salts with a cyclophane-type planar chirality **13–15** form a novel class of chiral ionic liquids, which



13 $R^1 = R^2 = H$
14 $R^1 = Me$, $R^2 = H$
15 $R^1 = R^2 = Me$



16 $R^1 = R^2 = H$
17 $R^1 = R^2 = Me$

(a) $X^- = Br$
(b) $X^- = (CF_3SO_2)_2N$
(c) $X^- = (C_2F_5SO_2)_2N$
(d) X^- = (1S)-(+)-10-camphorsulfonate

Figure 8. Cyclophane-type imidazolium salts.

realise both chemical stability and a well-defined three-dimensional dissymmetric structure (Fig. 8).[57]

It has been observed from different studies that cyclic imidazolium salts have higher melting points. A chiral cyclophane-type imidazolium salt **15** has been designed which possesses two methyl groups, a C(4) methyl group for the induction of planar chirality and a C(2) methyl for the suppression of a rope-skipping process, which would result in the racemisation of planar chiral cyclophanes. The introduction of a substituent at C(4) of the imidazolium ring not only induces planar chirality of **15**, but also dramatically lowers the melting point. The imidazolium bis(trifluoromethanesulphonyl)imide (**15b**) has a low melting point of 42–45 °C, compared with those of the analogues **13b** and **14b** with high symmetry. The planar chiral imidazolium cation **15** forms diastereomeric salts with the camphorsulphonate anion **15d**, and shows potential for the ionic liquid as a chiral solvent for asymmetric synthesis and/or optical resolution.

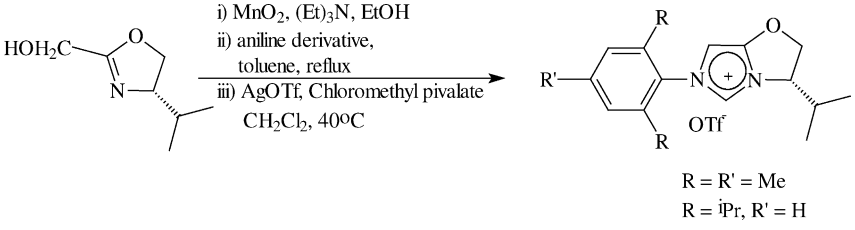
Another group has reported the use of oxazolines as chiral building blocks for imidazolium salts.[58] Enantiomerically pure imidazolium triflates were readily prepared from bioxazolines and oxazoline imines (Scheme 7).

3. Transition metal-catalysed reactions in ionic liquids

The advent of ambient-temperature, air- and water-stable 1-butyl-3-methyimidazolium tetrafluoroborate and hexafluorophosphate ionic liquids (Fig. 9) has provided a new impetus for the use of ionic liquids as immobilising agents for transition metal catalysts and their precursors. In biphasic transition metal-catalysed reactions, ionic liquids are better regarded as 'polymeric liquid supports' rather than as 'solvents'. Therefore, in most of the cases, the catalyst precursors are 'immobilised' in the ionic liquid rather than 'dissolved'. Pure imidazolium ionic liquids are highly ordered hydrogen-bonded polymeric liquids. Wet ionic liquids may not, however, be regarded as homogeneous structures (solvents), but have to be considered as nanostructures with polar and nonpolar regions, similar to those encountered in some liquid crystalline or concentrated surfactant media. These nano-inhomogeneties can be generated by the addition of controlled amounts of water or other molecules, which allows neutral molecules to reside in less polar regions and ionic species in the more polar or wet regions.

The separation of the products from the reaction mixture and the recovery of the catalyst are the major disadvantages in the homogeneous catalytic process. For these reasons, many homogeneous processes are not used on an industrial scale, despite other benefits. Among the various approaches to overcome these problems, liquid–liquid biphasic catalysis has emerged as one of the most important alternatives. These biphasic systems might combine the advantages of both homogeneous catalysis, such as greater catalytic efficiency and mild reaction conditions, and heterogeneous catalysis, such as ease of recycling and separation of the products.

There are many good reasons to study the well-known transition metal-catalysed reactions in ionic liquids as alternative solvents. Besides the environmental advantage of their non-volatile nature, the biphasic reactions with an ionic catalyst phase are of great interest. In these reactions, the possibility of adjusting solubility properties by different cation/anion combinations allows a systematic optimisation of the biphasic reaction, for example, with regard to product



Scheme 7.

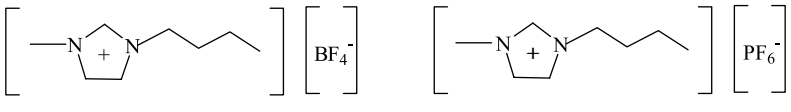
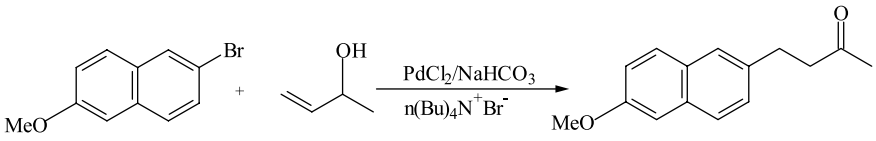


Figure 9. Important imidazolium cation-based ionic liquids.



Scheme 8.

selectivity. Attractive options to improve the selectivity in multiphase reactions derive from the preferential solubility of only one reactant in the catalyst solvent or from the in situ extraction of the reaction intermediates out of the catalyst layer. The ionic liquids have been shown to be superior solvents, with an enhancement of catalyst activity and stability for transition-metal catalysed reactions, in comparison to water and common organic solvents, especially when ionic complexes of transition metals are used as the catalysts.

In the following section, an overview of the recent developments in the field of transition-metal catalysed reactions in ionic liquids is described.

3.1. Carbon–carbon bond-forming reactions

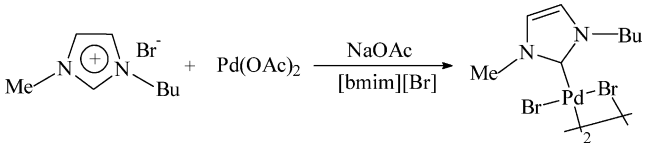
3.1.1. Heck reaction. The Heck reaction has received a great attention due to its major importance in organic synthesis and in the manufacture of fine chemicals.[59,60] Of late, quaternary ammonium,[61] pyridinium[62] and imidazolium[63] salts have been used as solvents for the Heck reaction of monosubstituted alkenes with aryl halides The first example of a Heck reaction in ionic liquids was reported for the synthesis of *trans*-cinnamate by the reaction of bromobenzene with butyl acrylate catalysed by palladium salts in molten tetraalkylammonium and tetraalkylphosphonium bromide salts.[64] No formation of palladium metal was observed and the product was isolated by distillation from the ionic liquid. The Heck coupling of aryl halides with allylic alcohols catalysed by $PdCl_2$ in molten tetraalkylammonium bromide gave the corresponding β-arylated carbonyl compounds (Scheme 8).[65]

Heck coupling in [bmim][PF_6] or *N*-hexylpyridinium hexafluorophosphate [HexPy][PF_6] using $PdCl_2$ or $Pd(OAc)_2$–Ar_3Ph as catalyst and Et_3N or $NaHCO_3$ as base was performed.[66,67] The high solubility of the catalyst in the ionic liquid allowed the product isolation by extraction into a non-polar organic solvent. In addition, if water was added, a triphasic system was obtained in which the salt formed in the reaction, Et_3NHBr, was extracted into the aqueous phase. The greater catalytic activity observed in the reactions performed in the imidazolium ionic liquids compared to those in the pyridinium analogues was attributed to the formation of palladium–carbene complexes in the former ionic liquid. N-heterocyclic carbene complexes of palladium are formed in situ in imidazolium ionic liquids.[68] Palladium–carbene complexes are formed by the deprotonation of the imidazolium cation of [bmim][Br] in the presence of the catalyst precursor (Scheme 9).[69]

The Heck reaction of iodo- or bromobenzenes having electron-withdrawing groups with styrene or acrylates was more efficient in [bmim][Br] than in [bmim][BF_4] and this could be attributed to the formation of more active carbene catalytic species in the imidazolium bromide ionic liquid. Ultrasonic irradiation facilitated the coupling of iodoarenes with alkenes and alkynes by Pd(II) compounds in imidazolium ionic liquids at room temperature.[70] The Heck reaction with a ligand-less palladium catalyst has been reported in biphasic conditions in a high-melting alkylammonium tetrafluoroborate and water or toluene.[71] This method overcomes the problem of solubility of the organic substrates and simplifies the work-up and separation of products and recycling of the reaction media.

Palladium nanoparticles of different origin were utilised in the Heck arylation of unsubstituted acrylates with styrene, but stereoselctivity was not observed.[72] Efficient stereoselectivity was achieved when tetrabutylammonium bromide (TBAB) was used as a solvent in the reaction of *trans*-ethyl cinnamate and aryl halides using palladium nanoparticles (Scheme 10).[73]

It was observed that subtle differences in basicity of the bases had a dramatic effect on the regio- and stereoselectivity in the arylation of disubstituted olefins. The base



Scheme 9.

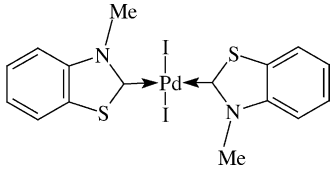
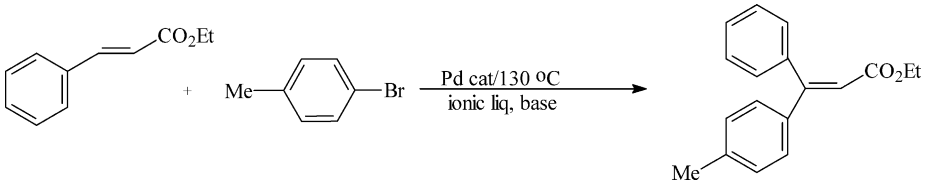


Figure 10. Pd catalyst used in Heck reaction.



Scheme 10.

Table 3. Base effect on the reaction of 4-bromotoluene with *trans*-ethyl cinnamate[a]

Run	Base	Catalyst	Solvent	*T* (h)	Conversion (%)	Yield (%)	*E*/*Z*[b] ratio
1	$NaHCO_3$	18	TBAB	7	100	97	59:41
2	K_3PO_4	18	TBAB	4	75	95	61:39
3	Spartein	18	TBAB	3	95	96	60:40
4	DABCO	18	TBAB	5	85	95	62:38
5	Na_2CO_3	18	TBAB	9	74	95	59:41
6	Bu_3N	18	TBAB	8	94	97	60:40
7	NaOAc	18	TBAB	8	92	97	64:36
8	$NaHCO_3$	18	[bmim][Br]	24	22	94	65:35
9	$NaHCO_3$	$Pd(OAc)_2/PPh_3$	TBAB	15	100	95	58:42

[a] Reaction conditions: TBAB (3 g), haloarene (5.68 mmol), cinnamate (5.68 mmol), catalyst (1.5 mol%), $T=130$ °C.
[b] Determined by GLC.

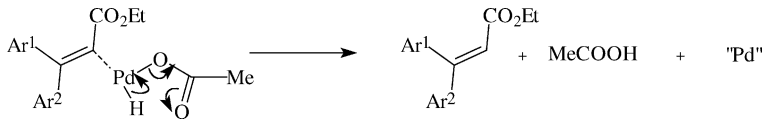
effect on the reaction of 4-bromotoluene with *trans*-ethyl cinnamate catalysed by the Pd catalyst **18** (Fig. 10) in TBAB or [bmim][Br] as solvents is given in Table 3.

The reaction rate or stereoselectivity is dependent on the choice of bases and solvents, with [bmim][Br] being much less efficient than TBAB. The reaction of the Pd catalyst **18** or $Pd(OAc)_2$ with tetrabutylammonium acetate (TBAA) dissolved in TBAB led to the rapid formation of Pd nanoparticles, which efficiently catalysed the stereospecific reaction of cinnamates with aryl halides to give β-aryl-substituted cinnamic esters. The role of TBAA was crucial in determining the formation of the nanoparticles and the stereospecificity of the C–C coupling process. The coupling of styrene and unsubstituted acrylates with aryl bromides catalysed by $Pd(OAc)_2$ or the Pd catalyst **18** in dimethylacetamide or dimethylformamide as solvents gave a much lower yield of the product.[46,74] Despite the observed beneficial effects exerted by quaternary ammonium salts on the Heck reaction,[75] the exact nature of this influence cannot be attributed a to single effect, such as the high polarity or phase-transfer ability, but rather to the superimposition of several factors. It has been speculated that the reaction of aryl halides with Pd nanoparticles affords an unstable 12-electron complex ArPdX, which is stabilised by interaction with TBAB or TBAA to give an anionic and more stable 16-electron complex $[ArPdX_3]^{2-}2NR_4^+$ ($X=Br^-$ and/or AcO^-). This is not surprising, since, in these solvents, the anions being poorly solvated are good nucleophiles for palladium. Furthermore, the ammonium cation electrostatically assists the polarisation or decomplexation of the Br^- ion from this anionic Pd(II) complex and this renders the Pd(II) complex more electrophilic for a fast olefin insertion. Evidence supporting this assumption was provided by the low reaction rates and the stability of the nanoparticles in [bmim][Br] as solvent (Scheme 11).

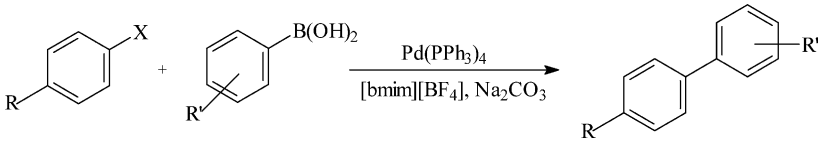
The observed stereospecificity in the presence of nanoparticles cannot be ascribed only to a better solubility of TBAA in TBAB, since other soluble bases such as amines did not increase the stereospecificity of the process. It is believed that acetate anions might participate in the fast elimination step of PdH. Whatever the real effect of TBAA may be,[76] it remains clear, however, that both the ionic liquid and the base play an important role in determining the reaction rate and stereospecificity of the C–C coupling process.

3.1.2. Coupling of aryl halides. Another promising application of biphasic catalysts using ionic liquids and involving a Pd-based catalyst is the Suzuki cross-coupling reaction for the preparation of C–C-coupled biaryls.[77] The Suzuki cross-coupling reaction using a Pd catalyst in an ionic liquid as the solvent has been reported to give an excellent yield and turnover numbers (TON^s) at room temperature.[78,79] An extremely large increase in the reaction rate was observed, compared with the conventional Suzuki conditions. The reaction of bromobenzene with phenylboronic acid under conventional Suzuki conditions gave 88% yield in 6 h (TON, $5\ h^{-1}$), while the reaction in $[bmim][BF_4]$ gave 93% yield in 10 min (TON, $455\ h^{-1}$) (Scheme 12). The reaction product was extracted using diethyl ether, while the by-products were removed by using excess water. After this treatment, the ionic liquid/catalyst system was used for three further reaction cycles with no decrease in the yields or TON^s.

The use of ultrasound in palladium-bis(carbene) complexes dissolved in $[bmim][BF_4]$ allowed the Suzuki coupling of



Scheme 11.

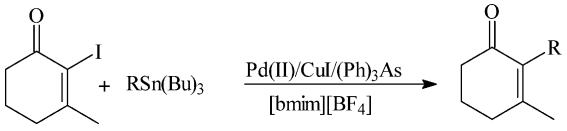


Scheme 12.

various aryl halides with phenylboronic acid to be conducted at room temperature.[80]

Nickel-catalysed homocoupling of various aryl halides was conducted in [bmim][PF_6]. The homocoupling reactions of iodo- and bromoarenes were performed by a catalytic system comprising a $NiCl_2$-$(PPh_3)_2$/Zn/PPh_3 mixture under reaction conditions similar to those employed in homogeneous conditions.[81] The yields obtained in [bmim][PF_6] as solvent were comparable to those observed in DMF, the usual solvent for this reaction.

3.1.3. Stille, Negishi and Trost–Tsuji reactions. The Stille coupling reaction has been one of the most widely used steps in the preparation of a wide variety of materials including polyarenes and diaryl and aromatic carbonyl compounds.[82] Like all transition metal-catalysed cross-coupling reactions, there is the problem of the expense of the catalyst and the need for expensive and/or toxic ligands. The use of palladium complexes immobilised in ionic liquids offers great advantages over the classical organic solvents used for Stille coupling reactions. A series of Stille coupling reactions with Pd(0) or Pd(II) catalyst precursors associated with Ph_3As in the presence of CuI has been demonstrated in [bmim][BF_4] (Scheme 13).[83] This procedure permitted extensive recycling of the solvent and catalyst without a significant loss in activity. Furthermore, an interesting selectivity for aryl bromides and iodides was observed.



Scheme 13.

Palladium-catalysed Negishi cross-coupling of organozinc reagents has also been achieved in a 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([bdmim][BF_4]) ionic liquid using a novel phosphine (Fig. 11), prepared by the reaction of PPh_2Cl with [bmim][PF_6].[84] Yields of 70–92% were obtained using variety of substrates, the fastest reaction being observed for aryl iodides. The catalyst in the ionic phase was recycled for three cycles, but the yield of the products decreased in each cycle.

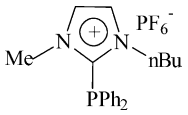
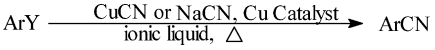


Figure 11.

The Trost–Tsuji coupling involving nucleophilic allylic substitution catalysed by Pd(0) complexes is an attractive method to form C–C bonds in organic synthesis. This reaction has also been performed in ionic liquids, both in a mono- and biphasic system, using $Pd(OAc)_2$-PPh_3/K_2CO_3 in [bmim][BF_4][85] and $PdCl_2$-TPPTS, (TPPTS = triphenylphosphine trisulphonate, sodium salt) in [bmim][Cl]/cyclohexene,[86] respectively (Scheme 14). An enhancement of the catalytic activity by 10-fold was observed in the ionic liquid biphasic condition, as compared to the aqueous reaction conditions. Furthermore, the reaction in biphasic ionic liquid conditions showed a significantly improved selectivity, since the formation of cinnamyl alcohol and of phosphonium salts was suppressed and very much decreased, respectively, in ionic liquids.

3.1.4. Rosenmund–Von braun reaction. Ionic liquids based on 1-butyl-3-methylimidazolium halide salts have been used as an effective re-usable reaction media in the Rosenmund–Von Braun reaction of aryl halides with CuCN or NaCN and Cu(I) salts as catalysts (Scheme 15).[87]

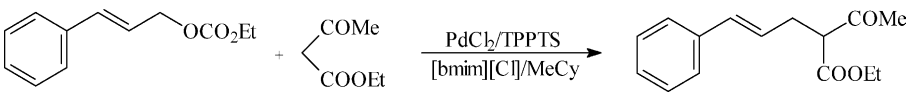


Scheme 15.

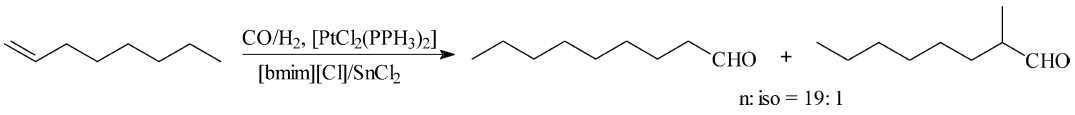
The mechanism of the Rosenmund–Von Braun reaction most likely involves a copper-assisted nucleophilic aromatic substitution, that's activation of the aromatic ring by cationic copper(I) species is achieved via the formation of a σ-complex between copper metal and the aromatic ring, and this is followed by nucleophilic attack of cyanide, which leads to the elimination of iodide. Copper(I) plays a catalytic role and the catalyst immobilised in the ionic liquid could be re-used several times without the loss of activity.

3.1.5. Hydroformylation. The hydroformylation of olefins is an industrially important catalytic chemical process. The oxo process is usually performed in industry using cobalt and rhodium complexes in homogeneous conditions or by aqueous rhodium complexes under biphasic conditions.[88] This reaction is one of the first to be investigated using molten salts as immobilising agents, but employing Ru catalyst precursors.[89,90]

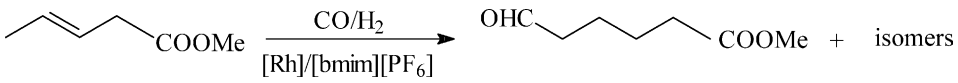
The hydroformylation of 1-hexene to heptanal using $Rh_2(OAc)_4$ and PPh_3 as the catalyst precursors and new high-melting phosphonium tosylates salts, such as *n*-butyltriphenylphosphonium tosylate, as the ionic liquid has been described.[91] The recovered ionic phase where the catalyst precursor is retained could be re-used several times, without any change in its catalytic activity. The rhodium-catalysed hydroformylation of 1-hexene has been studied by varying the nature of the cation,[92] for example, 1,3-dialkylimidazolium, 1,2,3-trialkylimidazolium and *N*,*N*-dialkylpyrrolidinium and the anion, for example, BF_4^-, PF_6^-, $CF_3CO_2^-$, $CF_3SO_3^-$ (OTf^-) and $N(CF_3SO_2)_2^-$ $(NTF_2)^-$. The problem of rhodium leaching was minimised by the modification of the phosphorus ligands with cationic (guanidinium or



Scheme 14.



Scheme 16.



Scheme 17.

pyridinium) or anionic (sulfonate) groups. By adjusting the ligand and the ions of the solvent, an excellent Rh retention was achieved. The platinum-catalysed hydroformylation of 1-octene in chlorostannate melts in [bmim][Cl] has been reported to give high *n/iso* selectivities (Scheme 16).[93] Despite the limited solubility of 1-octene in the ionic catalyst phase, a remarkable activity of the platinum catalyst was achieved. The biphasic nature of the reaction enabled a very simple product isolation, and leaching of the platinum catalyst into the product phase was not observed.

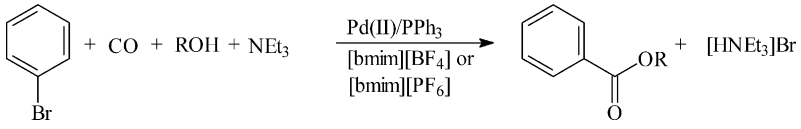
The hydroformylation of methyl3-pentanoate with $Rh(CO)_2(acac)$ associated with 2,2′-bis((((4-methyloxy-6-*t*-butyl)phenoxy)phosphino)oxy-1,1′-binaphthyl immobilised in [bmim][PF_6]has been achieved successfully (Scheme 17).[94] Recycling the same ionic catalyst solution 10-fold yielded a total TON of 6640, which is almost 7-fold greater than those obtained in reactions performed in organic solvents.

It is now apparent that a [bmim][PF_6] ionic liquid is the solvent of choice for the biphasic hydroformylation of olefins, in particular for the product isolation and catalyst recycling steps. The presence of water in [bmim][PF_6] caused a dramatic change in the selectivity of the hydroformylation of long-chain olefins.[95] This effect could be attributed to the changes in polymeric structure of this well-organised nanostructured ionic liquid.

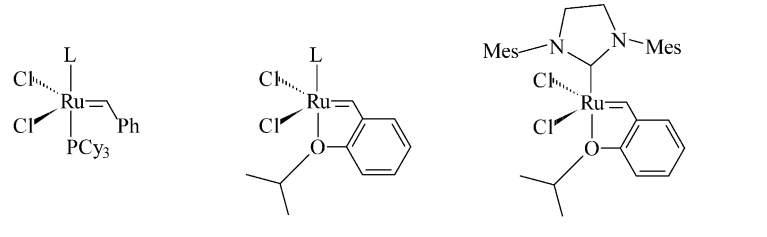
Rhodium-catalysed hydroformylation of olefins has been performed in 1,2,3-trimethylimidazolium and 1-ethyl-2,3-dimethylimidazolium triflate ionic liquids.[96] High conversions were obtained in the reactions performed in these ionic liquids, but they had a higher tendency towards olefin isomerisation and hydrogenation by-products, as compared to those performed in toluene.

3.1.6. Alkoxycarbonylation. Palladium-catalysed alkoxycarbonylation of aryl halides has been carried out in [bmim][BF_4] and [bmim][PF_6] (Scheme 18).[97] Enhanced reactivities were observed in ionic liquids, as compared to conventional media, and the ionic liquid-catalyst could be recycled. The biphasic alkoxycarbonylation of styrene catalysed by palladium compounds in a [bmim][BF_4]-cyclohexane system has also been reported.[98] $PdCl_2$-$(PhCN)_2$ was found to be the best catalyst precursor in combination with (+)-neomenthyldiphenylphosphine (NMDPP) and *p*-toluenesulphonic acid (TsOH) dissolved in [bmim][BF_4]. High regioselectivities (99.5%) were achieved for the branched ester. The alkoxycarbonylation reactions performed by the palladium compounds immobilised in the ionic liquids were greatly accelerated, compared to those in alcohols.

The intramolecular alkoxycarbonylation of alkynols has been successfully performed by Pd(II)/$PyPh_2P$ complexes immobilised in [bmim][BF_4] or [bmim][PF_6] to afford



Scheme 18.



19 L = PCy_3

20 L =

21 L =

22

23

Mes = 2,4,6-trimethylphen
Cy = cyclohexyl

Figure 12. Ruthenium carbene complexes used in RCM reaction.

selectively *exo*-methylene five- and six-membered lactones in high yields.[99]

3.1.7. Olefin metathesis. Olefin metathesis has become a powerful tool for the cleavage, as well as the formation of C=C bonds in fine chemicals, macrocycles or polymers[100] and in natural products.[101] Several well-defined homogeneous ruthenium–carbene complexes **19–23** are efficient catalyst precursors (Fig. 12), are air and moisture stable and are extremely tolerant towards different organic functional groups.[102]

Buijsman and co-workers reported that the Grubbs ruthenium catalyst precursor **19** dissolved in [bmim][PF_6] promoted the ring-closing metathesis (RCM) of several dienes for at least three cycles.[103] Among the metathesis catalysts, the cationic ruthenium allenylidene salts,[104] [(*p*-cymene)RuCl(PCy_3)(=C=C=CPh_2)]X (X = OTf, PF_6, BF_4), are valuable candidates for application in ionic liquids, due to their ionic character. These complexes were used for the RCM of various alkenes in [bmim][PF_6].[105] Although it was possible to re-use the catalyst, the yield decreased quickly after the second recycling. Following this observation, the ruthenium allenylidene catalyst was employed in the ring-opening metathesis polymerisation of cyclic olefins in the ionic liquid [bm_2im][PF_6] and showed a remarkable recyclability (Scheme 19).[106]

The best results were obtained by using a biphasic system comprising [bmim][PF_6] and toluene. The ionic liquid could be re-used after the sixth recycling for the same polymerisation reaction without any treatment simply by reloading a new portion of the cationic allenylidene complex. The polymer properties were also comparable to those obtained in the first set of the experiments, but without a significant influence on the molecular weight of the polymer after each successive run. Thus, it was seen that allenylidene catalysts, displayed better recycling capabilities than alkylidene catalysts probably because of their ionic character.

During the development of biphasic Rh-catalysed hydroformylation in ionic liquids, it has been clearly demonstrated that cationic ligands were especially suitable to avoid catalyst leaching from the ionic liquid layer.[107] In the light of these results, another strategy for RCM in ionic liquids was employed by the introduction of an ionic liquid pattern (as an alkylimidazolium salt) directly bound to the ligand to avoid the problem of catalyst leaching. The resulting ionic catalyst was found to be completely soluble in [bmim][PF_6] and allowed the RCM reaction to be carried out under standard homogeneous conditions (Fig. 13).[108]

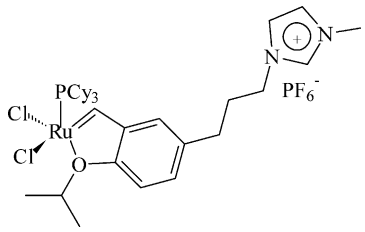


Figure 13. Ruthenium-ionic liquid catalyst used in RCM reaction.

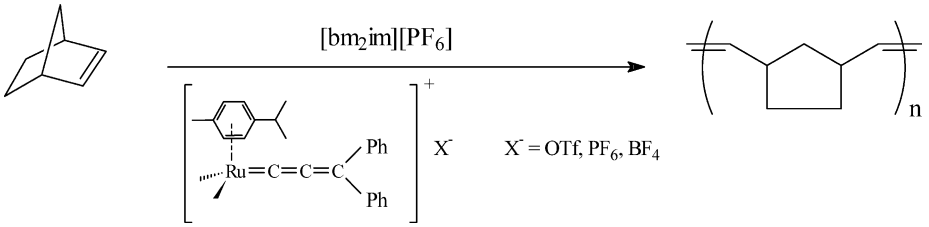
An excellent conversion was obtained for up to nine consecutive cycles of recycling and re-use. These results indicated that attaching an imidazolium ionic liquid pattern to the catalyst avoided its leaching from the ionic liquid phase.

Further, RCM reactions using ruthenium-based catalysts were conducted in [bmim][BF_4] ionic liquids and dichloromethane accelerated by microwave heating[109] and a dramatic reduction in the reaction time was witnessed (Table 4).

3.1.8. Michael addition reactions. The Michael addition reaction is one of the most useful C–C bond-forming reactions and has wide synthetic applications in organic synthesis[110] involving many homogenous[111] as well as heterogeneous catalysis.[112,113] The Lewis acids Ni(acac)$_2$, Yb(OTf)$_3$, and $FeCl_3 \cdot 6H_2O$ have been used for the metal-catalysed Michael addition in the ionic liquid [bmim][BF_4], focusing mainly on the addition of acetylacetone (Hacac) to methyl vinyl ketone as a model reaction (Scheme 20).[114] The results have been compared with those obtained using dioxane as a solvent or carrying out the reaction without solvents.

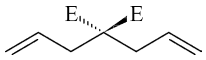
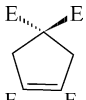
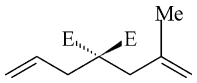
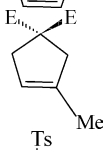
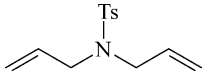
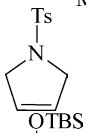
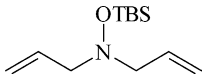
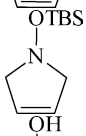
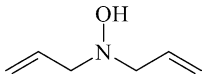
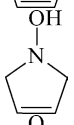
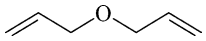
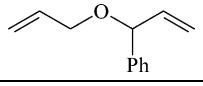
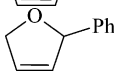
Among the catalysts tested in [bmim][BF_4], Ni(acac)$_2$ appeared to be outstanding in terms of activity, making up a recyclable catalytic system and affording a very high selectivity. On the contrary, both catalytic systems based on ytterbium and iron were less active in the ionic liquid than in the solvent-free conditions.

3.1.9. Dimerisation and polymerisation reactions. Chauvin et al. have described the oligomerisation of propene and butene using ionic liquids as a catalyst/solvent.[115] The authors used slightly acidic ionic liquids of the type [cation]X/$AlCl_3$/$AlEtCl_2$ as a solvent for a Ni(II) catalyst precursor known to produce highly branched dimeric products. The use of the ionic liquid solvent imparted a significantly higher activity to highly branched dimeric products. Moreover, the high solubility of the Ni complex, but poor solubility of the olefins in the ionic

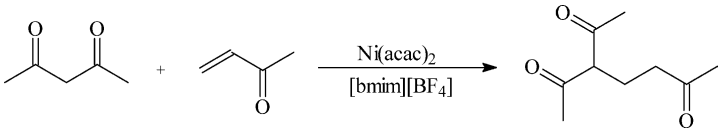


Scheme 19.

Table 4. Microwave-accelerated RCM in an ionic liquid [bmim][BF_4]

Entry	Substrate[a]	Product	Time (h)	Microwave conversion (%)[b]	Thermal conversion (%)[c]
1			15	100	3
2			15	100	0
3			15	100	0
4			45	100	12
5			30	55	0
6			60	No product	2
7			15	100	4

[a] E=CO_2Et, 0.02–0.04 M, 2–3 mol% Ru catalyst.
[b] Determined by ^{1}H NMR.
[c] Thermal reactions were conducted under conditions identical to those used in the microwave experiments.



Scheme 20.

liquid, facilitated a simple decantation step allowing the complex catalyst separation.

Keim and Wasserscheid[116] reported the use of the slightly acidic 1-butyl-4-methylpyridinium chloroaluminates, buffered with weak organic bases, as solvents for the linear dimerisation of 1-butene in the biphasic mode catalysed by the Ni complex (Fig. 14).

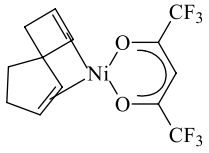
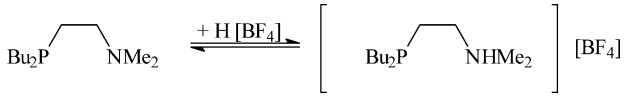


Figure 14. Nickel catalyst used in the dimerisation of 1-butene.

The use of the Ni catalyst in a slightly acidic melt, buffered with small amounts of weak organic bases, provided a solvent which prevented cationic side reactions and allowed a selective, ligand-controlled, biphasic reaction. The function of the base was to trap any free acidic species in the melt, which may initiate cationic side reaction. This method brought a new concept of producing a latent-acidic chloroaluminate ionic liquid, which avoided any addition of alkylaluminium and thereby allowed the use of reduction-sensitive metal complexes at higher temperatures.

In the dimerisation of butadiene, a significant rate enhancement was obtained by switching from organic solvents such as THF to [bmim][BF_4].[117] The biphasic Pd-catalysed dimerisation of methyl acrylate (MA) was realised by using a tetrafluoroborate ionic liquid as the catalyst medium and an ammonium phosphine ligand to immobilise and stabilise the Pd catalyst. A significant rate enhancement in the MA/ionic liquid mixture at comparable product selectivity was achieved and it was speculated that the ionic medium plays a role by lowering the activation barrier of the rate-determining step by stabilising the cationic transition state (Scheme 21).[118]



Scheme 21.

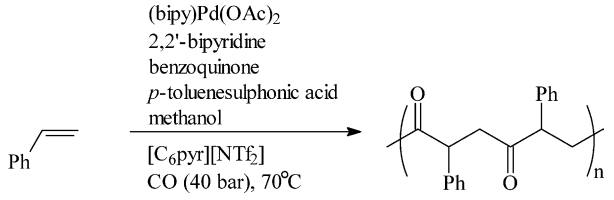
In all of the dimerisation reactions of MA (with and without added ionic liquid), the maximum MA conversion was about 80%, which indicated a potential product inhibition effect. The product inhibition problem could, however, be

efficiently solved by the continuous extraction of the product from the ionic catalyst solution. Further, the stabilisation and the activation of the Pd catalyst in an ionic liquid by means other than the formation of Pd–carbene complexes may further inspire Pd catalysis in ionic liquids.

There have been several investigations into radical polymerisation reactions in ionic liquids.[119,120] In general, these comment on the substantial increase in both the rate of polymerisation and molecular weight of the final polymer, compared to the polymerisation in conventional solvents.[121] The rate of propagation in the free-radical polymerisation of methyl methacrylate in an ionic liquid was determined and showed an unprecedented solvent-induced acceleration, partially explaining the surprising increase in the overall rates of polymerisation and molecular weights in these solvents. The dimerisation of butadiene to 4-vinylcyclohexene in the presence of $Fe(NO)_2$ as the catalyst was found to be effective in weakly coordinating [bmim][PF_6] and [bmim][SbF_6] ionic liquids.[122]

3.1.9.1. Copolymerisation of styrene and CO catalysed by cationic Pd catalysts. The insertion polymerisation of alkenes is typically catalysed by cationic metal complexes with weakly coordinated anions.[123] Polar non-coordinating ionic liquids are attractive solvents for these reactions, since they may stabilise the solvent-separated ion pairs that are necessary for a high activity. Chloroaluminate ionic liquids have been applied to the cationic,[124] metal-catalyzed oligomerisation and polymerisation of alkenes.[125] Ethylene oligomerisation and ethylene-linked polymerisation have been studied in air- and moisture-stable [C_4mim][PF_6].[126,127]

Ionic liquids have been shown to act as suitable solvents for the palladium-catalysed alternating copolymerisation of styrene and CO (Scheme 22).[128] The productivity of a standard catalytic system consisting of $LPd(OAc)_2$ (L= 2,2′-bipyridine and 1,10-phenanthroline) excess ligand, benzoquinone and *p*-toluenesulphonic acid was tested in



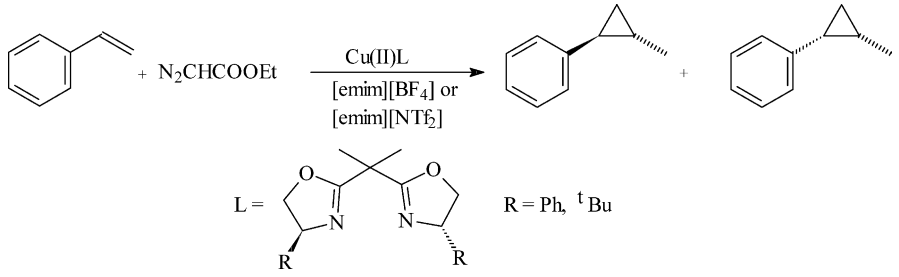
Scheme 22.

ionic liquid solvents.[129] The copolymerisation of styrene and CO in [C_6pyr][NTf_2] gave styrene homopolymer as a major product. Addition of methanol (10% v/v to the ionic liquid) gave a higher yield of copolymer, which suppressed the polystyrene formation. It has been reported that methanol reacts with L_nPd^{2+} and CO to form [$LPdC(O)OMe]^+$, which initiates the polymerisation. The best results were obtained in pyridinium-based ionic liquids, while lower yields were obtained in an imidazolium-based ionic liquid [C_4mim][NTf_2] and no copolymer was formed in phosphonium ionic liquids. Halides coordinate strongly to the vacant coordination site, inhibiting the catalyst activity. Thus, halide-free ionic liquid solvents are critical to achieve a high activity and molecular weight. During the recycling experiment, recycling the ionic liquid catalyst solution for a third time gave a significantly lower yield, which is most likely due to Pd precipitation during the polymerisation reaction or work up. In addition, extraction of the ionic liquid catalyst solution resulted in some mechanical loss. Despite these difficulties, there exists the potential for catalyst recycling using ionic liquid solvents, with [C_6pyr][NTf_2] being an effective solvent for the Pd-catalysed copolymerisation of styrene and CO. The catalyst productivity in [C_6pyr][NTf_2] approaches that obtained in polar non-coordinating solvents such as 2,2,2-trifluoroethanol while opening the possibility of catalyst recycling.[130]

A higher molecular weight of polymer and an improved catalyst stability were observed in [C_6pyr][NTf_2] as compared to methanol. Methanol acted as a chain-transfer agent and a reductant for the Pd(II) catalyst to inactive Pd(0) clusters. By replacing methanol with [C_6pyr][NTf_2], chain transfer and catalyst decomposition appear to be inhibited. The increased activity could be due to improved catalyst stability and for increased rate of propagation.

3.1.10. Cyclopropanation of styrene. A bis(oxazoline)-copper catalytic system immobilised in an ionic liquid such as 1-ethyl-3-methylimidazolium tetrafluoroborate [emim][BF_4] has been used for the enantioselective cyclopropanation of styrene with ethyl diazoacetate (Scheme 23).[131] The catalytic system was recyclable and isolation of the product was simple. Cyclopalladated compounds have also been effectively immobilised in [bmim][BF_4] and used as recyclable catalysts for the cyclopropanation of styrene with ethyl diazoacetate.[132]

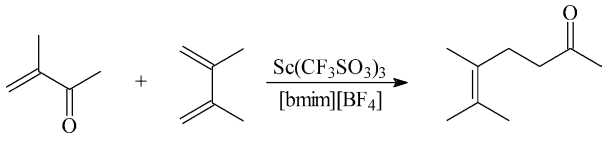
In a more recent report, rhodium acetate dimer, $Rh_2(OAc)_4$, has been immobilised in [bmim][PF_6] and used for the cyclopropanation reaction with ethyl diazoacetate.[133] The reaction products that are cyclopropane carboxylates were



Scheme 23.

obtained in high yields with a high *trans*-selectivity. The recovery of the catalyst was facilitated by the hydrophilic nature of [bmim][PF_6]. The recovered ionic liquid containing $Rh_2(OAc)_4$ was re-used for three to five runs with only a gradual decrease in reactivity.

3.1.11. Lanthanide triflate-mediated carbon–carbon and carbon-heteroatom bond-forming reactions. There have been a number of reports on reactions utilising neutral ionic liquids in combination with Lewis acids, in some cases with extremely large effects on the reactivity and selectivity.[134,135] Ionic liquids acting as solvents or additives in scandium triflate-catalysed Diels–Alder reactions have been investigated (Scheme 24), giving facile catalyst recovery, accelerated reaction rates and improved selectivity.[135]



Scheme 24.

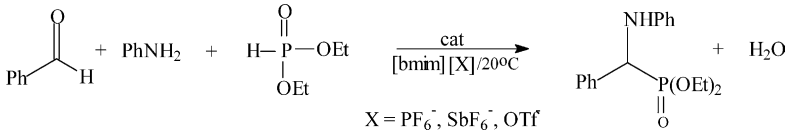
Lanthanide triflates have also been used to catalyse three-component reactions of benzaldehyde, aniline and diethyl phosphonate in ionic liquids[136] (Scheme 25). Among the different lanthanide triflate catalysts of Sc, Yb, Sm and Gd, $Sm(OTf)_3$ showed the best activity in ionic liquids while $Yb(OTf)_3$ was the most effective in organic solvents.

The imino-Diels–Alder reaction provides an easy access to the preparation of pyrano- and furanoquinolines.[137,138] Many of these reactions, however, cannot be carried out in a one-pot operation with the carbonyl compound, amine and enol ether or other dienophile, because the amine and water that exist during imine formation can decompose or deactivate the Lewis acids. Furthermore, most of the imines are hygroscopic, unstable at high temperatures and are difficult to purify by distillation or chromatography. Subsequently, a one-pot procedure has been developed for this transformation using a lanthanide triflate as the catalyst.[139] It was shown that cyclic enol ethers such as 3,4-dihydro-2H-pyran (DHP) undergo [4+2] cycloaddition reactions with imine in the presence of 3 mol% scandium triflate immobilised in [bmim][PF_6] under solvent-free conditions to afford the corresponding pyrano- and furano[3,2-*c*]quinolines in high yields (Scheme 26).[140,141]

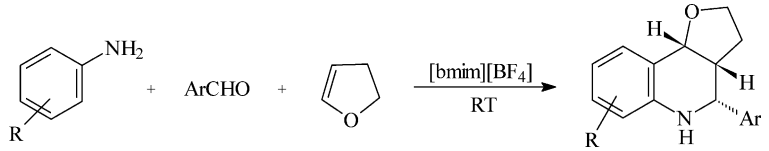
The catalytic activity of scandium triflate was found to be strongly influenced by the nature of the anion. When hydrophobic ionic liquids were used, the desired products were obtained in high yields, although scandium triflate was only slightly soluble and existed in a suspended form in these ionic liquids. In sharp contrast to these results, in the hydrophilic ionic liquids, such as [bmim][OTf] and [bmim][BF_4], the catalyst was highly soluble and totally immobilised in these ionic liquids, but the products were obtained in moderate yields. Further, asymmetric Diels–Alder reactions have been reported in [bm_2im][BF_4] and 1-butyl-3-hexylimidazolium tetrafluoroborate [bhim][BF_4] with excellent diastereoselectivity and enantioselectivity at room temperature.[142] The selectivities in room temperature ionic liquids rival the reaction in conventional solvents at −78 °C. Microencapsulated $Sc(OTf)_3$ immobilised in [emim][BF_4] has been used as a catalyst in aza Diels–Alder reactions.[143] The formation of 2-methyl-2,3-dihydrobenzo[*b*]furan has been reported via the $Sc(OTf)_3$-catalysed Claisen rearrangement/cyclisation sequential reaction of allyl phenyl ether in 8-ethyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulphonate [EtDBU][OTf].[144]

Cyclocondensation of homophthalic anhydrides with aldimines provides a useful access to the preparation of *cis*-isoquinoline acids.[145] Room temperature ionic liquids have also been reported to catalyse the one-pot, three-component coupling reaction of aldehydes, amines and homophthalic acids to afford the corresponding *cis*-isoquinoline acids in excellent yields and high *cis*-selectivity.[146] Compared to the conventional methods, this avoids the preparation and isolation of unstable imines prior to the reaction. Moreover, the use of ionic liquids as reaction media avoids the use of moisture-sensitive reagents or high-temperature reaction conditions to promote the reaction.

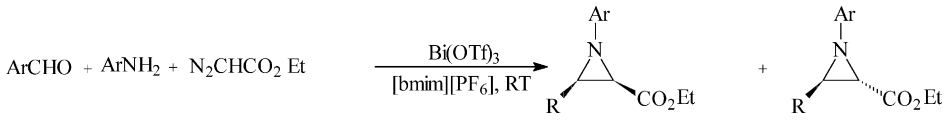
Scandium triflate in ionic liquids has also been utilised in the chemoselective thio-acetalisation and transthioacetalisation of carbonyl compounds[147] and for the Friedel–Crafts reaction.[148] Aziridines are well-known carbon electrophiles capable of reacting with various nucleophiles and their ability to undergo regioselective ring-opening reactions contributes largely to their synthetic value. The nucleophilic ring opening of aziridine carboxylates leads to many biologically active compounds such as α,β-unsaturated amino acid esters, β-lactam antibiotics and alkaloids.[149] Recently, bismuth(III) triflate has been used in an ionic liquid as a recyclable catalytic system for the synthesis of



Scheme 25.



Scheme 26.

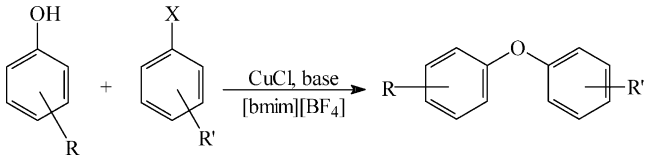


Scheme 27.

cis-aziridine carboxylates through the one-pot coupling of aldehydes, amines and ethyl diazoacetates (Scheme 27).[150]

3.2. Carbon–oxygen and carbon–nitrogen bond-forming reactions

We have demonstrated an efficient method for the synthesis of diaryl ethers from aryl halides and phenols in presence of a base catalysed by CuCl immobilised in [bmim][BF_4] (Scheme 28).[151] The reaction conditions were mild and the yield of the diaryl ethers was higher than those obtained in conventional solvents such as DMF.



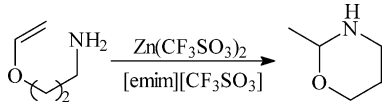
Scheme 28.

$InCl_3$ has been used in an ionic liquid as a recyclable catalytic system for the tetrahydropyranylation and furanylation of alcohols (Scheme 29).[152] A wide range of functional and protecting groups such as THP, TBDMS, TBDPS, PMB, MOM ethers, acetonides, olefins and epoxides were found to be compatible with the ionic liquid.

A Michael addition reaction of thiols to α,β-unsaturated ketones in the presence of quaternary ammonium salts, cinchona alkaloids and ionic liquids as a catalyst has been reported.[153] In a similar scenario, the conjugate addition of aliphatic amines to α,β-unsaturated compounds catalysed by quaternary ammonium salts and ionic liquids in water has been carried out under mild reaction conditions (Scheme 30).[154] It was found by control experiments that, in the absence of a catalyst, the addition of benzylamine to ethyl acrylate resulted in the formation of the desired product only in low yields (20%), thereby indicating that the quaternary ammonium salt was necessary to activate the aliphatic amines. Aromatic amines, however, failed to undergo an aza-Michael reaction under the same conditions in water.

Copper(II) acetylacetonate immobilised in ionic liquids efficiently catalysed aziridination of the olefins in good yields at a faster rate than the earlier reported methods using PhI=NTs as a nitrene donor with easy catalyst solvent recycling.[155]

The direct addition of NH across a CC multiple bond (hydroamination) has been efficiently catalysed in a liquid–liquid two-phase system comprising a polar catalyst phase of $Zn(CF_3SO_3)_2$ in the ionic liquid 1-ethyl-3-methylimidazolium trifluoromethanesulphonate and a substrate mixture in heptane (Scheme 31).[156] Under similar reaction conditions, the rate of reaction in the two-phase system was found to be higher than in the corresponding homogeneous catalysis using $Zn(CF_3SO_3)_2$ as the catalyst and this was speculated to be induced by a better stabilisation of the polar transition state at the ionic liquid interface.

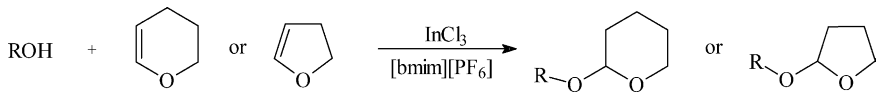


Scheme 31.

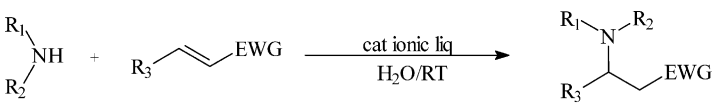
3.3. Hydrogenation

The initial investigations of hydrogenation reactions in ionic liquids were carried out by Chauvin et al. who used ionic liquids such as [bmim][BF_4], [bmim][PF_6] and [bmim][SbF_6] as solvents for the hydrogenation of olefins using Wilkinson's catalysts (Scheme 32).[157–159] These reactions were typically performed in liquid–liquid biphasic systems where the substrates and products are not miscible with the ionic catalyst solution. The products were removed from the reaction mixture by simple decantation, and the recovered ionic catalyst solution was re-used several times without any significant change in the catalytic activity and selectivity.

The observed reaction rates were found to be higher than those obtained with the classical water-soluble phosphine/transition–metal complexes, which generally gave a low

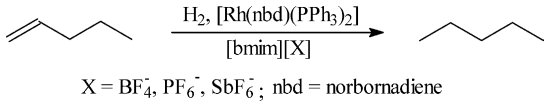


Scheme 29.



EWG = CN, COOEt, COOMe, COMe

Scheme 30.



Scheme 32.

turnover frequency and required the use of more drastic conditions. Alkene isomerisation products were not formed in the ionic liquids. It was observed, however, that alkene isomerisation products might form, when the ionic liquids contain trace amounts of the strongly coordinating chloride anions.[159] Moreover, in comparison to the aqueous biphasic catalytic systems, there was no formation of stable emulsions in all of the examples involving ionic liquids.

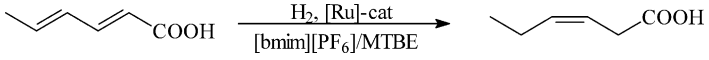
Olefin hydrogenation by Wilkinson's catalyst immobilised in [bmim][PF_6] and supercritical CO_2 gave similar results to those obtained in the absence of a co-solvent or when using hexane as a co-solvent.[160] The use of the supercritical CO_2/[bmim][PF_6] system for the reduction of CO_2 by $RuCl_2$-$(dppe)_2$ (dppe = diphenylphosphinoethane) in the presence of secondary amines, however, gave excellent yields of formamides. The cobalt catalyst precursor $Na_3Co(CN)_5$ dissolved in [bmim][BF_4] was shown to be extremely selective in the reduction of one double bond of 1,3-butadiene, producing 1-butene with 100% selectivity. In this particular case the ionic liquid catalyst solution could not be re-used. The selective hydrogenation of cyclohexadiene to cyclohexene has been described by making use of the biphasic reaction system based on the solubility of cyclohexadiene and cyclohexene in [bmim][SbF_6] ionic liquid.[157]

A stereoselective ruthenium-catalysed hydrogenation of sorbic acid to *cis*-3-hexanoic acid was successfully carried out in a [bmim][PF_6]/MTBE (MTBE = methyl *t*-butyl ether) system (Scheme 33).[161] In comparison to other polar solvents, for example, glycol, a > 3-fold increase in activity, with comparable selectivity, to *cis*-3-hexanoic acid was observed in the ionic liquid.

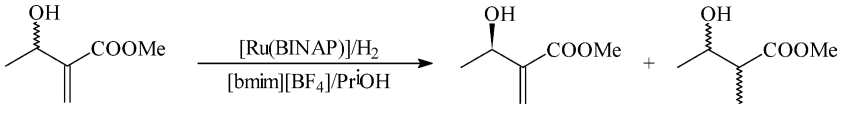
Classical Ru-BINAP complexes immobilised in [bmim][PF_6]/^{i}PrOH promote the kinetic resolution of methyl3-hydroxy-2-methylenebutanoate with the same degree of enantiomer selection as those obtained under homogeneous conditions in methanol (Scheme 34).[162]

In order to extend the use of ionic liquids in enantioselective synthesis, polar phosphonic acid-derived Ru-BINAP systems were used to catalyse the asymmetric hydrogenation of β-ketoesters with complete conversion and ee values higher than those obtained from the homogenous reaction in methanol (Scheme 35). In all these reactions, the catalyst was recycled by simple extraction and used 4–5 times without any loss of activity and selectivity. Asymmetric hydrogenation reactions were performed with classical rhodium and ruthenium complexes immobilised in ionic liquids. In these cases, the substrate was dissolved in suitable solvents and 2-propanol was shown to be the best solvent for these reactions. Cationic [Rh(cod)(-)-DIOP][PF_6] immobilised in [bmim][SbF_6] catalyzed the asymmetric hydrogenation of acetamidocinnamic acid to (*S*)-phenylalanine in 64% ee.[157] Similarly, optically active $RuCl_2$-(*S*)-BINAP precursor immobilised in [bmim][BF_4] was found to catalyse the asymmetric hydrogenation of 2-phenyl- and 6-methoxy-2-naphthyl-acrylic acid.[163] The enantiomeric excess obtained in these reactions was found to be similar to that obtained under homogeneous conditions. The catalyst was re-used with the same activity and enantioselectivity after decanting the hydrogenation products.

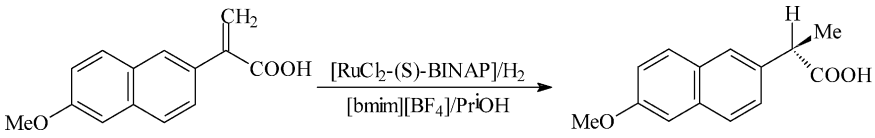
As described in Section 3.1.1 for the Heck reaction, the hydrogenation of olefins has also been carried out using ligand-stabilised palladium nanoparticles in ionic liquids.[164,165] In a further report, the nanoscale Pt(0) particles have been prepared in room temperature ionic liquids and used in hydrogenation reactions.[166] The reaction of $Pt_2(dba)_3$ (dba = bisdibenzylidineacetone) dispersed in room temperature [bmim][PF_6] with molecular oxygen (4 atm) at 75 °C led to stable and isolable nanometric Pt(0) particles. These isolated $[Pt(0)]_n$ nanoparticles were redispersed in ionic liquid or in acetone or used in solventless conditions for liquid–liquid biphasic, homogenous or heterogenous hydrogenation of alkenes and allenes under mild reaction conditions. The recovered Pt nanoparticles were re-used as a solid or redispersed in the ionic liquid several times without any significant loss in activity.



Scheme 33.



Scheme 34.



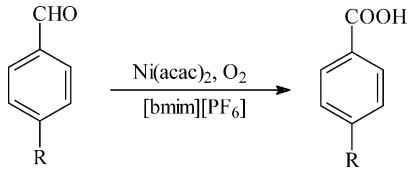
Scheme 35.

Aromatic compounds are notoriously difficult substrates to hydrogenate, although a wide range of reagents have been used for this purpose.[167] During the initial attempts to develop biphasic methodologies for the hydrogenation of arenes, a [bmim][BF_4]—organic system stable [$H_4Ru_4(\eta^6$-arene)][BF_4]$_2$ cluster was employed for the hydrogenation of aromatic compounds. The turnover frequencies obtained in the ionic liquids and aqueous resins were compared and found to be similar.[168] Another arene hydrogenation catalyst has been devised that is active in organic solvents but considerably more active in ionic liquids and, remarkably, hydrogenates the arene ring of allylbenzene without hydrogenating the alkene bond.[169]

The reaction of the triply bridged chloro-dimer, [(η^6-ρ-cymene)$_2$-$Ru_2(\mu$-Cl)$_3$][PF_6], with 2 equiv of 1,1,1-tris(diphenylphosphonium-ethyl)ethane (TRIPHOS) in the presence of 1 equiv of ammonium hexafluorophosphonate in methanol under reflux afforded [Ru(η^6-ρ-cymene)(η^2-TRIPHOS)Cl][PF_6] in high yields. With this catalyst, the highest turnover was observed for the hydrogenation of benzene, with the turnover decreasing as the size or number of alkyl substituents increases on the arene substrate. The catalyst was essentially inactive towards arenes such as styrene and 1,3-divinylbenzene with α-nitro substituents, whereas the turnover for the hydrogenation of allylbenzene to allylcyclohexane was considerably higher than expected. The alkene bond remained unhydrogenated and hydrogenation of alkene substrates such as 1-hexene and 1-octene gave very low TONs because of catalyst decomposition.

3.4. Oxidation and reduction reactions

3.4.1. Oxidation of alkyl groups, alcohols, aldehydes, oximes and thiols. Low-melting imidazolium and pyridinium ionic liquids are stable towards strong chemical oxidising agents and have a large electrochemical window and are therefore suitable media for oxidation reactions. Various transition metal-catalysed oxidation reactions have been performed in these ionic liquids and the results obtained so far demonstrate the advantage of the ionic liquids over other immobilising agents. Bis(acetylacetonato)nickel(II) immobilised in the ionic liquid [bmim][PF_6] promoted the oxidation of ethylbenzene at atmospheric pressure,[170] showing that this catalytic system is an important industrial alternative to the heterogeneous catalyst presently used for this oxidation process. Various aromatic aldehydes have been oxidised to the corresponding carboxylic acids using bis(acetylacetonato)nickel(II) immobilised in [bmim][BF_4] and dioxygen at atmospheric pressure (Scheme 36).[171]



Scheme 36.

Oxidation of alcohols to the corresponding aldehydes and ketones is one of the most important functional group transformations in organic synthesis. Of a number of methods that are employed, Seddon and co-workers demonstrated that benzyl alcohols could be oxidised selectively to benzaldehydes in dry ionic liquids using $Pd(OAc)_2$ as a catalyst and O_2 as an oxidant.[172]

In another method that has been developed, a room temperature ionic liquid containing a cyclic hexaalkylguanidinium cation (Fig. 15) was prepared and selective oxidation of a series of substituted benzyl alcohols was carried out in the ionic liquid with sodium hypochlorite as an oxidant.[173]

The room temperature ionic liquid acted as both phase-transfer catalyst and oxidant. The ionic liquid could be recycled after extraction of the benzaldehyde product with ether. This new hexaalkylguanidinium-based ionic liquid offered several advantages in this reaction. It could be used as a phase-transfer catalyst. Further, the positive charge in the guanidinium salts is delocalised over one carbon and three nitrogen atoms, which gives the salts a high degree of thermal stability as compared to their tetraalkylammonium counterparts.

Classical oxidation of alcohols promoted by tetra-*N*-propylammonium perruthenate has been performed in tetraethylammonium bromide or [bmim][BF_4].[174] The use of this catalytic system in the oxidation reactions with oxygen or *N*-methylmorpholine *N*-oxide allowed the facile recovery and re-use of the ionic solution. The ionic liquid [bmim][BF_4] was used to remove or extract excess MnO_2 and associated impurities from the oxidation reaction of codeine methyl ether to thebaine (Scheme 37).[175]

A mild TEMPO/CuCl- and TPAP/CuCl-catalysed aerobic oxidation of primary and secondary alcohols to the corresponding aldehydes and ketones was carried out in [bmim][PF_6], with no trace of over-oxidation to the carboxylic acids.[176,177]

We have developed a simple, efficient and eco-friendly method for the chemoselective oxidative cleavage of oximes with hydrogen peroxide catalysed by phosphotungstic acid in ionic liquids at room temperature to regenerate the corresponding carbonyl compounds in excellent yields (Scheme 38).

The reaction of phosphotungstic acid with hydrogen

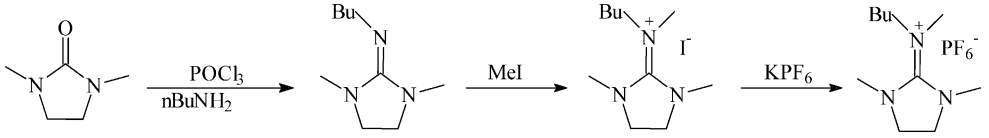
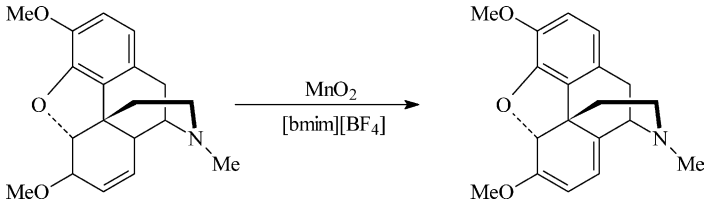
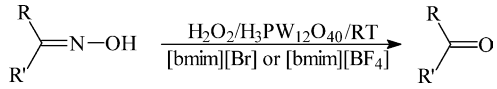


Figure 15.

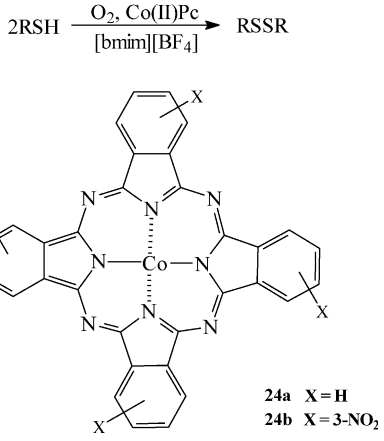


Scheme 37.



Scheme 38.

peroxide led to the formation of an active peroxo-polyoxometalate species which reacted with the respective aldoxime or ketoxime as a nucleophile, followed by subsequent transformations leading to the formation of the corresponding aldehyde or ketone. The ionic liquids are believed to stabilise this reactive intermediate, as they have been reported earlier to stabilise a manganese-oxo intermediate in manganese(III) porphyrin-catalysed oxygenation reactions.[178] Further, on addition of H_2O_2 to the solution of phosphotungstic acid in the ionic liquid, a new peak at 275 nm was observed in the UV–vis spectra, which, in the presence of oximes, decreased and finally disappeared, depending on the amount of oxime. The peak re-appeared, however, on addition of a fresh batch of H_2O_2 and subsequently decreased in the presence of the substrate. A similar peak at 280 nm has been reported to appear in the oxygen-atom transfer reactions by tungstate complexes.[179]



Scheme 39.

The metallophthalocyanines possess catalytic activity for a variety of organic reactions, but a decisive disadvantage of these catalysts is their low solubility in organic solvents and water. Further, water-soluble phthalocyanines have decreased activity in aqueous solution, due to the formation of a μ-oxo dimer. We carried out the reaction of thiophenol with molecular oxygen catalysed by cobalt(II) phthalocyanines **24** in an ionic liquid and found that changing the solvent from DMF or THF to the ionic liquid dramatically increased the yield of the disulphides to 95% in 45 min (Scheme 39).[180]

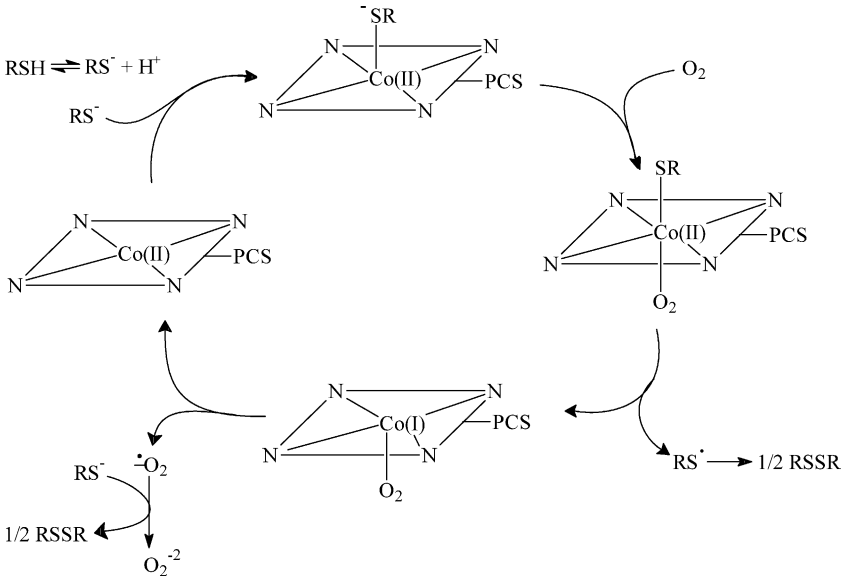
The yields for the oxidation of different thiols with molecular oxygen catalysed by cobalt(II) phthalocyanine **24a** and cobalt(II) tetranitro-phthalocyanine **24b** in [bmim][BF_4] ionic liquid are shown in Table 5.

In absence of the catalyst, only 7% of diphenyl disulphide was obtained under similar conditions. The catalytic activity of **24a** in the ionic liquid [bmim][BF_4] decreased gradually as the yield of the disuphide decreased with each run. Similar results were obtained for **24b**, but the yields of the disulphide were higher than that for **24a**. The nitro-complex **24b** showed a better catalytic activity as compared to **24a** in the oxidation reaction of thiols with molecular oxygen at room temperature. The ionised thiol group coordinated to the cobalt metal of the cobalt(II) phthalocyanine at the axial

Table 5. Oxidation of thiols to disulphides with molecular oxygen catalyzed by **24a**,**b** dissolved in [bmim][BF_4][a]

Entry	Substrate	Catalyst	Time (min)	Yield of disulphide[b] (%)	Mp or bp/mmHg (lit. mp or bp) (°C)
1	PhSH	**24a**	45	95 (92)[c,d]	57–59 (59–60)[181]
2	PhSH	**24b**	45	99 (95)[c]	57–59 (59–60)[182]
3	4-MeC_6H_4SH	**24a**	35	99 (97)[c]	51–53 (52–53)
4	2-$H_2NC_6H_4SH$	**24a**	60	95	75–77
5	2-Mercaptopurine	**24a**	60	93	243 (245)[183]
6	2-Mercaptopyridine	**24a**	60	94	103–105 (104)
7	BnSH	**24a**	45	93 (90)[c]	70–73 (71–72)
8	BnSH	**24b**	45	97 (93)[c]	70–73 (71–72)
9	$HOCH_2CH_2SH$	**24a**	45	91	113/7 (115/7)
10	BuSH	**24a**	45	92 (91)[c]	38–40 (40–41)
11	BuSH	**24b**	45	97	38–40 (40–41)[31]
11	OctSH	**24a**	60	87 (85)[c]	185–187/6 (187/6)[32]
12	OctSH	**24b**	60	93	185–187/6 (187/6)[32]

[a] All reactions were carried out using thiol (1.0 mmol) and **24a** or **24b** (1.0×10^{-3} mmol) in [bmim][BF_4] (2.0 ml).
[b] Yields calculated by HPLC analysis (μ-bondapack column, methanol/water=60:40 v/v, flow rate=0.5 ml/min, monitored at 220 nm).
[c] Isolated yields.
[d] 7% in the absence of **24a**.



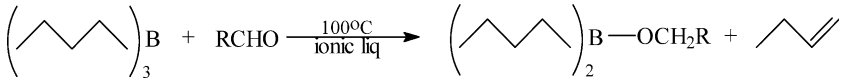
Scheme 40.

position to form a binary complex (Scheme 40). This binary complex then reacted with oxygen to form a highly unstable ternary thiolate-CoPc-O_2 complex. Decomposition of this ternary complex led to the formation of a thiol radical ($RS^{\bullet}$) and $O_2^{-\bullet}$. The disulphide was formed by the dimerisation of the thiol radicals. Further, the reaction of $O_2^{-\bullet}$ with ionised thiol formed a thiol radical, leading to disulphide formation along with the generation of O_2^{-}.

The UV–vis spectrum of Co(II) phthalocyanines **24a** in DMF showed two characteristic peaks at 660.0 and 600.0 nm, which shifted to 664.0 and 601.0 nm in the ionic liquid. When molecular oxygen was bubbled into the reaction mixture in absence of thiol, a new peak appeared at 426.0 nm. The addition of thiol to Co(II) phthalocyanine in the ionic liquid resulted in the appearance of new peaks at 677.0, 555.0 and 507.0 nm, which may be due to the coordination of thiol to the central metal atom. The peak at 426.0 nm in the UV–vis spectrum may be attributed to the formation of a Co(I)–O_2 complex. The absorption maximum at 426.0 nm gradually increased with respect to time and then decreased after 30 min, indicating that the oxidation process was initiated by the reaction of Co(I)–O_2 with thiol, which resulted in the formation of $RS^{\bullet}$. The combination of two $RS^{\bullet}$ radicals led to the formation of disulphide. Further, the peaks at 555.0 and 507.0 nm disappeared after the completion of the reaction, which showed the complete consumption of thiol. It is also noteworthy to mention the changes in colour during the course of the reaction. The bluish-green colour of Co(II) phthalocyanine dissolved in the ionic liquid changed to violet upon addition of thiol and remained the same during the process of oxidation (i.e., after bubbling molecular oxygen). After completion of the reaction, however, the violet colour changed back to the original bluish-green hue.

Kabalka and co-workers reported that ionic liquids such as [bmim][BF_4], [emim][PF_6] and [emim][BF_4] enhanced the rate of trialkylborane reductions of both aromatic and aliphatic aldehydes[184] (Scheme 41).

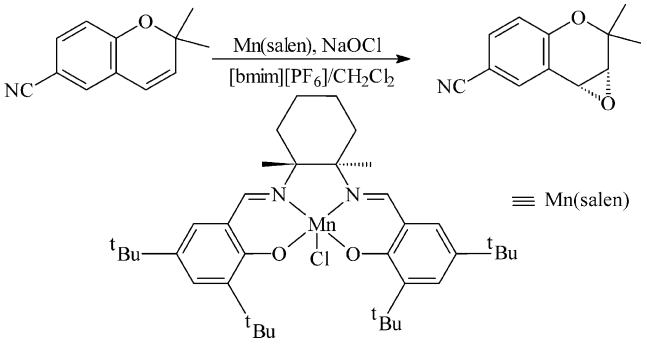
3.4.2. Oxidation of olefins. 3.4.2.1. Epoxidation. The epoxidation reaction of olefins with various oxidants using different catalysts has been extensively studied in ionic liquids. The first catalytic epoxidation system utilising a room temperature ionic liquid as the solvent, involved methyltrioxorhenium (MTO) as the catalyst and urea hydrogen peroxide (UHP) as the oxidant, both of which were completely soluble in [bmim][PF_6] giving a homogeneous solution. Alkenes and allylic alcohols were oxidised to their corresponding epoxides in high yields.[185] The kinetics of oxygen-atom transfer from the peroxo complexes of the MTO to alkenes in ionic liquids were investigated. The reaction of MTO and UHP in dry THF yielded essentially water and peroxide-free methyldiperoxorhenium (dpRe), which could be diluted into room temperature ionic liquids after the removal of the remaining solid UHP. The homogenous solution of the dpRe in ionic liquids was extracted with various olefins under pseudo-first order conditions. The kinetic profiles were bis experimental and the observed rate constants displayed first order dependencies on the olefin concentration. Based on kinetic simulations and their agreement with experimental data, the fast step was assigned to the reaction of olefins with dpRe and the slow step to the reaction of olefins with the monoperoxorhenium complex (mpRe). While mpRe was more reactive towards the alkene than dpRe in 1:1 MeCN/H_2O, the opposite effect was true for the reactions conducted in ionic liquids. The rate constants K_3 and K_4 were unaffected by the cation of the ionic liquids, but were sensitive to the anion. Epoxidation of lipophilic olefins has



Scheme 41.

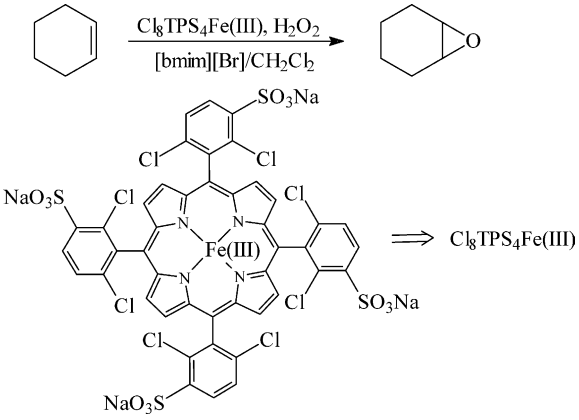
been achieved with manganese sulphate/bicarbonate immobilised in [bmim][BF_4] using hydrogen peroxide as the oxidising agent.[186]

Epoxidation of olefins with NaOCl using Jacobsen's chiral Mn(III) salen immobilised in a [bmim][PF_6] catalyst is an efficient and recyclable method for asymmetric epoxidation (Scheme 42).[187] The electrochemical investigation of the activation of molecular oxygen by Jacobsen's epoxidation catalyst immobilised in a [bmim][PF_6] ionic liquid showed the formation of the postulated high-valent manganese-oxo active intermediate, which was otherwise undetectable in organic solvents.[188] When 30% aqueous H_2O_2 was used as the oxidant, this led to ring opening of the sensitive epoxides. This observation has been used to develop a practical recycling procedure for the Cr-salen-catalysed asymmetric ring-opening reactions of *meso*-epoxides in ionic liquids.[189]



Scheme 42.

Studies in our laboratory showed that water-soluble iron(III) porphyrins immobilised in [bmim][Br] were an efficient catalytic system for the epoxidation of alkenes using hydrogen peroxide as the oxidising agent and dichloromethane as the co-solvent (Scheme 43).[190] The catalytic TON for the epoxidation was higher than for those in aqueous media. The iron(III) porphyrins immobilised in the ionic liquids were recycled for five consecutive cycles without an appreciable loss in activity of the catalyst. The mechanism of the reaction is believed to be the same as that in an aqueous medium and the yields of epoxides were high. Recently, alkene epoxidation using lipid-soluble manganese(II) porphyrins immobilised in [bmim][BF_4] and



Scheme 43.

iodobenzene diacetate as the oxidising agent has also been reported.[191,192] The use of ionic liquid media significantly enhanced epoxidation and it is assumed that this is due to better stabilisation of the Mn–oxo intermediate species in the ionic liquid.

3.4.2.2. Asymmetric dihydroxylation of olefins. Osmium catalysts have been used in asymmetric dihydroxylation reactions of the olefins. The high cost and toxicity of, and contamination of the product with, the osmium catalyst, however, restrict the use of the asymmetric dihydroxylation reactions in industry.[193] Different methods have been developed for immobilisation of the osmium catalyst such as by microencapsulation of OsO_4 in polystyrene-type capsules[194] or on silica-anchored tetra-substituted olefins[195] or by ion exchangers.[196] In an attempt to solve this problem, two independent groups have simultaneously reported the asymmetric dihydroxylation of olefins based on the anchoring of the osmium ligand catalyst in a room temperature ionic liquid.[197,198] Before this work, OsO_4^--catalysed olefin dihydroxylation using 4-methylmorpholine-*N*-oxide (NMO) as the co-oxidant in [bmim][BF_4] had already been reported.[199]

In one of the two reports, asymmetric dihydroxylation of the olefins was carried out following two protocols which comprised biphasic [bmim][PF_6]/water and monophasic [bmim][PF_6]/*tert*-butanol systems. Both procedures were applied to representative substrates using the chiral ligands, 1,4-bis(9-*O*-dihydroquinidinyl)phthalazine ($(DHQD)_2$-PHAL) and 1,4-bis(9-*O*-dihydroquinidinyl)biphenyl-pyrimidine $(DHQD)_2$PYR. After each cycle, diethyl ether was added to the reaction mixture and the aqueous and ethereal layers were removed, followed by the addition of more olefin and aqueous solution containing the co-oxidant and K_2CO_3. This method allowed the recycling and re-use of the osmium ligand catalyst. The use of supercritical carbon dioxide extraction helped in minimising the osmium leaching from the room temperature ionic liquid (RTIL) phase (Table 6).

In the second report, osmium catalysed asymmetric dihydroxylation of olefins was carried out in the ionic liquid [bmim][PF_6] by using NMO as a co-oxidant, in presence of the chiral ligands, 1,4-bis(9-*O*-dihydroquininyl)phthalazine ($(DHQ)_2$PHAL) and 1,4-bis(9-*O*-quininyl)phthalazine ($(QN)_2$PHAL) (Table 7).

After completion of the reaction, all of the volatiles were removed under reduced pressure and the chiral diols produced were extracted with pre-cooled (0 °C) diethyl ether from the residue. The re-use of the recovered ionic liquid phase resulted in a dramatic decrease in the yield of the product, due to the severe leaching of both the osmium and $(DHQ)_2$PHAL during the extraction with diethyl ether. Replacing $(DHQ)_2$PHAL by $(QN)_2$PHAL, that is, an alkaloid ligand, however, afforded the same yield and ees and resulted in a drastic improvement in the recyclability of both catalytic components. The recovered ionic liquid phase containing osmium was recycled several times and no leaching of the chiral ligand occurred during the extraction of the diols with diethyl ether.

Table 6. Asymmetric dihydroxylation of olefins using the ionic liquid [bmim][PF_6] as a co-solvent[a]

Olefin	Ligand[b]	*t*-BuOH/H_2O[c]		RTIL/H_2O[d]		RTIL/H_2O/*t*-BuOH[e]	
		Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)
Ph	PHAL[f]	88	97	87	62	86	94
	PYR[f]	91	93	86	75	90	89
Ph	PHAL[f]	83	92	80	66	85	84
	PYR[f]	95	77	77	71	97	80
Bu	PHAL[f]	92	90	71	90	88	89
	PYR[f]	93	94	96	90	96	91
	PHAL[g]	91	87	47	92	53	87
	PYR[g]	63	90	66	86	57	83
Ph Ph	PHAL[h]	89	96	87	98	92	99
	PYR[h]	94	87	81	96	79	77
Bu Bu	PHAL[h]	94	94	69	87	96	92
	PYR[h]	79	75	52	63	92	96

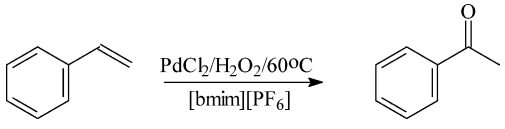
[a] All reactions carried out using olefin (0.5 or 1 mmol), $K_2OsO_2(OH)_4$ (0.5 mol%), ligand ($(DHQD)_2$PHAL or $(DHQD)_2$PYR, 1.0 mol%), $K_3Fe(CN)_6$ (3 mol equiv), solvent, rt, 24 h.
[b] PHAL and PYR refer, respectively, to $(DHQD)_2$PHAL and $(DHQD)_2$PYR.
[c] *t*-BuOH/H_2O (1:2, 1.5 ml).
[d] [bmim][PF_6]/H_2O (1:2, 1.5 ml).
[e] [bmim][PF_6]/H_2O/*t*-BuOH (1:1:2, 2 ml).
[f] Absolute configuration of diol is (*R*).
[g] Absolute configuration of diol is (1*S*,2*R*).
[h] Absolute configuration of diol is (*R*,*R*).

Table 7. Asymmetric dihydroxylation of olefins in [bmim][PF_6][a]

Entry	Ligand	Olefin	Yield (%)	Ee[b] (%)	Abs. config.
1[c]	$(DHQ)_2$PHAL	*trans*-Stilbene	95	85	*S,S*
2[d]	$(DHQ)_2$PHAL	*trans*-Stilbene	45	n.d	*S,S*
3	$(DHQ)_2$PHAL	*trans*-Stilbene	94	97	*S,S*
4	$(QN)_2$PHAL	*trans*-Stilbene	95	97	*S,S*
5	$(QN)_2$PHAL	Styrene	89	72	*S*
6	$(QN)_2$PHAL	β-Methyl-*trans*-styrene	92	90	*S,S*
7	$(DHQ)_2$PHAL	Methyl *trans*-cinnamate	96	91	*2R,3S*
8[e]	$(DHQ)_2$PHAL	Methyl *trans*-cinnamate	96	95	*2R,3S*
9	$(QN)_2$PHAL	Methyl *trans*-cinnamate	96	94	*2R,3S*
10	$(QN)_2$PHAL	Methyl *p*-methoxy-*trans*-cinnamate	93	96	*2R,3S*
11	$(QN)_2$PHAL	α-Methylstyrene	98	63	*S*

[a] Unless indicated otherwise, all reactions carried out with 1-mmol olefin using 1 mol% OsO_4, 2.5 mol% chiral ligand, 1.5 mmol NMO and 2 mmol ionic liquid in acetone–H_2O (v/v = 10:1, 10 ml) at 20 °C. Olefins were added for 12 h.
[b] Determined by chiral HPLC.
[c] Olefin was added in one portion. Reaction time 20 min.
[d] Reaction carried out with the recovered ionic liquid phase obtained from reaction in entry 1 without further addition of OsO_4 and $(DHQ)_2$PHAL.
[e] Olefin added in one portion. Reaction time 4 h.

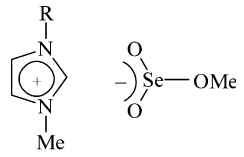
Wacker-type oxidation reactions have been performed with great advantage compared to the reactions performed in water by $PdCl_2$ immobilised in [bmim][BF_4] and [bmim][PF_6] using hydrogen peroxide as the oxidant (Scheme 44).[200]



Scheme 44.

3.4.3. Oxidative carbonylation of amines. Alkali metals containing selenium compounds are effective catalysts for the oxidative carbonylation of aniline to produce phenyl carbamate and diphenyl urea.[201] The major disadvantage of using these selenium compounds is the difficulty in separating the product and the catalyst from the reaction mixture, which arises from the co-production of insoluble diphenyl urea and soluble alkyl phenyl carbamate along with the toxic selenium species at relatively high reaction temperatures. This problem was solved by preparing ionic liquids containing anionic selenium species and these were found to show a high activity for the carbonylation of aniline, even at temperatures as low as 40 °C (Fig. 16).[202] Malodorous selenium species were not formed when the immobilised selenium compound was used as a catalyst for the carbonylation.

The activities of various ionic liquids consisting of imidazolium cations and selenium-based anions were evaluated as catalysts for the oxidative carbonylation of aniline and compared with the activities of [$KSeO_2$(OMe)] and 5% Pd/C–KI. In addition to the improved catalytic performance and the absence of the species potentially



R = Me, Et, Bu

Figure 16. Selenium anion-based imidazolium ionic liquids.

responsible for foul odours, the selenium-containing ionic liquid catalyst systems were recyclable without any loss of their initial activity. They were air stable and highly soluble in various organic solvents including CH_2Cl_2, $CHCl_3$ and MeCN.

4. Other organic reactions in ionic liquids

4.1. Carbon–carbon bond-forming reactions

4.1.1. Friedel–Crafts reaction. Earlier investigations of the Friedel–Crafts reaction of simple benzene derivatives were carried out by Wilkes[203] in an [emim]Cl–$AlCl_3$ system. This was followed by the work of Seddon and Adams, who carried out the acetylation reactions of carbocyclic aromatic compounds with acetyl chloride in acidic compositions of [emim][Cl]–$AlCl_3$.[204] These reactions worked efficiently giving the stereoelectronically favoured products. In the acetylation reaction of naphthalene, the major product was the thermodynamically unfavoured 1-isomer and the minor product was the 2-isomer with only 2% yield. This is in accordance with the best literature yield and selectivity.[205]

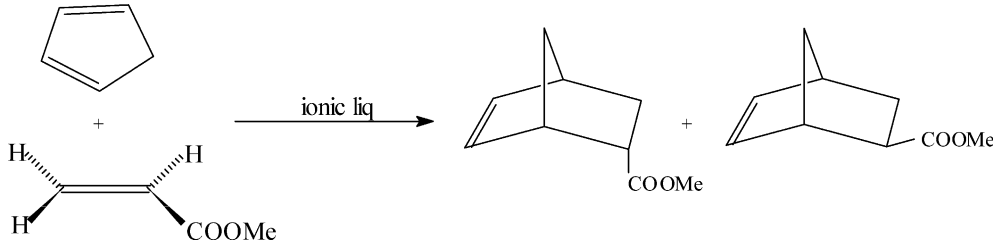
It has been suggested that the position of attack on naphthalene is determined to a large extent by steric factors. In the ionic liquids, the acetylating agent is thought to be the free acylium ions, which, being small, can attack at the sterically more hindered positions. In a similar manner, acetlyation reactions of anthracene, pyrene and phenanthrene were carried out and good yields of the acetylated products were obtained. These carbocyclic aromatics, however, formed highly coloured compounds in acidic [emim]Cl–$AlCl_3$, probably because of the formation of π-complexes as they are paramagnetic.[206]

4.1.2. Diels–Alder reaction. Ionic liquids such as [bmim][BF_4], [bmim][ClO_4], [emim][[CF_3SO_3], [emim][NO_3] and [emim][PF_6] were demonstrated as effective solvents for Diels–Alder reactions between cyclopentadiene and methyl acrylate and showed significant rate enhancements, high yields and strong *endo* selectivities comparable with the best results obtained in conventional solvents (Scheme 45).[207,208]

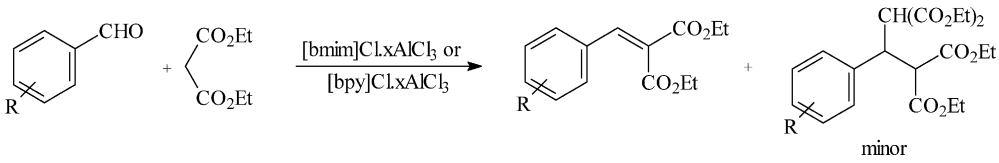
4.1.3. Kneovenagel condensation reaction. The past decade has witnessed a rapid emergence of heterogenous catalysts comprising mainly inorganic materials such as clays and zeolites.[209] These inorganic materials have been successfully applied in Kneovenagel reaction as they are ditopic in nature and contain both acidic and basic sites.[210] Some Lewis acid catalysts have also been exploited for this reaction.[211] Chloroaluminate-based ionic liquids, which have variable Lewis acidity, were used for carrying out Kneovenagel condensations.[212] The 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl·$AlCl_3$, $x(AlCl_3)=0.67$ where x is the mole fraction and 1-butylpyridinium chloroaluminate, [bpy]Cl·$AlCl_3$, $x(AlCl_3)=0.67$, ionic liquids were found to work well as the Lewis acid catalyst and solvent in the Kneovenagel condensation of benzaldehyde and substituted benzaldehydes with diethyl malonate to give benzylidene malonates, which subsequently underwent Michael additions with diethyl malonate (Scheme 46). The extent of the Michael product was found to vary with the Lewis acidity and the molar proportion of the ionic liquids. Considerable control over various products in these reactions was exercised by variation of the parameters associated with the ionic liquids.

In another attempt to perform a Kneovenagel condensation in air- and moisture-stable ionic liquids, the chloroaluminate melt was replaced by 1-hexyl-3-methyl imidazolium hexafluorophosphate, [6-mim][PF_6], and glycine was used as the base (Scheme 47).[213]

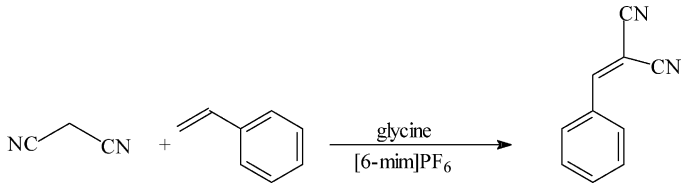
4.1.4. Aldol condensation reaction. The self-condensation reaction of propanal to form 2-methylpent-2-enal (Aldol I) has been carried out in non-coordinating imidazolium ionic liquids.[214] The reaction progressed through an aldol intermediate and produced the unsaturated aldehyde under



Scheme 45.



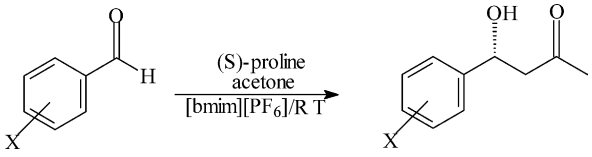
Scheme 46.



Scheme 47.

the applied reaction conditions. Of the various ionic liquids tested, the highest product selectivity was found for [bmim][PF_6]. The selective hydrogenation of the condensation product of Aldol I reaction gave a complex 2-methylpentanal which was further reacted with propanal in a cross-aldol condensation reaction (Aldol II). Similar to the results for the Aldol I reaction, a catalyst evaluation of the Aldol II reactions showed comparable conversion values for the basic ionic liquids and basic aqueous sodium hydroxide system. The selectivity towards the condensation products, however, significantly increased for the sodium hydroxide-containing ionic liquid phases.

The proline-catalysed asymmetric direct aldol reaction of different aromatic aldehydes with acetone and several other ketones in the ionic liquid [bmim][PF_6] achieved good yields of aldolisation products with reasonable enantioselectivities, even when 1–5% of proline was used as a catalyst (Scheme 48).[215]

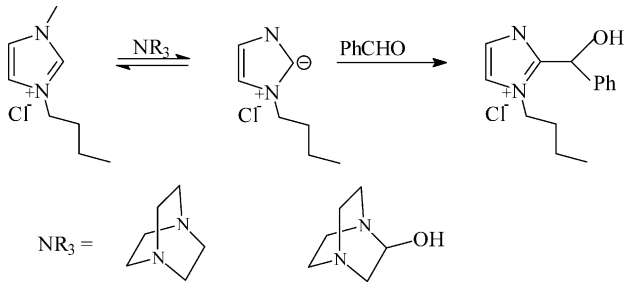


Scheme 48.

Further, immobilisation of the catalyst in an ionic liquid phase offers simple product isolation and re-use of the catalytic system in subsequent reactions.

4.1.5. Baylis–Hillman reaction. Afonso and co-workers have reported the beneficial properties of employing imidazolium salts in Baylis–Hillman reactions.[216] In this study, it was mentioned that the ionic liquids could be re-used 4-fold in the same Baylis–Hillman reaction and an increase in yield was observed with each cycle. In explanation, it was mentioned that, in those reactions where imidazolium salts were employed under basic conditions, they were deprotonated to give reactive nucleophiles. These nucleophiles reacted with the aldehydes under Baylis–Hillman reaction conditions, leading to the low yield of the products (Scheme 49).

In each successive recycle, more and more of the addition product which was formed between the deprotonated imidazolium salt and the aldehydes was accumulated. For this reason, less of the ionic liquid was left for reacting with the aldehydes to give the side reaction product and thus more of the aldehyde was available for the normal Baylis–Hillman reaction. This explained why the yield of the products increased with each recycle. 1,4-diazabicyclo-[2.2.2]octane (DABCO) is another popular catalyst for



Scheme 49.

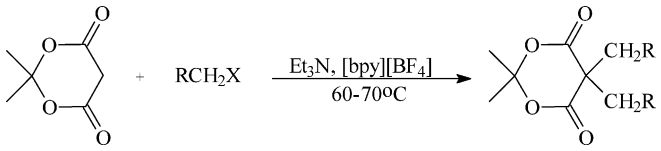
accelerating the sluggish Baylis–Hillman reaction. The reaction of the benzaldehyde with methyl acrylate in the presence of DABCO has been explored in the chloroaluminate ionic liquids.[217]

It was seen that 1-ethyl-3-methylimidazolium chloride EMIC + $AlCl_3$ is a more efficient chloroaluminate ionic liquid than 1-butylpyridinium chloride BPC + $AlCl_3$ as it offered higher yields in a comparatively shorter time. Further, the enhancement in the reaction rate was dependent upon the $AlCl_3$ content of the ionic liquid. Baylis–Hillman reactions are favoured in a basic environment, but, in this example, surprisingly, a rate enhancement of the Baylis–Hillman reaction due to a Lewis acid effect was observed. It is not possible, however, in the present situation to draw any conclusions on the role of ionic liquids and Lewis acids on the progress of the Baylis–Hillman reactions.

Further, ionic liquids [EtDBU][OTf] and 8-methyl-1,8-diazabicyclo[5.4.0]-7-undecenium trifluoromethanesulphonate [MeDBU][OTf] have been used to carry out the Horner–Wadsworth–Simmons reactions to give α-fluoro-α,β-unsaturated esters. Low yields of the products were obtained with ethylmethylimidazolium-based ionic liquids, while much higher yields were obtained with [EtDBU][OTf] and [MeDBU][OTf].[218] The low yields with the ethylmethylimidazolium-based ionic liquids were due to the side reactions.

Thus, the use of 1-butyl-3-methylimidazolium ionic liquids for the Baylis–Hillman reaction and other base-promoted reactions is not recommended. The side reaction dominates if 50 mol% ionic liquids are employed. This work highlights the need for caution when considering the use of ionic liquids under basic conditions.

4.1.6. Alkylation reactions. An efficient alkylation of the ambident nucleophiles, indole and 2-naphthol, has been carried out with simple alkyl halides at room temperature in [bmim][PF_6] using solid KOH to give exclusively *N*-alkylated and *O*-alkylated products, respectively.[219] The



Scheme 50.

alkylation of active methylene compounds is a very important method for the formation of C–C bonds in organic synthesis. A room temperature ionic liquid, *N*-butylpyridinium tetrafluoroborate [bpy][BF_4], has been used as a recyclable alternative to classical molecular solvents for the alkylation of Meldrum's acid.[220] The reaction of isopropylidene malonate with various alkyl halides at 60–70 °C using triethylamine as base gave almost exclusively the dialkylated products (Scheme 50).

4.1.7. Wittig reaction. The ionic solvent [bmim][BF_4] has been used as a medium to carry out Wittig reactions using stabilised ylides allowing easier separation of the alkenes from Ph_3PO and also recycling of the solvent.[221] Further, the *E*-steroselectivity was observed in the ionic liquid solvents, similar to that observed in organic solvents.

4.2. Carbon–oxygen bond-forming reactions

4.2.1. *O*-Acetylation of alcohols and carbohydrates. Dicyanamide-based ionic liquids behave as effective solvents and also as active base catalysts in the *O*-acetylation reactions of alcohols and carbohydrates.[222] They are low-viscosity solvents that dissolve a wider range of inorganic and organic compounds including unprotected saccharides as compared to other imidazolium ionic liquids[223] with bis(trifluoromethanesulphonyl)amide [tfsa], Cl^-, PF_6^- and BF_4^- anions.

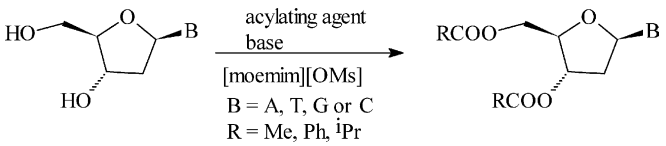
A number of simple alcohols such as 2-naphthol and *t*-butyl alcohol were readily acetylated using a dicyanamide ionic liquid and acetic anhydride, even in the absence of any other catalyst. Polyhydroxylated compounds such as *N*-acetylneuraminic acid, sucrose and raffinose were also completely acetylated within 24 h at room temperature. An increase in the reaction temperature is expected to speed up the reaction rate for the complex saccharides by increasing their solubility in the ionic liquids.

4.2.2. Glycosylation in ionic liquids. Alkyl glycosides and oligosaccharides are important intermediates and products in the synthesis of biologically active natural compounds and mimics. A variety of reagents are reported to promote the formation of a glycoside bond, which include classical glycosyl halides,[224] thioglycosides,[225] pentenylglycosides[226] and anomeric trichloroacetimides.[227] Relatively, few papers dealing with the chemistry of saccharides in ionic liquids such as the *O*-acetylation of carbohydrates[222] and the reaction of glycal with simple alkyl and aryl alcohols in the presence of dysprosium triflate[228] as catalyst have been reported. In a recent report, it was found that glycosyl trichloroacetimidates reacted smoothly in the presence of trimethylsilyl trifluoromethanesulphonate as a catalyst with a variety of alcohols and monosaccharides in [bmim][PF_6] as a solvent to afford the corresponding glycosides or disaccharides.[229] The method presented a mild and practical way of synthesising the glycosides and allowed the re-use of the ionic liquid and easy separation of the products, although the α/β selectivities were almost same as those found under classical conditions.

4.2.3. Acylation of nucleosides. Protected nucleosides serve as building blocks for synthetic oligonucleotides, extensively used as probes for diagnostic purposes in cancer,[230] antisense[231] and viral chemotherapy.[232] Thus, nucleoside chemistry is an active area of research in industry as well as academia, although the insolubility of nucleosides in many organic solvents is a major obstacle to the development of new methodologies. In order to employ ionic liquids as reaction media in nucleoside chemistry, solubility is an important criterion. The solubility of thymidine (T) has been studied in different neutral ionic liquids[233] and was found to be poor in ionic liquids with tetrafluoroborate and hexafluorophosphate anions and high in ionic liquids with methanesulphonate.[234] Sugarphilic ionic liquids have been designed containing ether side chains that can dissolve glycolipids.[235] The solubility of 2′-deoxynucleosides was studied in ionic liquids with methanesulphonate anions and methoxyethyl side chains in the cations. In these ionic liquids, the enhancement of solubility was attributed to the ability of the oxygenated anion to form hydrogen bonds with the 2′-deoxynucleoside. The acylation and peracylation of 2′-deoxynucleosides was studied in an ionic liquid 1-methoxyethyl-3-methylimidazolium methanesulphonate [moemim][OMs] with different acylating agents in the presence of 1-methylimidazole as base and 4-dimethylaminopyridine (DMAP) as catalyst (Scheme 51).[233]

The advantages of this protocol include ease of isolation of the product from the reaction mixture by simply extracting with ethyl acetate and recycling of the ionic liquid.

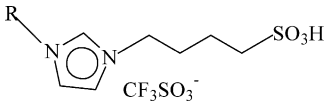
4.2.4. Esterification of aliphatic acids with olefins. It has been observed that aliphatic acids undergo addition reactions with olefins to give the corresponding ester in



Scheme 51.

SO_3H-functionalised ionic liquids, which serve as dual catalysts/solvents (Fig. 17). These SO_3H-functionalised ionic liquids exhibit a greater potential for the replacement of conventional homogenous and heterogenous acidic catalysts because they are flexible, non-volatile, non-corrosive and immiscible with various organic solvents.[236]

The esterification of acetic acid was carried out with different linear and cyclic olefins in the above-mentioned ionic liquids. Under these conditions, an acid catalyst oligomerisation of the olefins was not observed and, as a result, the ester selectivity obtained was very high. Further, all of the produced esters were less soluble in the SO_3H-functionalised ionic liquids and were simply decanted from the ionic liquid after the reaction, the recycling and re-use of the ionic liquid therefore being viable.



R= Me, Et, Bu, Hex

Figure 17. Sulphonic acid functionalised ionic liquids.

4.3. Carbon–nitrogen bond-forming reactions

4.3.1. Synthesis of symmetric urea derivatives with carbon dioxide in ionic liquids. Nitrogen-containing compounds such as isocyanates, carbamates and *N,N*-di-substituted urea derivatives are important chemicals and are mainly manufactured by the phosgenation of amines. In order to eliminate the use of phosgene altogether in the synthesis of isocyanates, many strategies for non-phosgene routes using carbon monoxide and carbon dioxide as the carbonyl source have been extensively studied.[237,238] The use of carbon dioxide directly for the carbonylation reaction gives good yields of the desired products, but requires large amounts of dehydrating agents such as PCl_5 and $POCl_3$, thereby giving large amounts of byproducts. An effective process for the direct synthesis and separation of symmetric urea derivatives in good yields from amines by using CO_2 in ionic liquids has been reported.[239] The recyclable catalytic system consisted of an ionic liquid [bmim][BF_4], [bmim][PF_6] or [bmim][Cl] and base CsOH. This system avoided the need for a stoichiometric quantity of the dehydrating agent and, additionally, the type of cations and anions of the ionic liquid had a strong impact on the formation of the urea derivatives. Further, the ionic liquid was found to be indispensable for the formation of the desired product, as dicyclohexyl urea was not obtained in the absence of the ionic liquid.

4.3.2. Synthesis of aryl amines. Aryl amines are very common structural components in biologically active natural products and medicinally important compounds. Classical methods for the synthesis of aryl amines typically require a large excess of base, and highly polar solvents such as DMF and dimethylsulphoxide (DMSO) at high temperature with highly activated aryl halides under high-pressure conditions.[240] The nucleophilic substitution of activated aryl halides with secondary amines has been carried out smoothly in [bmim][BF_4] and [bmim][PF_6] ionic liquids at room temperature to afford the corresponding aryl amines in excellent yields (Scheme 52).[241]

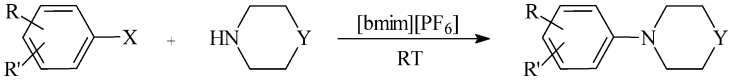
4.3.3. Synthesis of α-aminonitriles. The α-aminonitriles are very useful precursors for the synthesis of α-amino acids[242] and many other nitrogen-containing heterocycles[243] such as imidazoles and thiadiazoles. The Strecker reaction[244] is the most efficient and straightforward synthetic method for the synthesis of α-aminonitriles. A one-pot, three-component coupling of aldehydes, amines and trimethylsilyl cyanide using ionic liquids as novel promoters was carried out for the synthesis of α-amino-nitriles.[245] The use of ionic liquids as promoters for this transformation avoided the use of moisture-sensitive reagents and heavy-metal Lewis acids.

4.3.4. Synthesis of homoallylic amines. The imines derived in situ from aldehydes and amines were found to undergo smooth nucleophilic addition with allyltributylstannane in [bmim][BF_4] to afford the corresponding homoallylic amines in high yields with high selectivity.[246] The method is especially useful for the homoallylic amines from acid-sensitive aldehydes. The reaction was studied in hydrophilic [bmim][BF_4] and hydrophobic [bmim][PF_6] ionic liquids and [bmim][BF_4] was found to be superior in terms of yields and reaction rates. This three-component coupling reaction was not, however, found to be successful in other molten salts such as Bu_4NCl or [bmim][Cl].

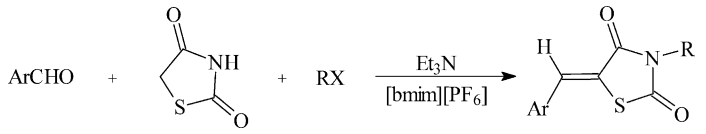
4.4. Carbon–carbon and carbon–nitrogen bond-forming reactions

4.4.1. Synthesis of 3-acetyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones. 3-Acetyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones display various biological and pharmaceutical activities, for example, as anthelmintic, antitubercular, insecticidal, bactericidal and fungicidal agents, and they are also an important class of synthetic intermediates in organic synthesis.[247,248] A one-pot synthesis of 3-acetyl-5-[(*Z*)-arylmethylidene]-1,3-thiazolidine-2,4-diones has been described using ionic liquids as the medium (Scheme 53).[249] The reaction of aryl aldehydes, alkyl halides and thiazolidine-2,4-dione in the presence of triethylamine in ionic liquids gave good yields of product, and an enhanced rate of reaction and selectivity were observed. The reaction was studied in organic solvents such as DMF, MeCN and toluene and the efficiency of the reaction was found to be greatly decreased under these conditions.

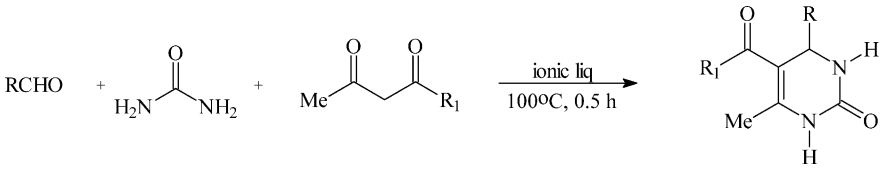
4.4.2. Biginelli reaction. Ionic liquids such as [bmim][BF_4] and [bmim][PF_6] have been used as catalysts for the



Scheme 52.



Scheme 53.



Scheme 54.

Biginelli condensation reaction under solvent-free conditions (Scheme 54).[250] With [bmim]Cl and Bu_4NCl as the catalysts, low and negligible yields of the products were obtained, respectively.

4.5. Carbon–sulphur bond-forming reactions

4.5.1. Conversion of oxiranes into thiiranes in ionic liquids: aqueous mixtures. A variety of epoxides responded rapidly with potassium thiocyanate in a [bmim][PF_6]–H_2O (2:1) solvent system at room temperature under mild and convenient conditions to produce the corresponding thiiranes in high yields (Scheme 55).[251] The use of ionic liquids for this transformation avoided the use of heavy-metal halides as promoters and chlorinated hydrocarbons as solvents. Addition of 1 equiv of water to the ionic liquid dramatically improved the reaction rate as well as the yield, probably due to the higher solubility of potassium thiocyanate in water. Of the two ionic liquids, [bmim][BF_4] and [bmim][PF_6], the latter was found to be the more superior in terms of conversion. The reaction conditions were mild enough not to induce isomerisation of CC multiple bonds during the preparation of thiiranes bearing allylic and propargylic functionalities and selective enough to convert oxiranes into thiiranes in the presence of acid-sensitive groups.

4.5.2. Transthioacetylation of acetals. The *trans* thioacetylation of *O,O*- and *S,S*-acetals is a synthetically useful transformation and is usually carried out with a variety of Lewis acids such as $MgBr_2$, $FeCl_3$, WCl_6, $ZrCl_4$, and SiO_2–$SOCl_2$ in methylene chloride and other organic solvents. TBAB in the molten state has been demonstrated to be a very efficient and recyclable catalyst for the transthioacetylation of the *O,O*-acetals to *S,S*-acetals with a thiol or a dithiol under solvent-free conditions (Scheme 56).[252]

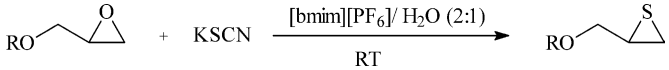
The reaction in molten TBAB is in general, very fast, efficient and clean. The absence of TBAB made the conversion very sluggish and led to considerable polymeric products, particularly in the reaction with propane-1,3-dithiol. No conversion was observed with solid TBAB at room temperature or under reflux in dichloromethane and

Scheme 56.

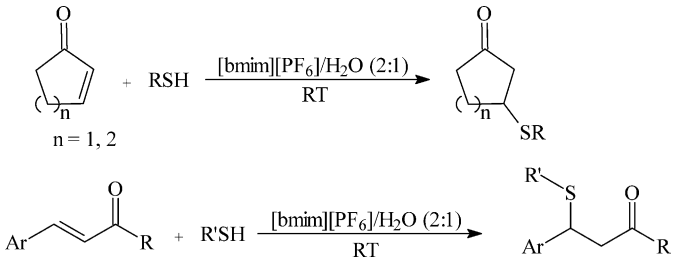
dichloroethane. In more polar solvents such as DMSO at 110 °C, however, transthioacetylation proceeded to a certain extent (40–50%), although the reactions were not always clean and were associated with other undesirable side products. Presumably, the molten TBAB acts as a ready source of bromide ion, which, by co-ordination with thiolate ion, a strong nucleophile, leads to efficient transthioacetylation, while the partial progress of the reaction with solid tetrabutylammonium bromide or sodium bromide in a highly polar solvent such as DMSO is due to the availability of bromide ion to a certain extent in the reaction media.

4.5.3. Conjugate addition of thiols to α,β-unsaturated ketones in [bmim][PF_6]/H_2O. The conjugate addition of nucleophiles to electron-deficient alkenes is one of the most effective methods for C–C bond formation and has many applications in organic synthesis.[253] Among the various nucleophilic additions, the reaction of thiols is of much importance as it leads to the synthesis of compounds with promising biological activities.[254] The α,β-unsaturated ketones underwent a rapid addition with thiols in a [bmim][[PF_6]/H_2O solvent system (2:1) in the absence of any acid catalyst to afford the corresponding Michael adducts in high yield with excellent 1,4-selectivity under mild and neutral conditions (Scheme 57).[255] The enones showed enhanced reactivity in ionic liquids, thereby reducing the reaction time and improving the yields significantly. The use of an ionic liquid helped to avoid the use of either acid or base catalysts for this conversion.

A similar conjugate addition of thiols to electron-deficient alkenes such as α,β-unsaturated nitriles, carboxylic esters, ketones, aldehydes and nitro-olefins catalysed by molten TBAB was carried out under solvent-free conditions.[256] No addition reaction was observed using solid TBAB at room temperature and reaction in the absence of TBAB at 100–150 °C gave a mixture of unidentified products. Thus,



Scheme 55.



Scheme 57.

the presence of molten TBAB was essential for an efficient and clean reaction.

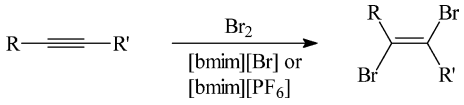
4.6. Carbon–halogen bond-forming reactions

4.6.1. Fluorination by nucleophilic substitution. Nucleophilic fluorination of 2-(3-methanesulphonyloxypropyl)-naphthalene has been studied with a variety of metal fluorides in the presence of [bmim][BF_4][257] and it was found that the higher periodic alkali metal fluorides demonstrated the greater reactivity. Fluorination using alkaline earth, transition and low periodic alkali metal fluorides under the same conditions, however, occurred rarely or not at all. The nucleophilic displacement of various sulphonates and halides by fluoride is a very typical method for the introduction of a single fluorine atom into aliphatic organic compounds.[258] An alkali metal fluoride such as potassium fluoride is the traditional reagent for this type of reaction, but its limited solubility in organic solvents and its low nucleophilicity require generally vigorous conditions. By replacing the organic solvents with an ionic liquid–water system, a significant enhancement in the reactivity of KF was observed, along with the reduced formation of byproducts such as alkenes or alcohols. The fluorination of 2-(3-methanesulphonyloxypropyloxy)naphthalene with KF in an organic solvent such as MeCN at 100 °C hardly occurred, even after 24 h, whereas the same reaction in [bmim][BF_4] was completed in 2 h (Scheme 58). The addition of water (5 equiv) completely eliminated the undesired alkene. When an excess of water was added, the hydroxylation of 2-(3-methanesulphonyloxypropyloxy)-naphthalene to the alcohol took place, although the fluoroalkene was still a major product implying that fluorination using [bmim][BF_4] did not require anhydrous conditions.

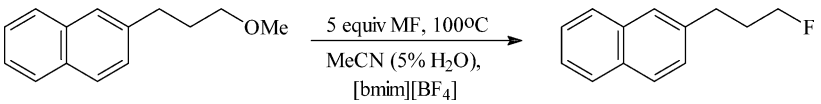
4.6.2. Fluorination by electrophilic substitution. The NF-fluorinating agent F-TEDA-BF_4 dication salt (Selectfluor™) (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) dissolved in the imidazolium-based ionic liquids [emim][OTf], [emim][BF_4], [emim][PF_6] and [bmim][BF_4], assisted by sonication, provided a convenient medium for the fluorination of arenes under essentially acid-free conditions in a simple setup, from which the ionic liquids could be easily recycled and re-used.[259] Comparative studies in [emim][OTf] with anisole as the substrate showed that Selectfluor™ was superior to NFTh–BF_4 (Accufluor®) (1-fluoro-4-hydroxy-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate) and that the of *N*-fluoro-pyridinium salt NFPy-B_2F_7 was least effective. The substrate selectivity ($k_{mesitylene}/k_{durene}=10$) measured in competitive experiments was clearly indicative of a conventional polar mechanism and without the ionic liquid in MeCN as solvent was also indicative of a polar mechanism, but exhibited a lower magnitude ($k_{mesitylene}/k_{durene}=6$).

An interesting recent study employed TfOH as a solvent, which substantially increased the yields. The observed $k_{toluene}/k_{benzene}=13.8$ clearly supported an electrophilic reaction with a reactive nucleophile proposed to be the *O*-protonated CF_3SO_2OF formed in situ.[260] Thus, it was shown that the yields of aromatic fluorination with the NF reagent in ionic liquids were comparable and, in some cases, exceeded those reported in MeCN and TFA, but were lower then those found in TfOH as solvent. This method, however, used only 1 equiv of the NF reagent and avoided the use of strong acids and aqueous work up.

4.6.3. Bromination of alkynes. The kinetic behaviour and the product distribution of the bromination of several arylalkynes with Br_2 in [bmim][PF_6] and [bmim][Br] were investigated at different temperatures (Scheme 59).[261] In [bmim][Br], alkynes stereospecifically gave the *anti* addition product, the reactions following a second order rate law. In [bmim][PF_6], mixtures of the *syn* and *anti* addition products were obtained and the reaction followed a second or third order rate law, depending on the structure of the alkyne and the concentration of Br_2. The data obtained for the reactions in [bmim][Br] were interpreted on the basis of the mechanisms involving a product- and a rate-determining nucleophilic attack by the bromide on the alkyne-Br_2 π-complex.



Scheme 59.



Scheme 58.

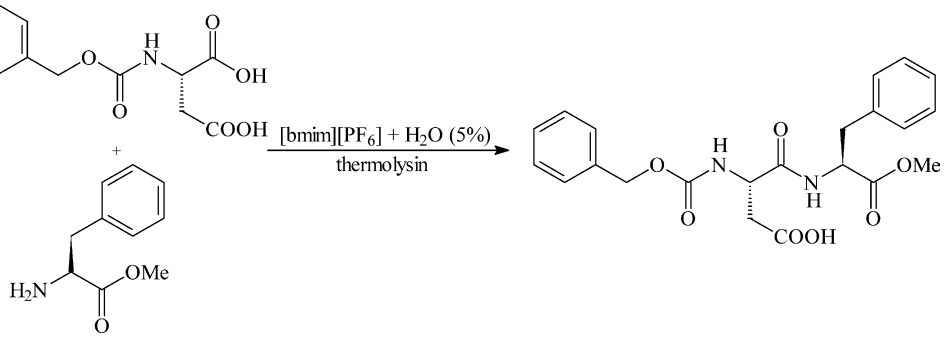
The stereochemical behaviour observed in the reaction of alkynes in [bmim][Br] is in agreement with the presence in solution of Br_3^- as an electrophile. This species is known to add to alkenes and alkynes in molecular solvents by a mechanism that does not involve an ionic intermediate and occurs through a product- and rate-determining attack by bromide on the olefin-Br_2 π-complex. In contrast, the formation of both diastereoisomers during the Br_2 addition to alkynes in [bmim][PF_6] indicates that open vinyl cations are formed as intermediates, similar to the observations in 1,2-dichloromethane.[262] The stereoselective formation of the *anti* addition product suggests the involvement of a bridged bromonium ion.

5. Biotransformations in ionic liquids

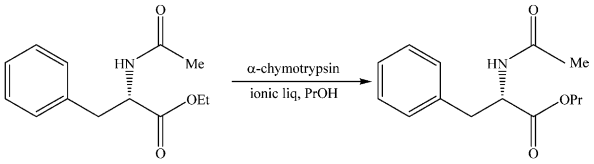
The use of enzymes in organic solvents rather than in aqueous media greatly enhances their technological applications.[263,264] Biocatalysis in organic solvents, however, often suffer from the disadvantages of reduced activity, selectivity or stability of the enzyme, as compared to aqueous media.[265] Polar substrates are insoluble in apolar organic solvents, whilst hydroxylic solvents, such as methanol and diethylene glycol, are unsuitable for lipase-catalysed reactions as they compete with the substrate. Further, the enzyme becomes denaturated in more polar solvents such as pyridine, DMSO and DMF.[266] Various methods such as molecular imprinting, immobilisation of the enzyme in a sol–gel,[267] reactions in microemulsions or supercritical fluids, enzyme modification, crosslinked enzyme crystals, and enzyme-coated microcrystals have been developed to prevent deactivation and enhance enzyme activity.[268] Although these modified methods exhibit better activity, selectivity or stability, the procedures for the preparation of the modified enzymes are rather complicated. Since volatile organic solvents have a detrimental impact on the environment, biocatalytic transformations in air- and moisture-stable ionic liquids have become the subject of intense research.[269–274] Ionic liquids are used in three different methods in the enzyme systems, namely 1) as a co-solvent in aqueous phase, 2) as a pure solvent and 3) as a two-phase system together with other solvents. The use of ionic liquids in biocatalytic transformations has solved some of the problems encountered in their applications in aqueous and organic solvents. Their use in lipase-catalysed reactions has increased the solubility of the substrate by 3-fold, and in the *N*-acetyl-lactosamine synthesis using β-galactosidase, the yield has been doubled by minimising the side reactions.[275] Enhanced enantioselectivity in dynamic, kinetic and distillative work-up is possible for lipases in ionic liquids and, additionally, the physical properties of the ionic liquids can be varied very widely by using different cation and anion combinations.[276,277] This makes it possible to dissolve enzymes directly in certain ionic liquids and to dissolve substrates (e.g., carbohydrates) that would not normally dissolve adequately in organic solvents.[278–280] Different enzymes such as hydrolases (proteases and lipases) and oxidoreductases (peroxidases and dehydrogenases) retain their activity when suspended in ionic liquids, which present a very promising 'green' alternative to organic solvents for enzyme-catalysed reactions. Cull et al. have published first results on the use of an ionic liquid as a reaction medium for whole-cell biotransformations.[281] They reported the use of a [bmim][PF_6] ionic liquid in a two-phase system for the hydration of 1,3-cyanobenzene catalysed by nitrile hydratase from *Rhodococcus* 312 to give 3-cyanobenzamide and 3-cyanobenzoic acid. The reaction showed a lower initial rate than that in an equivalent water–toluene system, but a slightly higher final yield. The enzyme was not active in [bmim][PF_6] and the ionic liquid acted as a reservoir for the substrates, the enzyme remaining in the aqueous phase. The easy separation of the two phases on completion of the reaction due to less cell aggregation was found to be advantageous for the work-up procedure. The enzyme activity was comparable to that observed in conventional organic solvents. The liquid–liquid extraction of erythromycin was also reported in this paper. At almost the same time, Erbeldinger et al.[282] reported the synthesis of *Z*-aspartame, catalysed by thermolysin in [bmim][PF_6] (Scheme 60), the reaction being carried out in [bmim][PF_6] containing water (5% v/v). The rate of the reaction was comparable to that observed in conventional organic solvents such as ethyl acetate and the enzyme maintained a high stability in the ionic liquid.

5.1. Transesterification reactions

The α-chymotrypsin-catalysed (protease enzyme) transesterification of *N*-acetyl-L-phenylalanine ethyl ester with 1-propanol in [bmim][PF_6] and 1-octyl-3-methylimidazolium hexafluorophosphate [omim][PF_6] was reported by Laszalo and Compton (Scheme 61).[283] The influence of the water content on the enzyme activity and on the ratio of transesterification and hydrolysis was investigated and it was found that the presence of a certain amount of water was necessary. The transesterification rates in ionic liquids



Scheme 60.



Scheme 61.

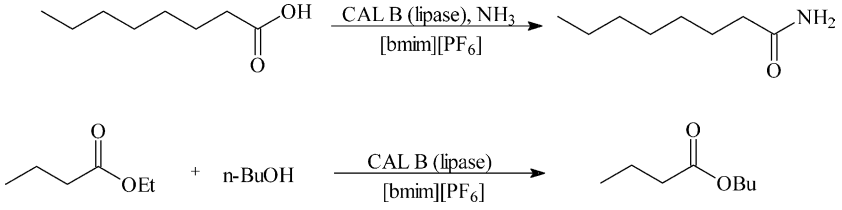
were of the same magnitude as those obtained in iso-octane or acetonitrile. The transesterification activity of α-chymotrypsin in [omim][PF_6] was increased by co-lyophilisation with poly(ethylene glycol) (PEG), but the effect was less than that in non-polar media. The lyophilisation of enzymes from solutions containing salts or amphiphilic compounds increased their activity in organic solvents.[284] The co-lyophilisation of the *Pseudomonas* lipase (PsL) and PEG increased the transesterification activity in [bmim][PF_6] by 5-fold, but no such effect was observed with the other lipases tested.[285] Two other groups, Lazano et al.[286] and Eckstein et al.,[287] have also reported α-chymotrypsin-catalysed transesterification. Lazano and co-workers[286] compared the transesterification and stabilisation of *N*-acetyl-L-tyrosine ethyl ester in five ionic liquids with the use of 1-propanol as the solvent. In all of the ionic liquids tested, the enzyme activity reached only 10–50% of the value in 1-propanol, but the final product concentration was higher in ionic liquids, as compared to 1-propanol, due to the increased stability. Eckstein et al.[287] reported the transesterification of *N*-acetyl-L-phenylalanine ethyl ester with 1-butanol in [bmim][Tf_2N] and [emim][Tf_2N].

The *Candida antarctica* lipase type B (CAL B)-catalysed transesterification in [bmim][BF_4] and [bmim][PF_6] has been reported (Scheme 62).[288] The transesterification of ethyl butanoate with butan-1-ol in both ionic liquids gave good yields of butyl butanoate with supported CAL B, while the reaction using free CAL B was much slower. The reaction rates were comparable with, or slightly better than, those observed in *t*-butanol or 1-butanol.

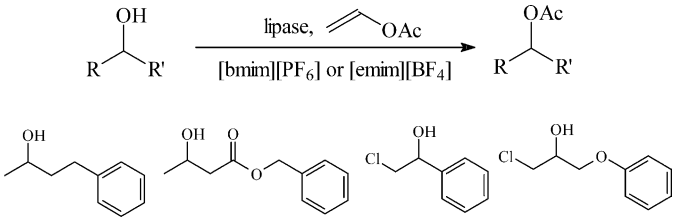
Laszalo and his co-workers[289] have used different ionic liquids, based on dialkylimidazolium cations associated with perfluorinated and bis(trifluoromethyl)sulphonyl amide anions, as reaction media for butyl butyrate synthesis catalysed by free CAL B lipase b at 2% (v/v) water content. CAL B showed an enhanced activity in all of the ionic liquids, as compared to organic solvents such as hexane and 1-butanol. This enhanced activity has been attributed to the increased polarity of the ionic liquids. The CAL B lipase has been shown to be over-stabilised in the continuous operation.

Transesterification catalysed by immobilised CALB, and *Pseudomonas cepacia* lipase (PCL, native) was studied in [emim][BF_4] and [bmim][PF_6] (Scheme 63).[290] The enantioselectivities of the lipases in ionic liquids were higher or comparable to those in organic solvents. The lipase enantioselectivity in ionic liquids reached a synthetically desirable level ($E=>400$) and the ionic liquids were re-used twice together with the enzyme without any loss in enantioselectivity and reactivity after the first run. The enantioselectivities of the lipases were, in general, higher in a hydrophobic [bmim][PF_6] than in a hydrophilic [bmim][BF_4] ionic liquid. The same author has reported transesterification with an ionic liquid-coated-enzyme (ILCE) in toluene.[291] The PCL was coated by mixing the enzyme with a novel ionic liquid [ppmim][PF_6] {[ppmim]=1-(3′-phenylpropyl)-methylimidazolium} above its liquid phase and then cooling. The ILCE-catalysed transesterification showed a better enantioselectivity and selectivity than those of native PCL. The ILCE-catalysed reactions were repeated 5-fold with recycling of the enzyme. In the first run, fresh ILCE showed less activity (65%) as expected from the native enzyme. The catalytic activity of the ILCE increased, however, during subsequent runs and was then slightly reduced in the following runs. After the fifth run, it retained 98% of the activity of its native counterpart.

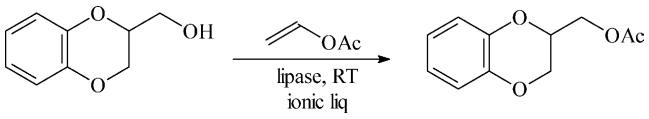
The transesterification of 2-hydroxymethyl-1,4-benzodioxane using vinyl acetate (Scheme 64) as an irreversible acyl donor catalysed by several lipases in [bmim][PF_6] and [bmim][BF_4] ionic liquids was reported by Salunkhe et al.[292] The PCL (free) showed a high initial rate in [bmim][PF_6] as compared to [bmim][BF_4] and



Scheme 62.



Scheme 63.



Scheme 64.

dichloromethane and the difference in activity in the two ionic liquids was attributed to their hydrophobicity. The rate of transesterification was reduced drastically in anhydrous [bmim][BF_4] and this was due to the stripping of essential water of the lipase. It is known that relatively hydrophobic solvents are capable of removing the essential water from the enzyme surface, leading to insufficient hydration of the enzyme, which may, in some cases, exert a strong influence on the enzyme and decrease its activity.[293] The solvent effects were less pronounced for the supported enzyme (immobilised on diatomite particles) and the initial rates were highest in [bmim][PF_6]. The ionic liquids with the enzyme were recycled for five consecutive runs without any substantial diminution in the lipase activity.

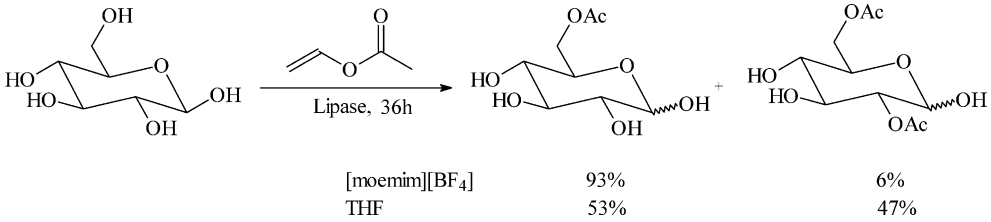
Ionic liquids are particularly attractive alternative media for the enzymatic reactions of carbohydrates, because their solubility is enhanced in ionic liquids. Swatloski et al.[279] reported up to 10% (w/w) dissolution of cellulose in [bmim][Cl] at 100 °C. The CAL B-catalysed esterification of glucose in [emim][BF_4] was selective and no formation of the diester was observed, as in conventional organic solvents (Scheme 65).[278] The reaction was much faster in [moemim][BF_4] in which, at 55 °C, glucose was 100-fold more soluble than in acetone. Maltose was also acylated with vinyl acetate catalysed by CAL B in [moemim][BF_4].

Recently, Kim et al.,[294] reported the acylation of 6-*O*-protected glycosides with *Candida rugosa* lipase (CRL) in [bmim][BF_4] and [moemim][BF_4] (Scheme 66). The reaction was fast and gave a higher yield than that in organic solvents. The regioselectivities were significantly more in ionic liquids, and, using methyl 6-*O*-trityl-α-D-glucopyranoside and methyl 6-*O*-trityl-α-D-galactopyranoside, only the 2-*O*-acylated products were obtained exclusively.

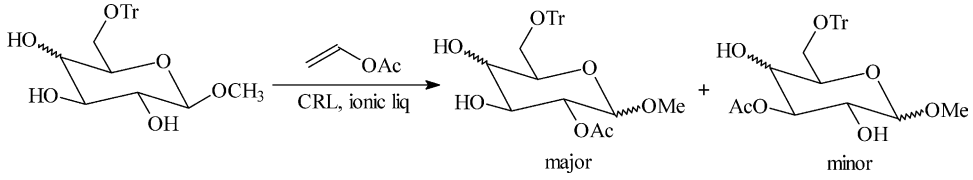
Polycondensation of dicarboxylic acid esters with 1,4-butanediol using free CAL in [bmim][BF_4] and [bmim][PF_6] generated oligomers (Mn = 350 Da) at ambient conditions and oligomers of increased molecular weight (M_n = 1500 Da) were formed at reduced pressure and increased polymerisation times.[295] The polyester synthesis has also been reported by the reaction of diethyl octane-1,8-dicarboxylate and 1,4-butanediol catalysed by PCL supported on celite, PCL-C in [bmim][PF_6] as the reaction medium (Scheme 67).[296] The polyester obtained after one day at room temperature possessed an average molecular weight of 2230 as determined by GPC analysis and practically no substantial change in the molecular weight was subsequently observed at room temperature with time. After seven days, however, there was a marginal decrease in the average molecular weight and this may be explained by a lipase-catalysed disproportionation of the polyester. The polymerisation was also studied at higher temperatures (≈60 °C). In addition, the polymer obtained by PCL-C-catalysed polymerisation in an ionic liquid [bmim][PF_6] exhibited a remarkable polydispersity and this was attributed to the insolubility of the polymer formed in the ionic liquid after it exceeded a certain molecular weight.

5.2. Stability and activity of enzymes

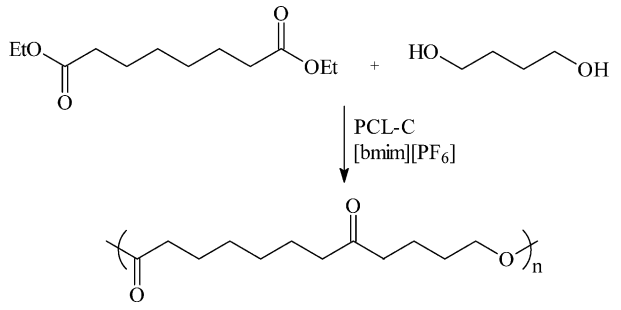
The activity and stability of lipase for the transesterification of methyl methacrylate and 2-ethylhexanol and the polytransesterification of divinyl adipate and 1,4-butanediol have been studied as a function of the physical properties of the ionic liquid (Scheme 68).[297] The dialkylimidazolium- and pyrrolidinium-based ionic liquids with a variety of anions such as hexafluorophosphate, nitrate, acetate, trifluoroacetate, methanesulphonate and trifluoromethylsulphonate were screened and it was found that the enzyme activity in the lipase-catalysed transesterification reaction in ionic liquids was anion dependent, with and [bmim][PF_6] being an effective solvent for this reaction. The anions such as nitrate, acetate and trifluoroacetate were more nucleophilic than hexafluorophosphate and coordinated more strongly to the positively charged sites in the lipase structure, causing conformational changes in the enzyme structure.[271] The reaction between divinyl adipate and



Scheme 65.



Scheme 66.



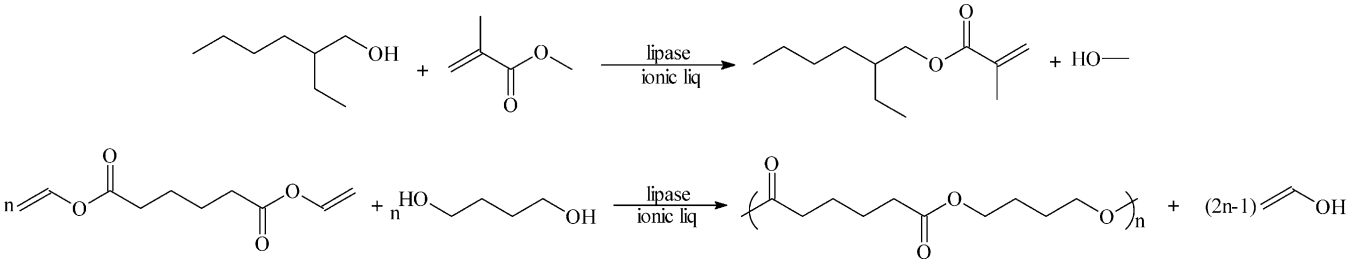
Scheme 67.

1,4-butanediol provided oligomers of high molecular weight (M_w=2900 Da, polydispersity index PDI=1.20). After a reaction time of 24 h, precipitation of the polymer from the ionic liquid was observed and low molecular weight oligomers remained in the reaction medium, therefore resulting in fractionation of the polymer.

Novozyme 435 and *Porcine pancreatic* lipase have been reported to retain a higher catalytic activity upon incubation in [bmim][PF_6] (67 and 94%), as compared to that in THF (21 and 61%). Further, the high levels of activity retention upon incubation in [bmim][PF_6] (20 and 48%) for 120 h at 70 °C indicated that both enzymes have increased thermal stability in the ionic liquid in comparison to octane (3 and 35%).[297] The stability of free CAL, Novozyme 435, crosslinked lipase crystals and crosslinked lipase aggregates in several ionic liquids was studied by Seddon et al.,[271] who reported that the free lipase activity increased (120%) after 100 h of incubation in [bmim][PF_6] at 80 °C. The increase in activity was 350% in comparison to the untreated free lipase for Novozyme 435 after incubation for 40 h at 80 °C.

The activity and thermal stability of CAL B and α-chymotrypsin have been studied in six different ionic liquids at low water (2% v/v) content at 50 °C.[298] The syntheses of butyl butyrate and *N*-acetyl-L-tyrosine propyl ester were taken as model reactions for CAL B and α-chymotrypsin, respectively. The synthetic activity and thermal stability of both enzymes were higher in ionic liquids as compared to those in organic solvents of similar polarity. The increase in chain length of both of the alkyl substituents of the cation and anion caused a decrease in the synthetic activity of both CAL B and α-chymotrypsin. The stability of these two enzymes was analysed by incubating them in the assayed ionic liquids and organic solvents, respectively, at 50 °C and 2% (v/v) water content (Fig. 18). The half-life time of CAL decreased slightly with decrease in polarity and the best result (Fig. 18A) was obtained in the most polar ionic liquid [emim][BF_4]. In the case of α-chymotrypsin, a decrease in the polarity of the ionic liquids caused an increase in its half-life (Fig. 18B).

PEG-lipase complexes have been shown to increase lipase activity in ionic liquids. The activity of the PEG-lipase complex for the reaction of vinyl acetate and 2-phenyl-1-propanol in imidazolium ionic liquids was higher than that in common organic solvents. The Michaelis constant (K_m) calculation for a kinetic study of the lipase-catalysed reactions of 2-phenyl-1-propanol with vinyl acetate in ionic liquids was half of that in *n*-hexane and suggested that the ionic liquids stabilised the enzyme substrate complex.[299] The CAL B-catalysed ester synthesis in an ionic liquid/supercritical carbon dioxide biphasic system was assayed in five different ionic liquids with functional side chains.[300] The suitability of ionic liquids based on quaternary ammonium cations with functional side chains, (3-hydroxypropyl)-trimethyl-, (3-cyclopropyl)-trimethyl-,



Scheme 68.

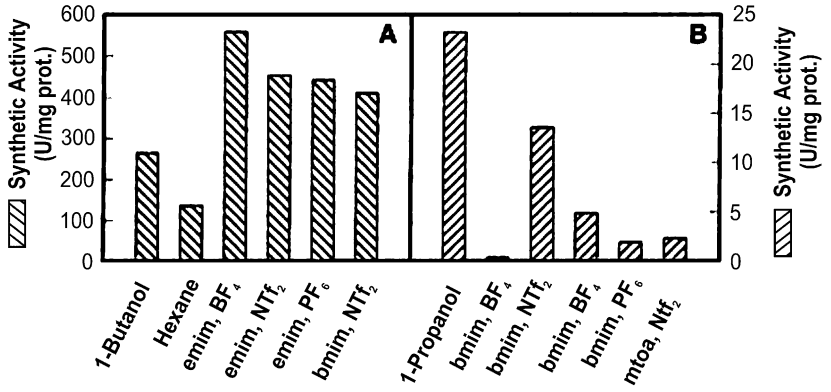


Figure 18. Synthetic activity of CAL B and α-chymotrypsin in different solvents.

butyl-trimethyl-, (5-cyclopentyl)-trimethyl- and hexyl-trimethyl-, associated with the same anion (bis(trifluoromethane)sulphonylamide) was tested for the kinetic resolution of *rac*-1-phenylethanol. The (5-cyclopentyl)-trimethylammonium cation-based ionic liquid was found to be best solvent for this reaction. The enzyme stability in all of the ionic liquids was studied at 50 °C over a period of 50 days and they acted as stabilizing agents with respect to hexane, producing an increase in free energy of deactivation and an improvement of half-life time of the enzyme. A systematic study on the irreversible solvent- and ionic strength-induced inactivation and unfolding of cellulase from *Trichoderma reese* was carried out in [bmim][Cl] and other solvent systems.[301] The ionic liquids, as well as dimethylacetamide-LiCl (a well-known solvent system for cellulose), inactivated cellulase under these conditions. Despite the cellulase inactivity, the results obtained from this study led to valuable insights into the requirements necessary for enzyme activity in ionic liquid systems. The protein stability of a PEG-supported cellulase in [bmim][Cl] solution was investigated and an increased stability/activity of the PEG-supported cellulase in both the [bmim][Cl] and citrate buffer solutions was detected.

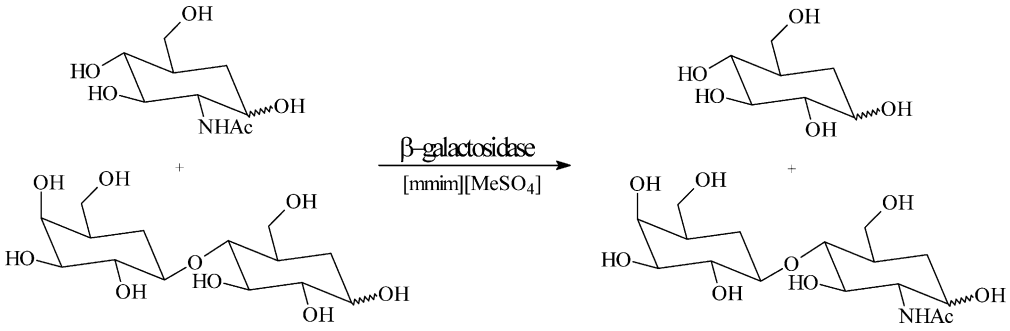
Room temperature ionic liquid-based supported liquid membranes have been used in the lipase-facilitated transport of 4-phenoxybutyric acid, 3-phenoxypropionic acid, 2-phenoxybutyric acid, 2-phenylpropionic acid and 2-amino-2-phenylbutyric acid.[302] Kaftizk et al., reported that β-galactosidase isolated from *Bacillus cirulans* catalysed the synthesis of *N*-acetyl-lactosamine from lactose and *N*-acetylglucosamine in aqueous [mmim][$MeSO_4$] (Scheme 69).[270,275] The reactivity in pure [mmim][$MeSO_4$] was low, but completely recovered on dilution with water. The yield of the product (60%) doubled the yield obtained in aqueous solution. In aqueous solution, the enzyme also catalysed the secondary hydrolysis of the product. The kinetic study showed that the enzyme activity was not influenced by the presence of the ionic liquid, but the stability of the enzyme under the reaction conditions increased and this resulted in an increased yield of the product. The enzyme was re-used after filtration with an ultrafiltration membrane. The β-galactosidase from *Escherichia coli* had only 6% activity remaining in 50% aqueous [bmim][BF_4], which was comparable to the activity of the enzyme in 50% aqueous ethanol and acetonitrile (7 and 3%, respectively).[303] Formate dehydrogenase tolerated aqueous ionic liquids much better than β-galactosidase,[275] the former enzyme retaining 98, 55 and 38% activity in [mmim][$MeSO_4$] (75% in buffer), [Et_3MeN][$MeSO_4$] (50% in buffer) and [bmim][TfO] (25% in buffer), respectively.

Several reports have appeared describing the increased activity and stability of enzymes in different ionic liquids, as compared to organic solvents, but there is no common reason or explanation for these observed effects and this aspect is still unclear.

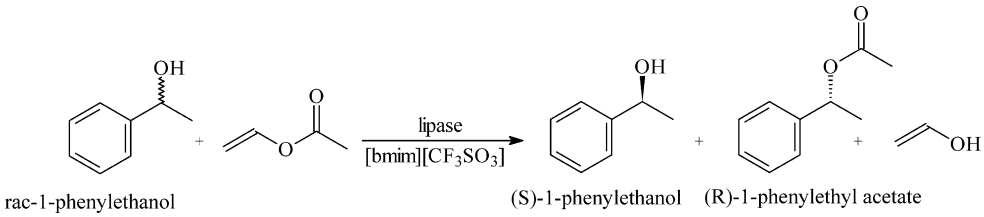
5.3. Enzymatic resolution

Itoh et al have studied the CAL-catalysed kinetic resolution of 5-phenyl-1-penten-3-ol by transesterification in [bmim][PF_6], [bmim][BF_4], [bmim][OTf], [bmim][SbF_6] and [bmim][TFA] in the absence of added water,[304] and found that a high reaction rate and high enantioselectivity was reached in [bmim][PF_6] and [bmim][BF_4]. The CAL could be recycled, but the reaction rate dropped considerably and this was caused by the inhibitory action of an acetaldehyde oligomer, which was accumulated in the solvent system.[304,305] This problem was solved while performing the acylation with methyl esters catalysed by CAL under reduced pressure at 40 °C.[306] The acylated compounds were obtained in an optically pure form and the lipase was recycled for three consecutive runs without loss in the reactivity, enantioselectivity and reaction rate, but this system could not be applied for volatile substrates. Recently, the same group has reported that [bdmim][BF_4] was the best solvent for recycling the enzyme in a lipase-catalysed transesterification using vinyl acetate as the acyl donor.[307] The accumulation of the acetaldehyde oligomer was not observed and a volatile substrate could also be used under these conditions. The enzyme was used repeatedly 10-fold, retaining perfect enantioselectivity and high reactivity. No reaction took place when [bdmim][PF_6] was used as the solvent in the lipase-catalysed reaction.

Different groups have studied the kinetic resolution of *rac*-1-phenylethanol by transesterification with vinyl acetate using lipases in ionic liquids as the reaction media.[270,278,308] Kragl et al.,[308] screened a set of nine lipases and two esterases for activity in ten different ionic liquids and compared the results with the reaction performed in MTBE as the solvent. MTBE is widely used as solvent for transesterification in industry and academia. The best results were obtained with CAL B and PsL in several ionic liquids. The enantioselectivity with PsL and the lipase from *Alcaligenes* sp. was very high in 1-butyl-3-methylimidazolium bis(trifluoromethyl)sulphonamide



Scheme 69.



Scheme 70.

[bmim]-[$(CF_3SO_2)_2N$] compared to the reaction in MTBE (Scheme 70). The CAL was re-used 3-fold with $<10\%$ loss of activity *per* cycle.

Eckstein et al.,[309] also reported an enhanced enantioselectivity of PsL at high temperature and fixed water activity in the ionic liquid, [bmim][$(CF_3SO_2)_2N$]. The water uptake by the ionic liquid was comparable to that in polar organic solvents. Furthermore, the kinetic resolution of (*R,S*)-1-phenylethanol catalysed by PsL had a higher selectivity in the ionic liquid at low water activity ($a_w<0.53$) than in MTBE. At 60–90 °C, an *E* value of about 150 occurred in the ionic liquid, while the enantioselectivity dropped to 4 in MTBE at the same temperature.

The combination of kinetic resolution in ionic liquids and selective extraction with supercritical carbon dioxide ($scCO_2$) has provided a new approach for the separation of enantiomers, as exemplified by the lipase-catalysed esterification of secondary alcohols.[310,311] $scCO_2$ has been described as an excellent solvent for the transport of hydrophobic compounds, because their solvent properties can be adjusted by changing either the pressure or the temperature when tuning the reaction conditions.[312] The activity of the enzyme for the transesterification of vinyl acetate with 1-octanol in [bmim][TBA] was constant for up to three runs and acetyl octanoate was isolated in 97, 98 and 98% yields, respectively.[311] The activity and enantioselectivity for the kinetic resolution of 1-phenylethanol also remained uniformly high in four consecutive runs.[311] The lipase showed increased reactivity and high selectivity at high temperature and this has been attributed to the low water content ($<4\%$ v/v).[310] The increase in synthetic activity with increasing temperature could also be related to a reduction in the $scCO_2$ density. The specific activity of the CAL B-[bmim][Tf_2N] system with $scCO_2$, however, was 10-fold lower than that observed without $scCO_2$. Enzymes exhibit an important deactivation phenomenon in $scCO_2$ due to chemical modification of proteins, local pH changes caused by CO_2 and/or conformational changes produced during the pressurisation/depressurisation step.[313,314] It has nevertheless been demonstrated that ionic liquids seem to be excellent reaction media for enzyme-catalysed reactions, as they exhibit an exceptional ability to stabilise the free enzymes, the ionic liquid providing a protective effect against the thermal and solvent denaturation of the enzyme. Lozano et al. have reported the kinetic resolution of *rac*-1-phenylethanol using CALB (free and immobilised) in [bmim][Tf_2N] and [emim][Tf_2N] with continuous processes under extreme denaturative conditions (120–150 °C and 10 MPa).[315] The bioreactor was a biphasic system, which combined the enzymatic reactions in the ionic liquid phase with the product extraction by the $scCO_2$ phase. The influence of two different ionic liquids (1-ethyl-3-methylimidazolium bis-triflimide, [emim][Tf_2N] and 1-butyl-3-methylimidazolium bis-triflimide [bmim][Tf_2N]) on the activity and stability of CALB (free and immobilised) was studied. The high catalytic activity of the enzymes under the extremely denaturative conditions can be explained by a double role of the ionic liquids immiscible with water. Firstly, the ionic liquid acts as a solvent and, provides an adequate microenvironment for the catalytic action of the enzyme (mass transfer phenomenon and active catalytic conformation) and, secondly, the ionic liquid can also be regarded as a liquid immobilisation support, because multiple enzyme ionic liquid interactions such as hydrogen bonding, ionic interactions and van der Waals interactions may occur, which result in a flexible supramolecular net able to maintain the active protein conformation in these highly denaturative conditions. An enhanced stereoselectivity was achieved in [bmim][PF_6] for the lipase-catalysed kinetic resolution of racemic *P*-chiral hydroxymethanephosphinates and a hydroxymethylphosphine oxide.[316] In [bmim][BF_4], no enantioselectivity was observed, although the reaction proceeded with rates comparable to those in [bmim][PF_6]. The lack of stereoselectivity in [bmim][BF_4] was attributed to the miscibility of [bmim][BF_4] with water. Excellent enantioselectivity was achieved upon conversion of alcohols into the corresponding acetates and laurates using various modifications of CAL B in imidazolium-based ionic liquids. The anion of the ionic liquid had a significant influence on the performance of the biocatalyst with bis(trifluoromethanesulfonamide) giving the best results.

The PEG-lipase complex has been used for the enantioselective transesterification of 1-phenylethanol and a high enantioselectivity was obtained in ionic liquids as compared to *n*-hexane.[299] The lipase-catalysed stereoselective hydrolysis of the racemic naproxen methyl ester has been reported in an aqueous organic biphasic system and an aqueous ionic liquid biphasic system.[317] The stereoselective hydrolysis of naproxen methyl ester in an aqueous ionic liquid system was comparable to that in the aqueous organic system, but the enantioselectivity of the lipase was higher than that in the aqueous organic system. The best activity and enantioselectivity were observed when the ratio of the aqueous phase to the ionic liquid phase was 1:1.

The α-amino acids are important building blocks for many pharmaceutically and biologically important compounds. Enzymatic resolution of amino acid derivatives is an efficient method to synthesise enantiomerically enriched amino acids.[318] The synthesis of homophenylalanine and piperazine-2-carboxylic acid esters and their enzymatic resolution has been reported in organic solvents.[319,320] Ionic liquids have also been used for the enzymatic resolution of

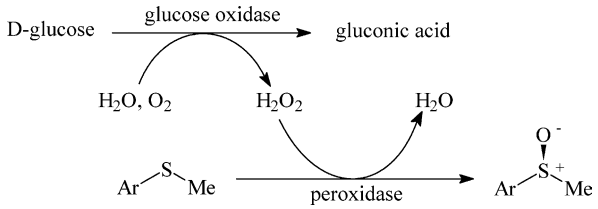
homophenylalanine esters with alkenes to replace the organic solvents.[321] Two ionic liquids [emim][BF_4] and [EtPy][BF_4] have been studied and a high enantiomeric excess and comparable yields of the L-isomer were obtained using these solvents (15 vol%). A change in the ionic liquid concentration beyond 20% resulted in a decrease in the ees of both isomers and this may be due to the fact that a high concentration of the ionic liquid causes a high ionic strength of the reaction media, which denaturates the enzyme and decreases the enantioselectivity. An increased concentration of the ionic liquid increased the non-enzymatic hydrolysis of the ester. *N*-ethylpyridinium trifluoroacetate has been used in place of traditional organic solvents for the enzymatic resolution of *N*-acetyl amino acid esters using a commercial protease. Products with a high enantiomeric excess were obtained in ionic liquids.[322] The specific activity, the stability of the enzyme and the enantioselectivity were high.

5.4. Oxidases

Oxidative enzymes have been reported to show catalytic activity in systems with ionic liquids.[323] The oxidative enzymes, horseradish and soyabean peroxidase, catalysed oxidation reactions in systems with ionic liquids where the water content of the latter varied from several vol% to an almost totally non-aqueous ionic liquid. The catalytic activity of the enzyme decreased by adding a water-miscible ionic liquid, 4-methyl-*N*-butylpyridinium tetrafluoroborate, or by suspending the enzyme in a water-immiscible ionic liquid [bmim][PF_6].

The sulphoxidation of thioanisole and methyl 2-naphthyl sulphide with glucose oxidase and peroxidase has been reported in an ionic liquid [bmim][PF_6] (Scheme 71).[324] Methyl 2-naphthyl sulphide was reported to be oxidised significantly slower than thioanisole in water, whereas, in the ionic liquid, the rate of oxidation of both sulphides was comparable and no further oxidation to the sulphone was observed. The glucose oxidase and peroxidase in ionic liquids were recycled and re-used. Further isolation of the sulphoxides was easier than from water, as the formation of an emulsion was not observed with organic solvents in ionic liquids, which is evident in water. The enantiomeric excess of the obtained sulphoxides was comparable to those in water and remained constant during the reaction.

It has been reported that the Fe(III)/Fe(II) redox couple of proptoporphyrin IX, hemin and hemin-modified electrodes is stable in [bmim][PF_6] without the need for an additional electrolyte.[325] The catalytic activity of cytochrome-c (cyt-c), microperoxidase-11 (MP-11) was hemin was studied in [bmim][PF_6], [omim][PF_6] and [bmim][Tf_2N].[326] The activity of hemin and MP-11 were significantly higher in the ionic liquids than in methanol or DMSO, while that of cyt-c was comparable between both types of solvents. It was proposed that the non-coordinating nature of the ionic liquids accelerated the reaction rate by stabilising the highly charged iron-peroxo or -oxo intermediate generated in the rate-determining step of the reaction. The hydrophobic and non-coordinating ionic liquids were shown to be less disruptive to the structure of cyt-c than molecular solvents of a similar polarity. Hemin required the presence of a



Scheme 71.

coordinating base, pyridine or *N*-methylimidazole, to produce an active complex. Cyt-c did not require exogenous ligands for activity in an ionic liquid, but their addition increased the peroxidase activity. Recently, it was reported that cyt-c immobilised on a gold electrode was not electrochemically active after prolonged exposure to ionic liquids.[327] The loss of the cyt-c redox activity was proposed to be due to the denaturing of the proteins caused by contact with the ionic liquids, resulting in a detrimental re-orientation of the heme groups away from the electrode surface. Polar organic solvents generally result in a loss of enzyme function and this is typically attributed to the propensity of the solvents to strip essential water from the enzyme, generating a protein conformation that is less active or inactive.[293,328]

5.5. Miscellaneous enzyme reactions

Baker's yeast is an important biocatalyst in synthetic organic chemistry. An ionic liquid [bmim][PF_6]–H_2O (10:1) system has been used as an alternative solvent for the Baker's yeast-mediated reduction of ketones.[329] The yields of the products were good and the reduction of aromatic ketones such as 4-bromoacetophenone was not observed. The enantiomeric excess obtained in an ionic liquid was comparable to those obtained in other media.

Ionic liquids have been investigated as novel and safe ion-conductive matrices.[330,331] Cyt-c modified with polyethylene oxide (PEO) chains was dissolved in 1-ethyl-3-methylimidazolium bis(trifluoromethanesulphonyl)imide and the electron transfer properties of this dissolved PEO-cyt-c were studied.[332] For cyt-c, at least ten PEO chains with an average molecular weight of over 2000 were required to solubilise it into ionic liquids whilst keeping the redox reactivity. It was also observed that the bulky organic ions were essential for ionic liquid formation, but they were definitely not suitable as electrolytes for proteins having an active centre in the folded polypeptide chains.

Aldol reactions of hydroxyacetone with 4- or 3-(trifluoromethyl)benzaldehyde in the aldolase antibody 38C2-ionic liquid ([bmim][PF_6]) has been reported.[333] Acetone, methyl ethyl ketone, methoxyacetone, fluoroacetone and chloroacetone did not react in this system. Moreover, in the cases of the aliphatic and/or α,β-unsaturated aldehydes, the aldol reaction did not proceed. The aldolase antibody 38C2-ionic liquid system was re-used in Michael additions and for the reaction of fluoromethylated imines. Successive re-use of the recovered antibody 38C2-ionic liquid system in the same reaction gave a higher yield than the first cycle for both 3- and 4-(trifluoromethyl)benzaldehyde and, in the third and fourth cycles, re-use of the system recovered from

the second cycle produced the same yield as in the first cycle. Ammonolysis of ethyl octanoate catalysed by CAL B showed a lower activity in [bmim][BF_4] than in *t*-butanol. Epoxidation of cyclohexene catalysed by CAL B in [bmim][PF_6] gave a slightly lower yield than those obtained in acetonitrile.[288]

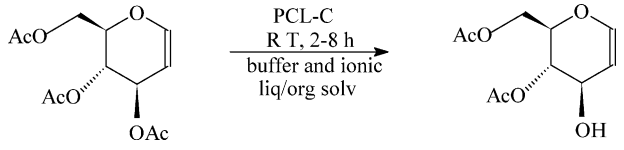
PCL supported on celite, PCL-C has been used to study the regioselective hydrolysis and alcoholysis of 3,4,6-tri-*O*-acetyl-D-glucal in an organic solvent, THF, and in two different ionic liquids, [bmim][PF_6] and [bmim][BF_4] (Scheme 72).[334] The influence of different reaction media on the rates and regioselectivity of enzyme catalysis has been demonstrated. A marked regioselectivity towards the formation of 4,6-di-*O*-acetyl-D-glucal was observed in [bmim][PF_6], with 84% product formation after 6 h with 98% selectivity in hydrolysis and 48% after 8 h with 98% selectivity in alcoholysis. On the contrary, the hydrophilic ionic liquid did not prove to be a good medium for any of the biotransformations investigated. These observations have been rationalised by the polarity, hydrophobicity and hydrophilicity of the solvent.

Soluble epoxide hydrolase (sEH) has been shown to catalyse the hydrolysis of epoxides using the ionic liquids [bmim][PF_6], [bmim][$N(Tf)_2$], and [bmim][BF_4] as a reaction medium (Scheme 73).[335] The reaction rates were comparable with those observed in buffer solution and, when the cress enzyme was used, the hydrolysis of *trans*-β-methylstyrene oxide gave, through a stereoconvergent process, the corresponding optically active (1*S*,2*R*)-*erythro*-1-phenylpropane-1,2-diol.

6. Other applications of ionic liquids

6.1. Use of ionic liquids in MALDI mass spectroscopy

Matrix-assisted laser desorption/ionisation (MALDI) mass spectroscopy is one of the soft ionisation methods for analysing polar, non-volatile and thermally labile biomolecules and synthetic polymers with high molecular weights.[336,337]



Scheme 72.

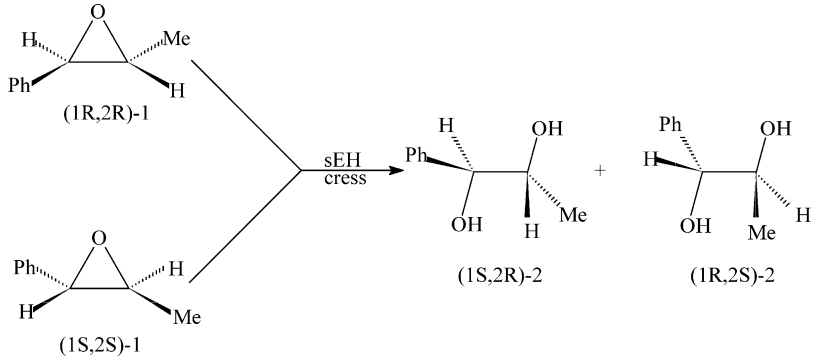
Room temperature ionic liquids with a high solubilising power, negligible vapour pressure, a broad liquid range and the ability to absorb laser light have been designed for use as MALDI matrices. They have found wide applications in peptide and protein quantification, as well as in the analysis of phospholipids. The resolving power, reproducibility, and ability to quantify was found to be improved by using ionic liquid matrices in MALDI. Two effective and five ineffective room temperature ionic liquids were evaluated as MALDI matrices using the solvation model.[338]

Figure 19 represents a plot illustrating the magnitude of each interaction parameter at 70 °C. Ideally, the interaction parameters can predict whether a particular room temperature ionic liquid would be an effective MALDI matrix by demonstrating substantial hydrogen bond acidity and a significant r-term, signifying an aromatic moiety.[338] It was shown that the room temperature ionic liquids, tributylammonium α-cyano-4-hydroxycinnamate (NHB_3-CHCA) and tributylammonium sinapinate acid (NHB_3-SA), had appreciable hydrogen bond ability and a significant ability to interact with n- and π-electrons. These characteristics were absolutely necessary for the MALDI matrix to be effective. Other room temperature ionic liquids with zero or negative r-terms failed to provide adequate signals, probably due to lack of ionisation of the solute.[339]

6.2. Dissolution of cellulose with ionic liquids

Cellulose consists of polydispersed linear polymer chains which form hydrogen-bonded supramolecular structures and is insoluble in water and most common organic liquids. Graenacher[340] first suggested in 1934 that molten *N*-ethylpyridinium chloride, in the presence of nitrogen-containing bases, could be used to dissolve cellulose. This was, however, of little practical importance, since the molten salt system was somewhat isoteric and had a high melting point (118 °C).

It has recently been found that ionic liquids can be used as non-derivatising solvents for cellulose. Ionic liquids incorporating anions which are strong, hydrogen-bond acceptors were the most effective, especially when combined with microwave heating, whereas ionic liquids



Scheme 73.

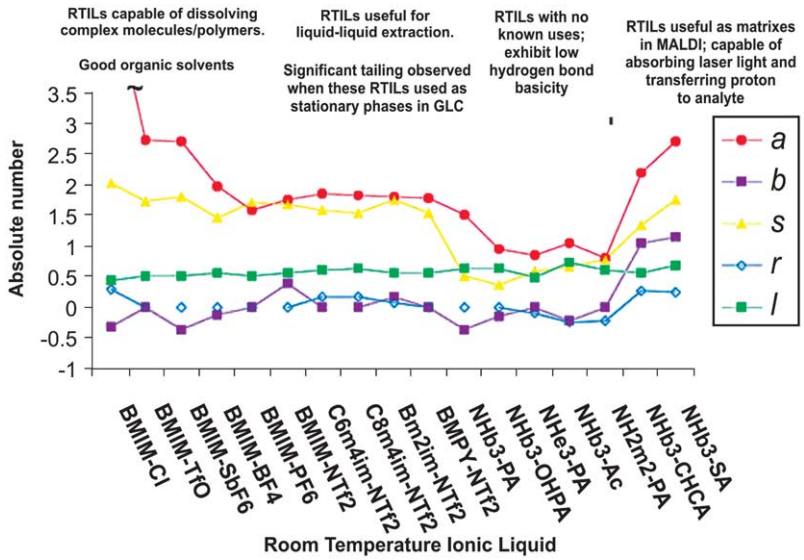


Figure 19. Plot representing interaction parameters of different ionic liquids. (*a*) hydrogen bond basicity, (*b*) hydrogen bond acidity, (*r*) interaction via nonbonding and ∂-electrons, (*s*) dipolarity/polarisability and (*l*) dispersion forces.

containing non-coordinating anions including BF_4^- and PF_6^- were non-solvents. Chloride-containing ionic liquids appeared to be the most effective solvents, presumably solubilising cellulose through hydrogen bonding from the hydroxyl functions to the anions of the solvent.[279] The presence of water in the ionic liquid was shown to significantly decrease the solubility of cellulose, presumably through competitive hydrogen bonding to the cellulose microfabrics, which inhibited stabilisation.

Cellulose could be precipitated from the ionic liquid solution by the addition of water or some other precipitating solution including ethanol and acetone. The macroscopic morphology of the regenerated cellulose varied, depending on how the contracting of the ionic liquid solution and the regeneration liquid was achieved.

6.3. Liquid clathrate formation in ionic liquid-aromatic mixtures

1-Alkyl-3-methylimidazolium-containing ionic liquids with hexafluorophosphate, bis(triflyl)amide tetrafluoroborate and chloride anions have been shown to support liquid clathrate formation when mixed with aromatic hydrocarbons. In the system, 1,3-dimethylimidazolium hexafluorophosphate-benzene, the aromatic solute was trapped in the solid state, forming a crystalline 2:1 inclusion compound.[341] Liquid clathrate formation finds applications in coal liquefaction and the separation of aromatics from hydrocarbons.[342,343] Atwood described[342] the first example of liquid clathrate formation by the reaction between highly reactive air-sensitive alkylaluminium salts and aromatics and an expanded range of organic salts with halide-containing anions, for example, $[AlCl_4]^-$, X_3^- and BF_4^-. Recently, PF_6^- and NTf_2^- salts, which, unlike halide salts, are hydrophobic and contain weakly coordinating non-reactive anions, were shown to support liquid clathrate formation when mixed with different aromatic hydrocarbons. When ionic liquids and an excess of aromatic hydrocarbons were mixed, liquid clathrate phases formed spontaneously under ambient conditions. The ionic liquid-rich phases exhibited typical liquid clathrate characteristics such as low viscosity (relative to the initial neat ionic liquids), immiscibility with excess aromatic solvent and non-stoichiometric, but reproducible, compositions. In all of the liquid clathrates, it was observed that the miscibility with benzene was the greatest and the maximum aromatic content in the lower, salt-rich phase of the liquid clathrate biphase decreased following the order[341] benzene > toluene > xylenes.

6.4. Chemical and biochemical transformations in supercritical carbon dioxide-ionic liquid systems

$scCO_2$ has received attention as a versatile, environmentally benign solvent for a variety of applications.[344,345] The high volatility and low polarity of $scCO_2$ makes it an interesting solvent partner with non-volatile and fairly polar ionic liquids. The different miscibilities of $scCO_2$ and ionic liquids lead to two-phase systems that have found applications in several areas. The success of this two-phase system is based on the solubility of $scCO_2$ in the ionic liquid, which is controlled by pressure, but the insolubility of the ionic liquid in $scCO_2$. Subsequently, biphasic ionic liquid/$scCO_2$ systems have been utilised in several metal-catalysed organic reactions.[346] Both batch and continuous-flow processes were developed, in which the reactants were introduced into the ionic liquid directly or with a flow of CO_2 and the products were recovered from $scCO_2$. These transformations include the catalytic hydrogenation of alkenes with chiral and achiral organometallic catalysts in batch process[347] and hydroformylation and asymmetric hydrovinylation reactions in continuous-flow ionic liquid/$scCO_2$ systems.[348] Chemical fixation of CO_2 to produce cyclic carbonates is an important reaction, as carbonates are widely used as a starting monomer of polymers. The synthesis of propylene carbonate from propylene oxide and carbon dioxide under supercritical conditions was carried out in the presence of [omim][BF_4]. The yield of product as well as the selectivity was found to be nearly 100% within

5 min.[349] A series of imidazolium ionic liquids with different alkyl chain lengths from C_2 to C_8 were investigated and it was found that $scCO_2/[C_8\text{-mim}]^+[BF_4]^-$ was the most effective ionic liquid for CO_2 fixation to carbamate.

In the enzyme-catalysed transformations in ionic liquids, the products are extracted either by the use of hazardous molecular organic solvents or by distillation, which leads to an appreciable decrease in enzyme activity when the ionic liquid/enzyme mixture is re-used. Very recently, two groups reported almost simultaneously success with an ionic liquid/$scCO_2$ system for biocatalytic transesterification reactions and kinetic resolution of 1-phenyl ethanol.[350,351] In both investigations, the ionic liquids were 1-alkyl-3-methylimidazolium bis(trifluoromethanesulphonyl)imides. A primary advantage of such systems was the solubility or stability of the organometallic or enzymatic catalysts in the ionic liquids and their negligible solubility in $scCO_2$. The advantages of using $scCO_2$ as an extraction medium include low cost, non-toxic nature, recoverability and ease of separation from the reaction products. The primary disadvantage, however, of these biphasic systems is the cost of equipment for producing and handling $scCO_2$. Further, the development of continuous-flow catalytic systems in which both the ionic liquid/catalyst and the CO_2 can be recycled would be an important advance en route to large-scale commercial applications.[346]

6.5. Use of ionic liquids in materials chemistry

Ionic liquids have been used as electrolytes in electromechanical actuator systems based on conducting polymers[352] and in P-conjugated polymer electrochemical devices.[353] Trialkylimidazolium-based ionic liquids have been developed as novel, thermally stable treatments for layered silicates and graphite for the purpose of preparing high-quality polymer nanocomposites by Aida and co-workers, who discovered that carbon nanotubes and room temperature ionic liquids can be blended to form gels that may be used to make novel electronic devices, coating materials, and antistatic materials.[354]

7. Conclusions

There are millions of simple and complex ionic liquid systems which can be synthesized, but selecting the best system for a particular process is a real problem and challenge. Ionic liquids have a huge potential for the pharmaceutical industries as they are efficiently applicable in any synthesis where a higher-yield, selective or 'green' process is required. There are, however, a few issues that need to be addressed before ionic liquids become a routine tool in the manufacture of pharmaceutically active ingredients, the biggest perhaps being the toxicity, where very small quantities of the ionic liquid solvent remain in the product and need to be removed.

Further, in biocatalysis, ionic liquids provide a stable and congenial environment for the enzymes where they retain their catalytic activity and the enzyme-catalysed reactions on polar substrates can therefore be carried out in non-aqueous media. Such reactions are becoming increasingly important, because natural building blocks such as peptides, sugars, nucleotides and biochemical intermediates are important starting materials for pharmaceuticals, fine chemicals and materials such as hydrogels and nanoparticles. Ionic liquids may be a key technology to enable such reactions to work efficiently. Improvements in product isolation are essential, especially for polar non-volatile materials. The efficient re-use and purification of ionic liquids, the possibility of using other ionic liquids bearing 'greener' anions and a reduction in the cost factor of the ionic liquids are further important issues to be considered for their industrial applications in the future.

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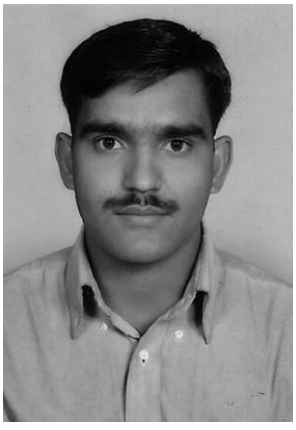

Anil Kumar was born in Gugalwa, a small village in Churu, Rajasthan, India in 1975. He studied chemistry at Hindu College, Delhi, India and received his BSc and MSc degrees in 1997 and 1999, respectively. After completing his MSc he joined Professor S. M. S. Chauhan's group and worked on heterogeneous catalysis in organic synthesis. He was awarded research fellowship by University Grant Commission, New Delhi. He received his PhD degree in organic chemistry from University of Delhi, Delhi India in 2004. Currently he is a postdoctoral fellow in Dr. K. Parang's group at Biomedical and Pharmaceutical Sciences, University of Rhode Island, USA. His research interest lies in medicinal chemistry, design and development of newer synthetic methodologies and green chemistry.

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S. M. S. Chauhan obtained his PhD degree under the joint guidance of Professor H. Junjappa and Dr. Nityanand, at Central Drug Research Institute, Lucknow. He did post-doctoral work at IIT, Kanpur with Professor M. V. George and University of Alberta, Canada with Professor J. W. Lown. After a brief stay at IIT, Bombay, he joined the Department of Chemistry, University of Delhi in 1984 where he has been a Professor since 1996. His major research interests are the development of chemical models of Cytochrome P450, flavin and pteridine monooxygenases and their applications in the biomimetic oxygenations and oxidations of organic substrates. He is a recipient of the Basudev Banerjee Memorial award in 1993 by Indian Chemical Society, Professor R. C. Shah Memorial award in 1997 by Indian Science Congress Association, and bronze medal in 2004 by Chemical Research Society of India. He has published over 100 papers in national and international journals. He is active member of many chemical societies and executive member of Indian Society of Chemists and Biologists.

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Synthesis of southern (C1′–C11′) fragment of pamamycin-635A

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Abstract—The synthesis of the southern (C1′–C11′) fragment of pamamycin-635A, isolated from *Streptomyces alboniger*, was achieved via an Evans aldol reaction, a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps.

1. Introduction

A series of antibiotic pamamycins have been isolated from various *Streptomyces* species (Fig. 1).[1] Among them, pamamycin-607 **1** was isolated from *Streptomyces alboniger*, and showed aerial mycelium-inducing activity in an aerial mycelium-less mutant of *S. alboniger*.[1b] Some total[2] and many partial syntheses[3] have been reported for **1**, but only two partial synthesis of a homologue pamamycin 635A **2**[1c] have been reported to date,[4] perhaps because of its structural complexity. We began the synthesis for **2** to supply a sample for further biological studies. Here we describe an enantioselective synthesis of the southern (C1′–C11′) hydroxy acid fragment **3**, also a constituent of pamamycins-621B[1e], 635C[1e] and 649B[1c] (*S. alboniger*) and 621A (*S. alboniger*[1e] and *S. aurantiacus* IMET 43917[1d]).

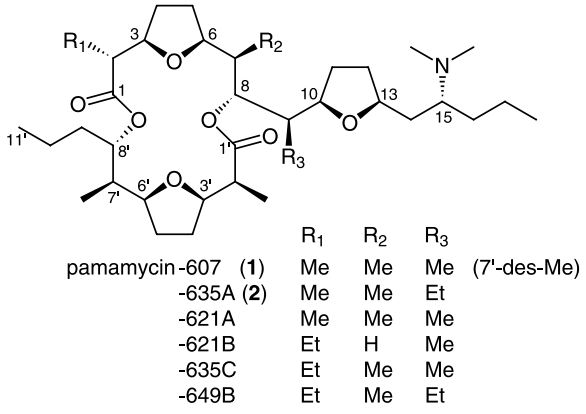
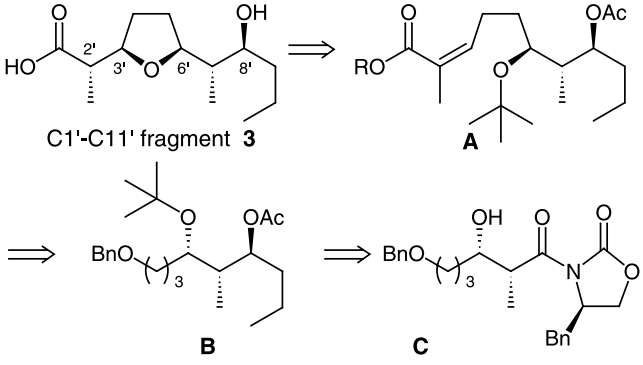


Figure 1. Structures of pamamycins.

2. Results and discussion

Scheme 1 depicts our synthetic plan.† The *cis*-tetrahydrofuran ring of **3** could be constructed by iodoetherification[5] of the corresponding (*Z*)-γ,δ-unsaturated *tert*-butoxy compound **A**, itself prepared from **B**. The *syn*-aldol moiety of **B** could be derived from the Evans aldol reaction[6] product **C**.[7,8]



Scheme 1. Retrosynthetic analysis of **3**.

As shown in Scheme 2, the known *syn*-aldol compound **5** (**C**)[8] was prepared by Evans reaction from **4**, which was then converted into its *tert*-butyl ether **6**.[3c,7] This compound was diastereomerically pure by ^{1}H NMR analysis. Then the Evans' oxazolizinone was replaced by ethanethiol to give **7**. This thioester was reduced with DIBAL and the resulting

Keywords: Pamamycins; Iodoetherification; Synthesis; Evans aldol reaction.
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† The carbon numbers will be described without primes for clarity.

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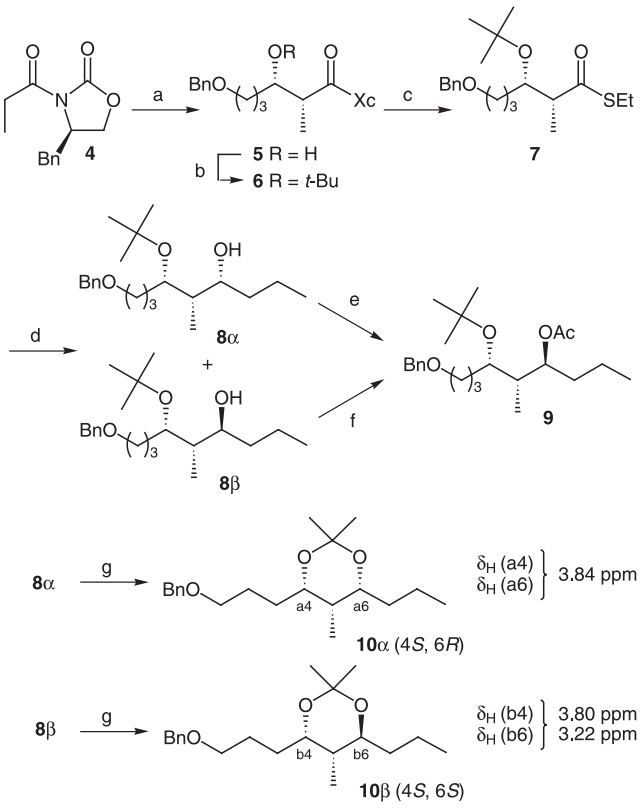
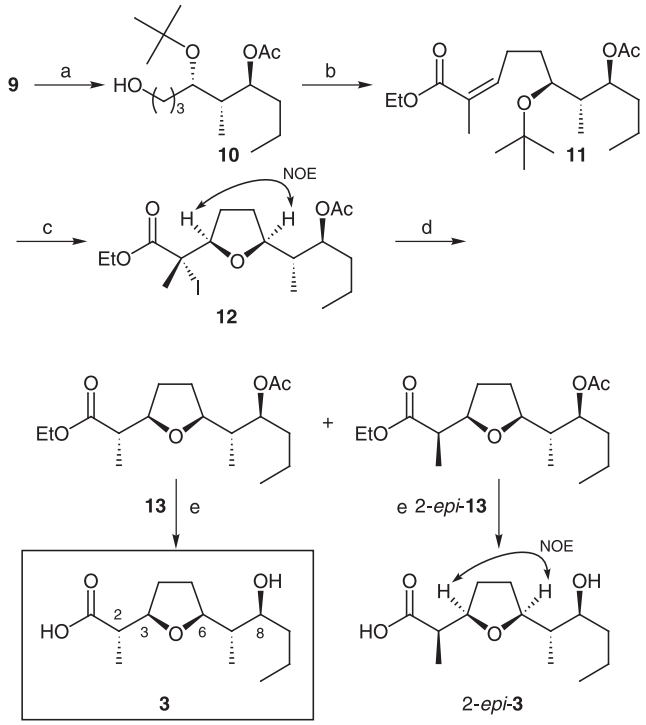


Scheme 2. Synthesis of the southern part of **2**. (a) *n*-Bu_2OTf, *i*-Pr_2NEt, CH_2Cl_2, −78 °C to rt (95%). (b) Amberlyst H-15, isobutene, hexane, −78 °C to rt (71%, and 20% of **5**). (c) *n*-BuLi, EtSH, THF, 0 °C. (d) (i) DIBAL, CH_2Cl_2, −78 °C (95%). (ii) *n*-PrMgBr, THF, −78 °C (70% of **8α** and 18% of **8β**). (e) (i) MsCl, Et_3N, CH_2Cl_2, 0 °C. (ii) KOAc, 18-c-6, toluene, reflux (56%). (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt (94%). (g) (i) TsOH, MeOH, 80 °C. (ii) 2,2-dimethoxypropane, TsOH, acetone, 0 °C (43% for **10α**, 23% for **10β**).

aldehyde treated with *n*-PrMgBr to afford alcohols **8α** and **8β** (80:20). These compounds were separated and converted to acetate **9**. To determine the relative stereochemistry, **8α** and **8β** were transformed to their corresponding acetonides **10α** and **10β**, respectively. The ^1H NMR chemical shift values in **10α**, $\delta_{a4}=\delta_{a6}=3.84$ ppm, showed that the 1,3-dioxane ring of **10α** had a *pseudo* mirror plane, therefore, the structure was determined as indicated. In addition, the selectivity of the reaction was consistent with Felkin–Anh model transition state.

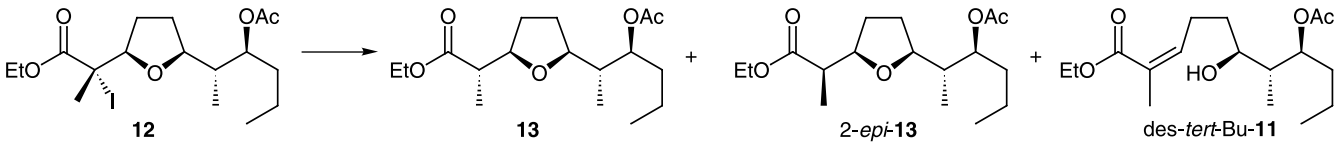
Removal of the benzyl protecting group of **9** gave alcohol



Scheme 3. Synthesis of **3** and its 2-epimer. (a) H_2, Pd-C, MeOH (97%). (b) (i) Dess–Martin periodinane, Et_2O, 0–20 °C. (ii) ethyl 2-(di-*o*-tolyl)phosphonopropanoate (77% in 2 steps). (c) ICl, $NaHCO_3$, CH_3CN, 20 °C (53% of **12** and 43% of recovered **11**). (d) $NaBH_4$, DMSO (60% of **13**, 23% of 2-*epi*-**13** and 17% of *des*-*tert*-butyl-**11**). (e) KOH, MeOH-H_2O (quant. yield for **3** and 78% for 2-*epi*-**3**).

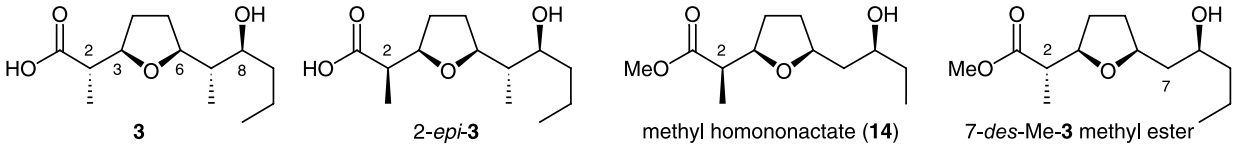
10 (Scheme 3). The alcohol **10** was converted to enone **11** (**A**) by Dess–Martin oxidation followed by Ando's modified Horner–Wadsworth–Emmons olefination (77%, *Z*/*E*=94:6).[9] Next, we tried the key iodoetherification. Treatment of compound **11** with iodine at 30 °C resulted in no reaction, but by screening other iodonium ion donors (IBr, NIS, iodonium dicollidine perchlorate: IDCP), we found ICl to be the reagent of choice. The yield of iodide **12** (*cis* only) was 53% but 43% of **11** was recovered. The *cis* stereochemistry of the tetrahydrofuran ring was confirmed by the observation of NOE between 3- and 6-protons of **12** and 2-*epi*-**3**. Reductive removal of the iodo group of **12** was done under various conditions (Table 1). The reaction proceeded with inversion of configuration using $NaBH_4$ in DMSO[10] at 10 °C to afford the desired **13** and 2-*epi*-**13** in 60 and 23%, respectively, along with 17% of *des*-*tert*-butyl-**11**. Radical

Table 1. Reductive deiodination of **12**



Entry	Conditions	**13** (%)	2-*epi*-**13**	des-*tert*-Bu-**11**	**12** (recovery)
1	$NaBH_4$, MeOH, 20 °C	52	40	4	4
2	$NaBH_4$, MeOH, −20 to 0 °C	53	29	10	8
3	$NaBH_4$, DMSO, −10 to 10 °C	60	23	17	—
4	$NaBH_4$, MeOH, 20 °C	52	40	4	4
5	$NaBH_3CN$, HMPA, 20–45 °C	19	18	—	63
6	*n*-Bu_3SnH, AIBN, CH_2Cl_2, −78 °C, *hv*	8	47	—	—

Table 2. Selected ^{1}H NMR data of **3** and the related compounds



3 2-*epi*-**3** methyl homononactate (**14**) 7-*des*-Me-**3** methyl ester

Position	Natural **3**[a]	**3**	2-*epi*-**3**	**3** Methyl ester[b]	**3** Methyl ester	2-*epi*-**3** Methyl ester	Methyl homononactate (**14**)[c]	7-*des*-Me-**3** methyl ester[d]
2	2.62	2.72	2.54	2.57	2.61	2.56	2.54	2.59
3	3.96	3.97	3.95	3.90[e]	3.94	3.95	3.94	3.99[e]
6	4.13	4.12	4.18	4.06[e]	4.10	4.12	4.14	4.13[e]
8	3.63	3.63	3.61	3.53[e]	3.58	3.57	(3.73)	3.84[e]
11	0.91	0.93	0.92	0.88,m	0.93	0.93	—	0.93
7-Me	0.88	0.90	0.91	0.88,m	0.88	0.89	—	—
2-Me	1.21	1.22	1.17	1.19	1.22	1.14	1.13	1.23

[a] Ref. 1d.
[b] Ref. 4a.
[c] Ref. 13.
[d] Ref. 2e.
[e] Not assigned.

reaction conditions resulted in the opposite selectivity.[11] In this case, the chirality of 2-position was lost through the radical intermediate, and the preferential formation of 2-*epi*-**13** is consistent with Guindon's results.[11] Finally, alkaline hydrolysis of **13** and 2-*epi*-**13** gave **3** and 2-*epi*-**3**, respectively, in an overall yield of 19% for **3**. Their methyl esters were prepared for spectral comparison.[4a] Selected ^{1}H NMR spectroscopic data are shown in Table 2. The chemical shift values of our synthetic compounds were slightly different from those reported, however, their structures are supported by Guindon's results[11] and the downfield chemical shifts of 2-methyl protons: comparison of (2*S**,3*R**)-configuration of pamamycin and (2*R**,3*R**)-configuration of nonactic acid derivatives (**14**).[4a,12,13]

3. Conclusion

Synthesis of the southern fragment of antibiotic pamamycin-635A, isolated from *Streptomyces alboniger*, was achieved in 19% overall yield using an Evans aldol reaction, a *cis*-selective iodoetherification and a stereospecific deiodination as the key steps. The structure of this hydroxy acid was confirmed by NMR data.

4. Experimental

4.1. General

Optical rotation values were measured by a Horiba Sepa-300 polarimeter. IR spectra were recorded as films by a Jasco IR Report-100 spectrometer, ^{1}H- and ^{13}C NMR spectra were recorded with a Varian Inova 600 (600 MHz for ^{1}H and 150 MHz for ^{13}C), Inova 500 (500 MHz for ^{1}H and 125 MHz for ^{13}C) and Gemini 2000 (300 MHz for ^{1}H and 75 MHz for ^{13}C) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard, and mass spectra were recorded with a Jeol JMS-700 spectrometer. Elemental compositions were analyzed by Perkin–Elmer 2400II CHN analyzer. Merck silica gel 60 (70–230 mesh) was used for column chromatography.

4.1.1. (4*R*,2′*R*,3′*S*)-4-Benzyl-3-[(6′-benzyloxy-3′-*tert*-butoxy-2′-methyl)hexanoyl]-2-oxazolidinone (6). A 40 ml, pressure-bottle equipped with a magnetic stirrer bar was charged with **5** (1.2 g, 2.9 mmol) and dry hexane (3.5 ml) at room temperature, and the mixture was stirred for 12 h. To this was added isobutene (ca. 10 ml) at −78 °C and the bottle cap was closed tightly. The mixture was gradually warmed to room temperature and stirred for 2 d. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (6:1) gave **6** (0.93 g, 2.0 mmol, 71%) as a colorless oil and recovered **5** (0.23 g, 0.55 mmol, 20%) as a colorless oil. **6**; R_f: 0.54 (hexane/EtOAc=2:1), $[\alpha]_D^{24}$ −50° (c=0.78, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 (s, 9H, *t*-Bu), 1.21 (d, 3H, J=6.9 Hz, 2-Me), 1.49–1.73 (m, 4H, 4′-H and 5′-H), 2.75 (dd, 1H, J=9.3, 13.5 Hz, NCHCH_2Ph), 3.30 (dd, 1H, J=3.3, 13.5 Hz, NCHCH_2Ph), 3.44–3.50 (m, 2H, 6′-H), 3.81 (m, 1H, 4-H), 3.94–4.12 (m, 3H, 5-H_2 and 3′-H), 4.48 (s, 2H, OCH_2Ph), 4.53 (m, 1H, 4-H), 7.20–7.34 (m, 10H, Ph). FABMS (glycerol+NOBA): m/z=468 $(M+H)^+$, 412 $(M^+ + H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{28}H_{38}NO_5$ $(M+H)^+$, 468.2750; found, 468.2754.

4.1.2. (2*R*,3*S*)-6-Benzyloxy-3-*tert*-butoxy-2-methyl-hexanoic acid *S*-ethyl ester (7). A 300 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a 50 ml pressure-equalizing addition funnel, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with EtSH (2.5 ml, 34 mmol) in THF (50 ml) at 0 °C. 1.6 M *n*-BuLi in hexane (17.5 ml, 28 mmol) was added dropwise to the solution and stirred for 1 h. Then the mixture was cooled to −78 °C and was added **6** (5.20 g, 11.1 mmol) in THF (50 ml). The reaction mixture was gradually warmed to 0 °C and stirred for 2 h. This was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was

chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **7** (mw: 352.53, 3.70 g, 10.5 mmol, 95%) as a colorless oil; R_f: 0.63 (hexane/EtOAc=4:1), $[\alpha]_D^{24}$ −35° (c=1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=1.16 (d, 3H, J=7.1 Hz, 2-Me), 1.18 (s, 9H, t-Bu), 1.23 (t, 3H, J=7.4 Hz, SCH_2CH_3), 1.39–1.76 (m, 4H, 4-H and 5-H), 2.77–2.91 (m, 3H, 2-H and SCH_2), 3.46 (t, 2H, J=6.3 Hz, 6-H), 3.74 (q, 1H, J=10.7, 5.2 Hz, 3-H), 4.50 (s, 2H, OCH_2Ph), 7.26–7.34 (m, 5H, Ph). ^{13}C NMR (125 MHz, $CDCl_3$): δ=13.87, 14.59, 23.19, 25.27, 28.73 (Me_3C), 30.26, 52.78 (2-C), 70.51, 72.57, 72.72, 73.90, 127.41, 127.55, 128.29, 128.61, 202.48 (C=O). IR (film): ν=2980 (s) cm^{-1}, 2880 (m), 1680 (s, C=O), 1455 (m), 1365 (s), 1190 (s), 1100 (s), 1010 (s). FABMS (glycerol+NOBA): m/z=353 $(M+H)^+$, 297 $(M+H\text{-}t\text{-}Bu)^+$, 235 $(M+H\text{-}t\text{-}Bu\text{-}HSEt)^+$. HR-FABMS: calcd for $C_{20}H_{33}O_3S$ $(M+H)^+$, 353.2151; found, 353.2151. Found: C, 68.18%; H, 9.72%. Calcd for $C_{20}H_{32}O_3S$: C, 68.14%; H, 9.15%.

4.1.3. (4*R*,5*S*,6*S*)-9-Benzyloxy-6-*tert*-butoxy-5-methyl-4-nonanol (8α) and its (4*S*)-isomer (8β). A 200 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with **7** (3.70 g, 10.5 mmol) in dry CH_2Cl_2 (100 ml) at −78 °C. To the solution was added 0.95 M DIBAL-H in hexane (12 ml, 12 mmol). After 2 h, the reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with CH_2Cl_2. The combined extract was washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated in vacuo to give aldehyde as a pale yellow oil in an almost quantitative yield. ^1H NMR (300 MHz, $CDCl_3$): δ=1.04 (d, 3H, J=7.1 Hz, 2-Me), 1.19 (s, 9H, t-Bu), 1.40–1.75 (m, 4H, 4-, 5-H), 2.57 (ddq, 1H, J=3.7, 1.1, 6.8 Hz, 2-H), 3.45 (dd, J=2.5, 6.3 Hz, 6-H), 3.47 (dd, J=2.5, 6.3 Hz, 6-H), 3.84 (m, 1H, 3-H), 4.50 (s, 2H, OCH_2Ph), 7.26–7.36 (m, 5H, Ph), 9.82 (d, 1H, J=1.1 Hz, CHO). This aldehyde was used in the next step without further purification.

A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with crude aldehyde (210 mg, 0.72 mmol) in THF (7 ml) at −78 °C. To the solution was added dropwise 2.2 M n-PrMgBr in THF (0.50 ml, 1.1 mmol). After 1 d, the reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **8α** (mw: 336.51, 172 mg, 0.51 mmol, 70% from **7**) and **8**β (43 mg, 0.13 mmol, 18% from **7**) as colorless oils.

4.1.4. (4*R*,5*S*,6*S*)-6-[(3-Benzyloxy)propyl]-2,2,5-trimethyl-6-propyl-[1,3]dioxane (10α) and its (4*S*)-isomer (10β). A 20 ml, two-necked round-bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser and a septum was charged with **8α** (or **8**β) in MeOH at room temperature. To the solution was added a catalytic amount of p-TsOH and the mixture was stirred under reflux for 26 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave (4*S*,5*S*,6*R*)-1-benzyloxy-5-methyl-4,6-nonanediol (or (4*S*,5*S*,6*S*)-1-benzyloxy-5-methyl-4,6-nonanediol).

A 10 ml, two-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with the diol in acetone and 2,2-dimethoxypropane (2 equiv) at room temperature. To the solution was added a catalytic amount of p-TsOH at 0 °C and stirred for 1 h. The reaction mixture was quenched with sat. aq. $NaHCO_3$ soln. and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **10α** (mw: 320.47, or **10**β).

Compound **10α**. ^1H NMR (300 MHz, $CDCl_3$): δ=0.83 (d, 3H, J=6.9 Hz, 5-Me), 0.92 (t, 3H, J=6.9 Hz), 1.23–1.72 (m, 8H), 1.38 [s, 6H, $C(CH_3)_2$], 3.43–3.55 (m, 2H, CH_2OBn), 3.85–3.82 (m, 2H, 4-H and 6-H), 4.51 (s, 2H, OCH_2Ph), 7.27–7.35 (m, 5H, Ph).

Compound **10**β. ^1H NMR (300 MHz, $CDCl_3$): δ=3.22 (q, 1H, J=6.4, 13.3 Hz, 6-H), 3.45–3.52 (m, 2H, CH_2OBn), 3.80 (q, 1H, J=5.0, 13.4 Hz, 4-H).

4.1.5. (1*S*,2*R*,3*S*)-6-Benzyloxy-3-*tert*-butoxy-2-methylhexyl acetate (9). *From* **8**β. A 20 ml, one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with **8**β (90 mg, 0.27 mmol) in dry CH_2Cl_2 (2 ml). To the solution was added Et_3N (0.34 ml, 3.36 mmol), Ac_2O (0.12 ml, 1.17 mmol) and DMAP (19 mg, 0.16 mmol) at room temperature and stirred for 18 h. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with CH_2Cl_2. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave **9** (95 mg, 0.25 mmol, 94%) as a pale yellow oil.

From **8α**. A 100 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with **8α** (1.1 g, 3.3 mmol) in dry CH_2Cl_2 (20 ml) at room temperature. To the solution was added Et_3N (2.7 ml, 19.4 mmol), cooled to 0 °C and added MsCl (1.2 ml, 15.4 mmol). After 1 h, the reaction mixture was diluted with CH_2Cl_2, washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $CaCl_2$ and concentrated in vacuo. The residue was used to next step without further purification.

A 300 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a Dimroth condenser, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with crude mesylate in toluene (100 ml) at room temperature. To the solution was added KOAc (3.9 g, 40.0 mmol) and 18-crown-6 (1.7 g, 6.4 mmol), and stirred under reflux for 1 d. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was diluted with water and extracted with EtOAc. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **9** (700 mg, 1.85 mmol, 56% from **10α**)

as a pale yellow oil; R_f: 0.52 (hexane/EtOAc=4:1), $[\alpha]_D^{26}$ +2.55° (c=1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.84–0.92 (m, 6H, 2-Me and 3′-H), 1.15 (s, 9H, *t*-Bu), 1.26–1.68 (m, 8H), 1.84 (m, 1H), 2.02 (s, 3H, Ac), 3.46–3.50 (m, 3H, 3-H and 6-H), 4.51 (s, 2H, CH_2Ph), 4.85 (dt, 1H, J=3.3, 7.4 Hz, 1-H), 7.29–7.35 (m, 5H, Ph). IR (film): ν=2960 (s), 2870 (m), 1730 (s, C=O), 1455 (w), 1365 (m), 1245 (s), 1195 (m), 1100 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=379 $(M+H)^+$, 323 $(M+H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{23}H_{39}O_4$ $(M+H)^+$, 379.2849; found, 379.2851.

4.1.6. (1*S*,2*R*,3*S*)-3-*tert*-Butoxy-6-hydroxy-2-methyl-1-propylhexyl acetate (10). A 20 ml, one-necked round-bottomed flask equipped with a magnetic stirrer bar was charged with **9** (281 mg, 0.74 mmol) in dry MeOH (6 ml) at room temperature. To the solution was added 10% Pd-C (60 mg) and stirred for 18 h at 1 atm H_2. The reaction mixture was filtered and the filtrate was concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) gave **10** (207 mg, 0.72 mmol, 97%) as a pale yellow oil; R_f: 0.25 (hexane/EtOAc=2:1), $[\alpha]_D^{26}$ −8.40° (c=1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.89–0.93 (m, 6H, 2-Me and 3′-H), 1.19 (s, 9H, *t*-Bu), 1.24–1.77 (m, 8H), 1.89–2.00 (m, 1H), 2.04 (s, 3H, C(O)CH_3), 2.57 (bs, 1H, OH), 3.44–3.49 (m, 1H, 3-H), 3.64 (bs, 2H, 6-H), 4.86–4.92 (m, 1H, 1-H). IR (film): ν=3425 (m, OH), 2975 (s), 2875 (m), 1735 (s, C=O), 1460 (m), 1370 (m), 1250 (s), 1195 (m), 1060 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=289 $(M+H)^+$. Found: C, 66.63%; H, 11.23%. Calcd for $C_{16}H_{32}O_4$: C, 66.63%; H, 11.18%.

4.1.7. Ethyl (6*S*,7*R*,8*S*)-8-acetoxy-6-*tert*-butoxy-2,7-dimethyl-2-undecenoate (11). A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with Dess–Martin periodinane (310 mg, 0.73 mmol) in dry ether (4 ml) at 0 °C. To the mixture was added **10** (150 mg, 0.52 mmol) in dry ether (5 ml) at 0 °C and stirred for 8 h at room temperature. The reaction mixture was filtered and the filtrate concentrated in vacuo. The residue was diluted with ether and washed with sat. aq. $NaHCO_3$ soln. and brine, dried over $MgSO_4$ and concentrated in vacuo to give aldehyde as a pale yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ=0.98 (d, 3H, J=7.1 Hz, 5-Me), 0.91 (t, 3H, J=7.3 Hz, 9-H), 1.16 (s, 9H, *t*-Bu), 118–1.60 (m, 4H), 1.73–1.92 (m, 3H), 2.56 (dt, 2H, J=1.4, 7.7 Hz, 2-H), 3.46 (q, 2H, J=5.2 Hz, 4-H), 4.84 (ddd, 1H, J=3.0, 5.7, 8.8 Hz, 6-H), 9.82 (m, 1H, CHO). The aldehyde was used to next step without further purification.

A 25 ml, three-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with 60% NaH (29 mg, 0.71 mmol) at room temperature. To this was added ethyl 2-(di-*o*-tolyl)phosphonopropanoate (185 mg, 0.51 mmol) in THF (2.5 ml) at 0 °C and stirred for 15 min. Then to the solution was added crude aldehyde (130 mg, 0.45 mmol) in THF (0.9 ml) at −78 °C and warmed gradually to 0 °C for over 2 h. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with EtOAc. The combined extract was washed with water and brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (10:1) gave *11* (148 mg, 0.40 mmol, 77% from **10**) as a pale yellow oil; R_f: 0.55 (hexane/EtOAc=4:1), $[\alpha]_D^{25}$ +5.3° (c=1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ=0.85 (d, 3H, J=7.1 Hz, 7-Me), 0.90 (t, 3H, J=7.1 Hz, 11-H), 1.15 (s, 9H, *t*-Bu), 1.30 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.44–1.64 (m, 6H), 1.86 (m, 1H), 1.90 (dt, 3H, J=1.4, 1.7 Hz, 2-Me), 2.03 (s, 3H, OCH_3), 2.45 (pseudo q, 2H, J=7.4 Hz, 4-H), 3.49 (m, 1H, 6-H), 4.20 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.85 (dt, 1H, J=3.3 and 7.4 Hz, 8-H), 5.90–5.91 (tq, 1H, J=7.4, 1.7 Hz, 3-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=10.37, 14.21, 14.29, 18.00, 20.71, 21.39, 26.08, 29.00 (Me_3C), 33.05, 33.53, 39.19, 60.04, 71.39, 73.07, 75.70, 127.12, 142.65, 168.07, 170.70. IR (film): ν=2975 (s), 2875 (m), 1735 (s, C=O), 1720 (s, C=C), 1460 (m), 1370 (s), 1245 (s), 1200 (s), 1150 (s), 1020 (s). FABMS (glycerol+NOBA): m/z=371 $(M+H)^+$, 315 $(M+H\text{-}t\text{-}Bu)^+$. HR-FABMS: calcd for $C_{21}H_{39}O_5$ $(M+H)^+$, 371.2798; found, 371.2798.

4.1.8. Ethyl (2*R*,3*R*,6*S*,7*R*,8*S*)-8-acetoxy-3,6-epoxy-2-iodo-2,7-dimethylundecanoate (12). A 20 ml, two-necked round bottomed flask equipped with a magnetic stirrer bar, a N_2 inlet adapter and a septum was placed under a nitrogen atmosphere. The flask was charged with ICl (ca. 1 g, ca. 6 mmol) and $NaHCO_3$ (ca. 1 g, ca. 12 mmol) in dry CH_3CN (6 ml) at 0 °C, and stirred for 15 min. To the suspension was added **11** (146 mg, 0.394 mmol) and the mixture was stirred at 20 °C for 7.5 h. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ soln. and extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) gave **12** (92.0 mg, 0.209 mmol, 53%) as a pale yellow oil and recovered **11** (65 mg, 0.169 mmol, 43%).

Compound **12**. R_f: 0.48 (hexane/EtOAc=4:1), $[\alpha]_D^{26}$ −35.3° (c=1.00, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$): δ=0.91 (t, 3H, J=7.4 Hz, 11-H), 1.01 (d, 3H, J=7.0 Hz, 7-Me), 1.29 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.49–1.95 (m, 8H), 1.98 (s, 3H, 2-Me), 2.05 (s, 3H, C(O)CH_3), 3.73–3.80 (m, 1H, 6-H), 4.23 (q, 2H, J=7.1, 14.3 Hz, OCH_2CH_3), 4.28–4.33 (m, 1H, 3-H), 4.86–4.91 (m, 1H, 8-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=10.29, 13.75, 14.00, 18.95, 21.32, 25.89, 28.10, 30.39, 31.97, 41.21, 43.27, 61.92, 76.05, 80.87, 84.01, 170.84, 171.80. IR (film): ν=2960 (m), 2875 (m), 1730 (s, C=O), 1465 (w), 1380 (w), 1250 (s), 1060 (m), 1020 (m). FABMS (glycerol+NOBA): m/z=441 $(M+H)^+$, 381 $(M+H\text{-}AcOH)^+$. HR-FABMS: calcd for $C_{17}H_{30}O_5I$ $(M+H)^+$, 441.1138; found, 441.1138.

4.1.9. Ethyl (2*S*,3*R*,6*S*,7*R*,8*S*)-8-acetoxy-3,6-epoxy-2,7-dimethylundecanoate (13). A 5 ml round bottomed flask, equipped with a magnetic stirrer bar, was charged with **12** (16.2 mg, 0.0368 mmol) and $NaBH_4$ (3.8 mg, 0.1 mmol) in DMSO (0.5 ml) at −10 °C. The mixture was stirred for 2 h while the temperature of the solution was gradually raised to 10 °C. The reaction mixture was quenched with sat. aq. NH_4Cl soln. and extracted with ether. The combined extract was washed with brine, dried over $MgSO_4$ and concentrated

in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (20:1) and toluene/EtOAc (20:1) gave **13** (6.9 mg, 0.022 mmol, 60%), 2-*epi*-**13** (2.7 mg, 0.0085 mmol, 23%) and des-*tert*-butyl-**11** (2.0 mg, 0.0063 mmol, 17%) as pale yellow oils.

Compound **13**. R_f: 0.57 (toluene/EtOAc=5:1), $[\alpha]_D^{25}$ +5.3° (c=0.14, $CHCl_3$) ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.896 (t, 3H, J=7.4 Hz, 11-H), 0.936 (d, 3H, J=7.4 Hz, 7-Me), 1.223 (d, 3H, J=7.1 Hz, 2-Me), 1.250 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.33 (pseudo dd, 1H, J=7.4, 10.5 Hz), 1.45–1.54 (m, 2H), 1.62–1.72 (m, 2H), 1.80 (m, 1H), 1.86–1.99 (m, 2H), 2.04 (s, 3H, $C(O)CH_3$), 2.45 (quint, 1H, J=7.1 Hz, 2-H), 3.71 (pseudo dt, 1H, J=7.7, 6.0 Hz, 6-H), 3.90 (pseudo dt, 1H, J=8.2, 6.3 Hz, 3-H), 4.12 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.88 (pseudo dt, 1H, J=8.2, 4.4 Hz, 8-H). IR (film): ν=2960 (s), 2875 (m), 1735 (s), 1730 (s), 1465 (m), 1375 (m), 1245 (s), 1180 (m), 1070 (m), 1015 (m). FABMS (glycerol+NOBA): m/z=315 $(M+H)^+$, 255 (M^++H-AcOH). HR-FABMS: calcd for $C_{17}H_{31}O_5$ $(M+H)^+$, 315.2172; found, 315.2172.

Compound 2-*Epi*-**13**. R_f: 0.50 (toluene/EtOAc=5:1), $[\alpha]_D^{26}$ −31° (c=0.45, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.888 (t, 3H, J=7.1 Hz, 11-H), 0.934 (d, 3H, J=6.8 Hz, 7-Me), 1.094 (d, 3H, J=6.9 Hz, 2-Me), 1.256 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.30–1.73 (m, 5H), 1.86–1.95 (m, 2H), 1.82 (m, 1H), 2.04 (s, 3H, $C(O)CH_3$), 2.49 (dq, 1H, J=8.2, 6.9 Hz, 2-H), 3.70 (dt, 1H, J=7.4, 6.3 Hz, 3-H), 3.97 (dt, 1H, J=8.2, 6.3 Hz, 3-H), 4.09–4.20 (m, 2H, OCH_2CH_3), 4.84 (ddd, 1H, J=9.0, 5.0, 3.6 Hz, 8-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=10.18, 13.28, 13.96, 14.23, 18.89, 21.29, 28.55, 29.38, 31.85, 41.58, 45.26, 60.24, 76.03, 80.24, 80.34, 170.80, 174.98. IR (film): ν=2960 (s), 2875 (m), 1735 (s), 1465 (m), 1380 (m), 1245 (s), 1070 (m), 1020 (m). FABMS (NOBA): m/z=315 $(M+H)^+$. FABMS (glycerol+NOBA): m/z=315 $(M+H)^+$, 255 $(M+H\text{-}AcOH)^+$. HR-FABMS: calcd for $C_{17}H_{31}O_5$ $(M+H)^+$, 315.2172; found, 315.2177.

4.1.10. (2*S*,3*R*,6*S*,7*R*,8*S*)-3,6-Epoxy-8-hydroxy-2,7-dimethylundecanoic acid (3). A solution of **13** (mw 314, 6.3 mg, 20 μmol) in 0.5 M KOH in MeOH-H_2O (1:1, 1 ml) was stirred at 20 °C for 12 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O. This was washed with ether and the aqueous layer was acidified with dil. HCl. This was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (4:1) and hexane/EtOAc/AcOH (2:1:0.1) gave **3** (5.0 mg, 20 μmol, quant.) as a colorless oil; $[\alpha]_D^{27}$ +8.0° (c=0.25, $CHCl_3$). ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.902 (d, 3H, J=7.1 Hz, 7-Me), 0.931 (t, 3H, J=7.0 Hz, H-11), 1.221 (d, 3H, J=7.0 Hz, 2-Me), 1.35 (m, 1H, H-10), 1.45–1.55 (m, 3H, 10-H), 1.68–1.8 (m, 2H), 1.8–1.92 (m, 2H), 2.00 (m, 1H, 4-H), 2.72 (quint, 1H, J=6.8 Hz, 2-H), 3.63 (pseudo q, 1H, J=5.9 Hz, 8-H), 3.97 (pseudo q, 1H, J=6.8 Hz, 3-H), 4.12 (m, 1H, 6-H). ^{13}C NMR (150 MHz, $CDCl_3$): δ=12.05, 13.49, 14.18, 18.62, 26.74, 27.99, 37.23, 39.86, 43.25, 73.73, 80.20, 81.45, 177.06. IR (film): ν=3700–2200 (br, s), 1710 (s), 1260 (s), 1170 (s), 665 (m). FABMS (glycerol): m/z=245 $(M+H)^+$, 227 $(M+H\text{-}H_2O)^+$, 185, 93. HR-FABMS: calcd for $C_{13}H_{25}O_4$ $(M+H)^+$, 245.1753; found, 245.1759.

Compound **3** *methyl ester*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.884 (d, 3H, J=7.0 Hz, 7-Me), 0.934 (t, 3H, J=7.3 Hz, H-11), 1.225 (d, 3H, J=7.0 Hz, 2-Me), 1.36 (m, 1H), 1.45 (m, 2H), 1.54 (m, 1H), 1.65–1.75 (m, 2H), 1.83 (m, 2H), 1.97 (m, 1H), 2.61 (dq, 1H, J=7.3, 7.0 Hz, 2-H), 3.31 (br, 1H, OH), 3.58 (m, 1H, 8-H), 3.68 (s, 3H, OMe), 3.94 (pseudo q, 1H, J=7.0 Hz, 3-H), 4.10 (m, 1H, 6-H).

4.1.11. (2*R*,3*R*,6*S*,7*R*,8*S*)-3,6-Epoxy-8-hydroxy-2,7-dimethylundecanoic acid (2-*epi*-3). A solution of 2-*epi*-**13** (mw 314, 20.7 mg, 65.9 μmol) in 0.5 M KOH in MeOH-H_2O (1:1, 1 ml) was stirred at 20 °C for 12 h. The reaction mixture was concentrated in vacuo and the residue was diluted with H_2O. This was washed with ether and the aqueous layer was acidified with dil. HCl. This was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with hexane/EtOAc (2:1) and hexane/EtOAc/AcOH (2:1:0.1) gave 2-*epi*-**3** (12.6 mg, 51.6 μmol, 78%) as a colorless oil; $[\alpha]_D^{26}$ −17.3° (c=0.375, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ=0.911 (t, 3H, J=7.1 Hz, 11-H), 0.923 (d, 3H, J=7.1 Hz, 7-Me), 1.168 (d, 3H, J=6.9 Hz, 2-Me), 1.35 (m, 1H, H-10), 1.4–1.6 (m, 3H, H-9, 10), 1.64 (m, 1H, H-4), 1.76 (m, 1H, H-5), 1.83 (m, 1H, H-7), 1.87 (m, 1H, H-5), 2.03 (m, 1H, H-4), 2.54 (d of quint, 1H, J=8.2, 6.9 Hz, H-2), 3.61 (pseudo dt, 1H, J=4.9, 6.6 Hz, H-8), 3.95 (dt, 1H, J=8.2, 7.1 Hz, H-3), 4.18 (ddd, J=7.7, 7.1, 3.3 Hz, 1H, H-6). ^{13}C NMR (150 MHz, $CDCl_3$): δ=12.03 (7-Me), 13.69 (2-Me), 14.18 (11), 18.72 (10), 26.75 (5), 29.01 (4), 37.20 (9), 39.85 (7), 44.57 (2), 73.98 (8), 80.86 (3), 81.42 (6), 177.08 (1). IR (film): ν=3700–2200 (br, s), 1710 (s), 1200 (s), 1170 (s), 665 (m). FABMS (glycerol): m/z=245 $(M+H)^+$, 227 $(M+H\text{-}H_2O)^+$, 154, 136. HR-FABMS: calcd for $C_{13}H_{25}O_4$ $(M+H)^+$, 245.1753; found, 245.1757.

2-*Epi*-**3** *methyl ester*. ^{1}H NMR (600 MHz, $CDCl_3$): δ=0.891 (d, 3H, J=7.0 Hz, 7-Me), 0.927 (t, 3H, J=7.3 Hz, H-11), 1.135 (d, 3H, J=7.0 Hz, 2-Me), 1.36 (m, 1H), 1.44 (m, 2H), 1.48–1.64 (m, 2H), 1.75 (m, 1H), 1.8–1.9 (m, 2H), 1.99 (m, 1H), 2.56 (m, 1H, 2-H), 3.32 (d, 1H, J=4.7 Hz, OH), 3.57 (m, 1H, 8-H), 3.69 (s, 3H, OMe), 3.95 (pseudo q, 1H, J=7.0 Hz, 3-H), 4.12 (m, 1H, 6-H).

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A novel and efficient catalytic epoxidation of olefins and monoterpenes with microencapsulated Lewis base adducts of methyltrioxorhenium

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Abstract—The reactivity of methyltrioxorhenium in the epoxidation of olefins can be tuned by the presence of Lewis bases as ligands of the metal center. Unfortunately, a large excess of ligand is usually required to obtain high yields and selectivities mainly because of the fluxional behaviour that these compounds show in solution. We describe here the microencapsulation technique that can resolve this problem. Microencapsulated Lewis base adducts of methyltrioxorhenium with nitrogen containing ligands are highly efficient and selective catalysts for the epoxidation of several olefins and monoterpenes with hydrogen peroxide even in the case of the most sensitive substrates. These systems show the advantages of the ligand accelerated catalysis and the benefits of heterogeneous compounds. They can be easily recovered from the reaction mixture and used for more transformations.

1. Introduction

During the last years methyltrioxorhenium (CH_3ReO_3, MTO)[1] showed excellent catalytic properties in oxidation of olefins,[2] alcohols,[3] arenes,[4] carbonylmetal derivatives,[5] phosphorous and sulphur compounds,[6] olefin metathesis,[7] aldehyde olefination,[8] Bayer–Villiger rearrangement[9] and hydrocarbon C–H oxygen atom insertions.[10] The epoxidation of olefins with hydrogen peroxide (H_2O_2) received special attention. The mayor drawback of this trasformation is the ring-opening of the newly formed oxiranyl moiety with concomitant formation of diols. This side-reaction is mainly due to the acidity of the catalyst system.[11] Lewis base adducts of MTO with nitrogen containing ligands, such as pyridine,[12] pyridine derivatives,[13] pyrazole[14] and others, decrease the formation of diols, especially in the case of sensitive substrates, and increase the catalytic efficiency. MTO reacts with monodentate and bidentate ligands to give trigonal bipyramidal and distorted octahedral adducts, respectively.[15] The activity of these complexes in several oxy-functionalizations was found to be dependent on different experimental parameters, such as the redox stability of the ligand and the reaction temperature.[16] Lewis base adducts of MTO undergo exchange of both the metal-coordinated base ligands and the oxo ligands in solution in the presence of water or other nucleophilic solvents.[17] For this reason a large excess of ligand is necessary (at least fivefold excess) to obtain the maximum turnover frequencies (TOF), epoxide yield and conversion of substrate.[15] Unfortunately, the excess of ligand can be a synthetic limitation in the case of expensive and chiral Lewis bases.

It was quickly detected that MTO can form adducts with ligands immobilized on inorganic and organic host.[18,19] In these systems the active rhenium species is localized in a specific microenvironment whose properties can differ from that of the bulk of the solution. Recently, we reported the use of poly(4-vinylpyridine)/MTO compounds as efficient catalysts for the epoxidation of olefins,[19] monoterpenes,[20] phenol and anisole derivatives,[21] flavonoids,[22] pyrrolidines[23] and hydrocarbon derivatives.[24] Alternative strategies to further improve heterogeneous MTO-catalyzed epoxidations can involve the immobilization of previously synthesized Lewis base adducts of MTO on polystyrene by use of the microencapsulation technique.[25] In principle, the reactivity and selectivity of MTO in these compounds can be tuned by the chemical–physical properties of the ligand and of the support showing the advantages of the ligand

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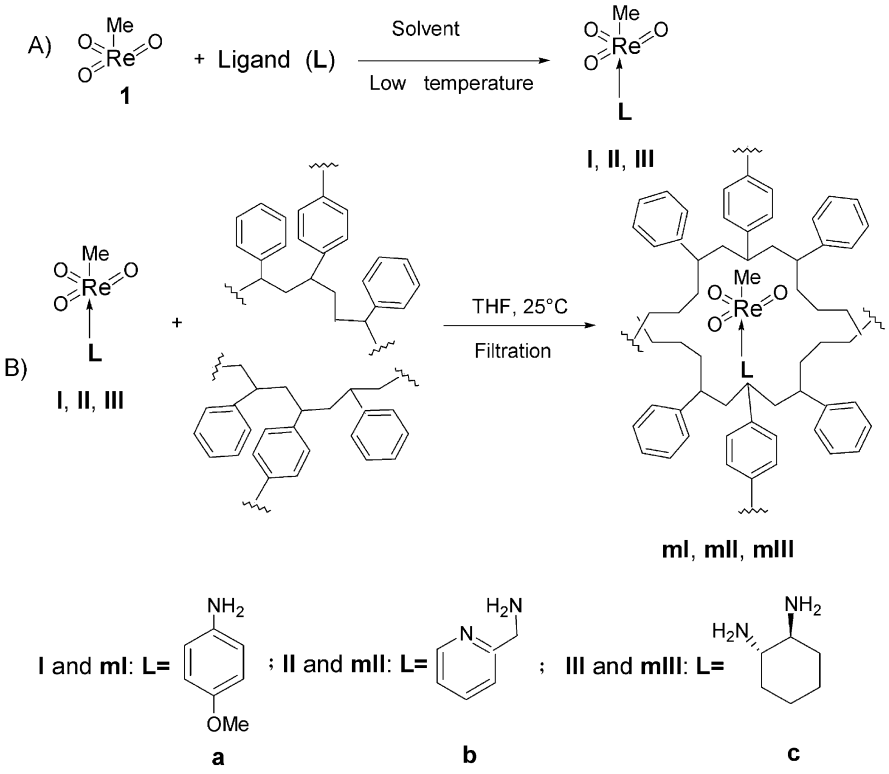


Figure 1. Preparation of microencapsulated Lewis base adduct of MTO **mI**, **mII** and **mIII**, and of their parent compounds **I**, **II** and **III**.

accelerated catalysis and the environmental benefits of heterogeneous systems. We report here the preparation and applicability of novel microencapsuled Lewis base adducts of MTO with monodentate and bidentate, aromatic and aliphatic nitrogen containing ligands, for the epoxidation of olefins and monoterpene derivatives, including acid-sensitive substrates. Environment friendly H_2O_2 was used as primary oxidant. Noterworthy, microencapsulated Lewis base adducts of MTO were more reactive than their homogeneous parent compounds even in the absence of the excess of ligand. They were also stable catalytic systems for several oxidations.

2. Results

Lewis base adducts of MTO **I–III** with the monodentate ligand 4-methoxyaniline (**a**) and the bidentate aromatic and aliphatic ligands, 2-methyl aminopyridine (**b**) and racemic *trans*-1,2-diaminocyclohexane (**c**), respectively, were prepared as model compounds following a synthetic procedure previously reported in the literature.[26,27] In order to obtain these adducts, MTO **1** and the appropriate Lewis base were mixed in toluene, the reaction mixture was concentrated and cooled to −35 °C, and the yellow precipitates isolated by filtration (Fig. 1, equation A). Microencapsulated Lewis base adducts of MTO **mI–mIII** were then obtained by encapsulation of freshly prepared adducts **I–III** on polystyrene (2% cross-linked with divinylbenzene).[19b]

Briefly, to a suspension of polystyrene (600 mg) in tetrahydrofuran was added to the appropriate adduct **I–III** (0.3 mmol). After 1 h, hexane was added to harden the capsule walls, the solvent was removed by filtration and compounds **mI–mIII** were dried and used without any further purification (Fig. 1, equation B). In each case adducts **mI–mIII** were completely bound to the polystyrene as confirmed by spectroscopic analysis of the residue obtained after evaporation of the organic layer. Figure 2 shows a scanning electron microscopy (SEM) photograph of the surface of particles of catalyst **mIII**. Particles are characterized by a regular spherical shape of 50 μm. Fragments are probably formed by a mechanical damage of particles during the preparation of the sample.

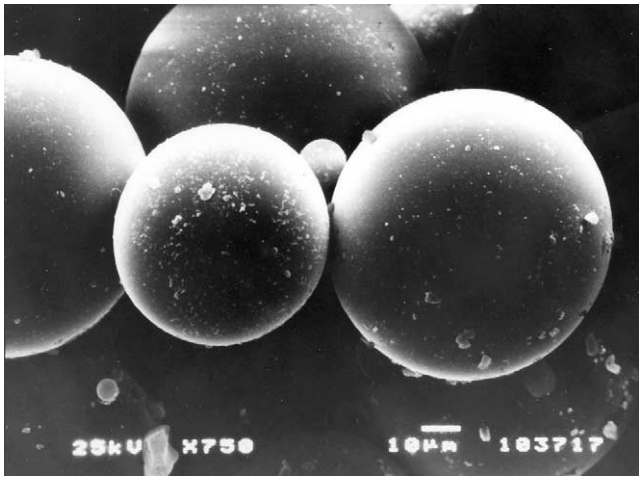


Figure 2. Scanning electron microscopy (SEM) photograph of the surface of particles of catalyst **mIII**.

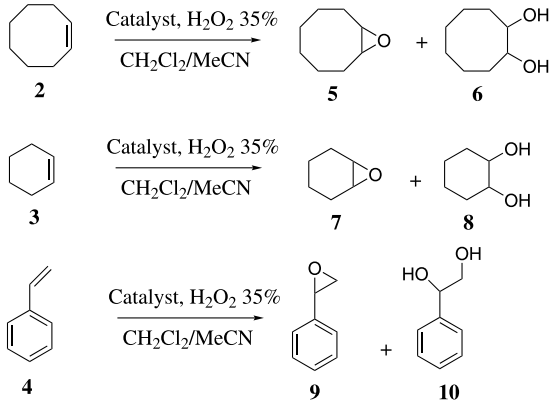
Epoxidations with catalysts **mI–mIII** and H_2O_2 (35% aq solution) were first investigated using reactive olefins, cyclooctene **2** and cyclohexene **3**, and moderately active

Table 1. Epoxidations of olefins with microencapsulated Lewis base adduct of MTO

Entry	Substrate	Catalyst[a]	Reaction time (h)	Conversion (%)	Epoxide yield (%)	Diol yield (%)
1	Cyclooctene	**1**	0.5	94	60	18
2	Cyclooctene	**I**	3.0	85	65	10
3	Cyclooctene	**mI**	3.0	98	70	12
4	Cyclooctene	**II**	2.5	88	>98	0
5	Cyclooctene	**mII**	2.5	>98	>98	0
6	Cyclooctene	**III**	0.5	90	>98	0
7	Cyclooctene	**mIII**	0.5	>98	>98	0
8	Cyclohexene	**1**	1.0	>98	55	45
9	Cyclohexene	**I**	2.5	89	62	21
10	Cyclohexene	**mI**	2.5	95	70	14
11	Cyclohexene	**II**	2.5	80	>98	0
12	Cyclohexene	**mII**	2.5	>98	>98	0
13	Cyclohexene	**III**	1.0	87	>98	0
14	Cyclohexene	**mIII**	1.0	>98	>98	0
15	Styrene	**1**	6.0	65	80	20
16	Styrene	**I**	8.0	58	73	21
17	Styrene	**mI**	8.0	63	75	15
18	Styrene	**II**	9.5	54	95	0
19	Styrene	**MII**	5.0	62	95	0
20	Styrene	**III**	1.5	86	>98	0
21	Styrene	**MIII**	1.5	>98	>98	0

All the reactions were performed in CH_2Cl_2/MeCN (5.0 mL, 1:1 v/v) at room temperature, with H_2O_2 (35% aq solution), using a value of the catalyst loading factor of 1.0.

[a] Catalyst: MTO **1**, MTO/4-methoxyaniline **I**, microencapsulated MTO/4-methoxyaniline **mI**, MTO/2-aminomethylpyridine **II**, microencapsulated MTO/2-aminomethylpyridine **II**, MTO/*trans*-1,2-diaminocyclohexane **III**, microencapsulated MTO/2-aminomethylpyridine **mIII**.



Scheme 1.

styrene **4**, as representative model substrates. All the reactions were performed in CH_2Cl_2/CH_3CN (5 mL, 1:1 v/v) at room temperature using 1% in weigth of active species and a value of the loading factor of 1.0 (the loading factor is defined as mmol of active species for gram of support). Reactions with MTO **1** and compounds **I–III** were also performed as references. In the absence of catalyst, less than 5% conversion of substrates took place under otherwise identical conditions. The oxidation results are summarized in Table 1 and Scheme 1.

The oxidation of olefins **2** and **3** with MTO gave the cycloalkene oxides **5** and **7** as the main products and diols **6** and **8** as side products (Table 1, entries 1 and 8). Lewis base adducts of MTO with monodentate ligand, **I** and **mI**, behave in a similar way and appreciable amounts of diols **6** and **8** were again observed in the reaction mixtures (Table 1, entries 2, 3 and 9, 10). Accordingly, Kühn and co-workers described the poor yield of cycloalkene oxides during the oxidation of olefins with Lewis base adducts of MTO in a 1:1 ratio.[13b] It is worth noting that the highest reactivity and selectivity were obtained with bidentate Lewis base adducts of MTO, **mII** and **mIII**, in which cases a quantitative conversion of substrate and yield of cycloalkene oxides **5** and **7** were obtained (Table 1, entries 5, 7, 12 and 14). Catalysts **mII** and **mIII** were more reactive than their parent compounds **II** and **III** (see for e.g., entry 5 vs 4 and entry 7 vs 6), **mIII** being the most reactive catalyst (Table 1, entries 6 and 14). Microencapsulated adducts **mII** and **mIII** were more efficient than **II** and **III** also during the synthesis of the sensitive styrene oxide **9** (see for e.g., Table 1, entries 19 and 21 vs entries 18 and 20, respectively). Under similar experimental conditions, MTO **1** and catalysts **I** and **mI** showed a lowest selectivity affording appreciable amounts of diol **10** (Table 1, entries 15–17).

In a test for checking the leaching of catalysts, the oxidation of **2** with **mIII** was stopped at ca. 50% conversion. After centrifugation the colourless solution lost the catalytic activity. Even if Lewis base adducts of MTO usually show a pronounced water sensitivity, catalysts **mII** and **mIII** were stable enough to perform at least five recycling experiments in the oxidation of **2** with similar conversion and selectivity (Table 2). In the fifth recycling step a very slight decrease in activity occurred with catalyst **mII**.

On the basis of these data it is reasonable to suggest that the higher activity and selectivity of Lewis base adducts **mII** and **mIII** with respect to their homogeneous parent compounds **II** and **III** can be due to the microencapsulation process. Usually, Lewis base ligands of MTO undergo exchange reactions in the presence of water (even in the case of more stabilizing bidendate ligands) by hydroxide nucleophilic substitution followed by fast decomposition of the complex with formation of methane and perrhenate.[15] Probably, the low-polarity of the microenvironment inside the polystyrene capsules stabilizes the fluxional behaviour of the MTO adducts inducing beneficial effects on the

Table 2. Stability of microencapsulated Lewis base adducts of MTO in the oxidation of **2**[a]

Catalyst[b]	Conversion (%)				
	Run. no. 1	Run. no. 2	Run. no. 3	Run. no. 4	Run. no. 5
mII	97 (>98)[a]	98(>98)	96 (>98)	95 (>98)	91 (>98)
MIII	98 (>98)	95 (>98)	97 (>98)	98 (>98)	96 (>98)

All the reactions were performed in CH_2Cl_2/MeCN (5.0 mL, 1:1 v/v) at room temperature, with H_2O_2 (35% aq solution), using a value of the catalyst loading factor of 1.0.

[a] Cycloalkene oxide yields are given in parentheses.

[b] Catalyst: MTO **1**, MTO/4-methoxyaniline **I**, microencapsulated MTO/4-methoxyaniline **mI**, MTO/2-aminomethylpyridine **II**, microencapsulated MTO/2-aminomethylpyridine **II**, MTO/*trans*-1,2-diaminocyclohexane **III**, microencapsulated MTO/2-aminomethylpyridine **mIII**.

Table 3. Epoxidations of monoterpenes with microencapsulated Lewis base adduct of MTO

Entry	Substrate	Catalyst[a]	Time (h)	Temp (°C)	Conversion (%)	Epoxide yield (%)	Diol yield (%)
1	1*S*(+)3-Carene	**1**	2.5	25	>98	20	78
2	1*S*(+)3-Carene	**II**	4.0	25	88	49	44
3	1*S*(+)3-Carene	**II**	2.5	−10	87	75	7
4	1*S*(+)3-Carene	**mII**	1.5	25	87	58	29
5	1*S*(+)3-Carene	**mII**	1.5	−10	89	91	3
6	1*S*(+)3-Carene	**III**	0.5	−10	>98	>98	0
7	1*S*(+)3-Carene	**mIII**	0.5	−10	>98	>98	0
8	*R*(+)Limonene	**1**	1.5	25	70	5	63
9	*R*(+)Limonene	**II**	2.0	25	80	25	52
10	*R*(+)Limonene	**II**	2.0	−10	98	85	0
11	*R*(+)Limonene	**mII**	2.0	25	81	55	43
12	*R*(+)Limonene	**mII**	2.0	−10	98	98	0
13	*R*(+)Limonene	**III**	1.0	−10	95	98	0
14	*R*(+)Limonene	**mIII**	2.5	−10	96	98	0
15	1*R*(+)-α-Pinene	**1**	1.0	25	>98	9	75
16	1*R*(+)-α-Pinene	**II**	1.5	25	85	16	70
17	1*R*(+)-α-Pinene	**II**	1.5	−10	>98	>98	0
18	1*R*(+)-α-Pinene	**mII**	1.5	25	95	30	55
19	1*R*(+)-α-Pinene	**mII**	2.0	−10	94	90	0
20	1*R*(+)-α-Pinene	**III**	1.0	−10	>98	>98	0
21	1*R*(+)-α-Pinene	**mIII**	1.0	−10	>98	>98	0

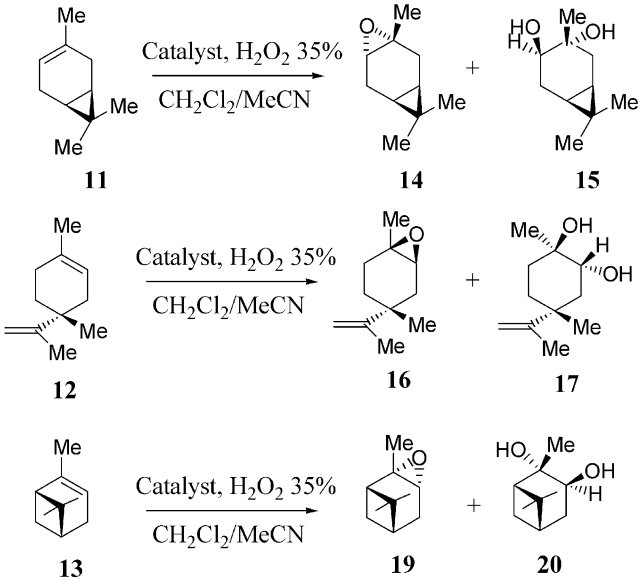
All the reactions were performed in CH_2Cl_2/MeCN (5.0 mL, 1:1 v/v), with H_2O_2 (35% aq solution), using a value of the catalyst loading factor of 1.0.

[a] Catalyst: MTO **1**, MTO/4-methoxyaniline **I**, microencapsulated MTO/4-methoxyaniline **mI**, MTO/2-aminomethylpyridine **II**, microencapsulated MTO/2-aminomethylpyridine **II**, MTO/*trans*-1,2-diaminocyclohexane **III**, microencapsulated MTO/2-aminomethylpyridine **mIII**.

catalyst properties. This hypothesis is in accord with data previously reported in the literature on the exchange phenomena for MTO adducts in solution, in which case an higher stability was observed in low polarity and non donating media with respect to polar donor solvents.[15] Under these experimental conditions microencapsulated Lewis base adducts **mII** and **mIII** are more reactive and selective than that with monodentate ligand, compound **mI**, probably because of the known higher stability of the complexes between MTO and bidentate ligands.

The attention was next addressed to the epoxidation of different representative monoterpene derivatives, 1(*S*)-(+)-3-carene **11**, *R*-(+)-limonene **12** and 1*R*-(+)-α-pinene **13** to evaluate the generality of this procedure. In the transformation of monoterpenes to perfumes, detergents, flavours and biologically active substances, the oxidative functionalization often starts with a selective epoxidation.

The reactions were performed with the most reactive catalysts **mII** and **mIII**, and in the presence of MTO and their parent compounds **II** and **III** as references as previously described. In the absence of catalyst, less than 5% conversion of substrates took place under otherwise identical conditions. The oxidation results are summarized in Table 3 and Scheme 2. The oxidation of **11** with catalyst **II** at room temperature gave the *trans*-3,4-epoxycarene **14** and the diol **15** in ca. 1:1 ratio (Table 3, entry 2). This reaction pattern was similar to that obtained with MTO



Scheme 2.

alone, in which case the diol **15** becomes the major product (Table 3, entry 1). A higher selectivity was obtained when the oxidation of **11** with catalyst **II** was performed at −10 °C. In this latter case the epoxide **14** was recovered in 75% yield beside to a small amount of diol **15** (Table 3, entry 3). Again, better results were obtained after the microencapsulation process. Thus, the epoxide **14** became the major reaction product in the oxidation of **11** with catalyst **mII** already at room temperature (Table 3, entry 4), while 89% conversion of substrate and 91% yield of **14** were obtained working at −10 °C (Table 3, entry 5). The oxidation of **11** performed both with catalysts **III** and **mIII** at −10 °C gave quantitative conversion and yield of epoxide **14** (Table 3, entries 6 and 7).

Similar results were obtained in the oxidation of *R*-(+)-limonene **12**. Thus, the reactions performed with MTO and **II** at 25 °C showed a low selectivity toward the epoxide **16**, the diol **17** being the main reaction product (Table 3, entries 8 and 9). Moreover, a quantitative conversion and 85% yield of **16** were obtained with **II** at −10 °C (Table 3, entry 10). After the microencapsulation process **II** showed the highest selectivity. Accordingly, the oxidation of **12** with **mII** afforded 55 and 98% yield of **16** at 25 and −10 °C, respectively (Table 3, entries 11 and 12). The oxidation of **12** performed both with catalysts **III** and **mIII** at −10 °C gave quantitative conversion and yield of epoxide (Table 3, entries 13 and 14). It is worthy of note that highly sensitive terpenic epoxides, such as α-pinene oxide, can be obtained in excellent yield using microencapsulated Lewis base adducts of MTO **mII** and **mIII**. Treatment of 1*R*-(+)-α-pinene **13** with **mII** and **mIII** at −10 °C afforded the α-pinene oxide **18** in quantitative conversion and yield (Table 3, entries 15 and 16). Under these experimental conditions pinanediol or products of oxiranyl ring rearrangement (campholenic aldehyde, isopinocamphone) were not identified in the reaction mixture. Again catalyst **II** increased its reactivity and selectivity after the microencapsulation process (see for e.g., Table 3 entry 18 vs entry 16 and entry 19 vs entry 17). Irrespective of the experimental conditions, compounds **III** and **mIII** were the best catalytic systems (Table 3, entries 20 and 21).

3. Conclusions

The possibility to tune the reactivity and selectivity of MTO in the oxidation of the carbon–carbon double bond is a relevant tool to further generalize the use of this compound in synthetic transformations including industrial applications. This result can be obtained performing the oxidations in the presence of Lewis bases which act as buffers of the reaction medium and as ligands for the metal atom. To date, a large excess of Lewis base is necessary to obtain high conversion of substrate and yield of product mainly because of the low stability of the adducts of MTO under the usual experimental conditions and the easy oxidation of the ligands when they are free in solution. Moreover, these catalytic systems cannot be recovered from the reaction mixture at the end of the oxidation increasing the cost of the process and the toxicity of wastes. In principle, the microencapsulation technique can resolve these problems. During the microencapsulation process the active species is entrapped inside the capsules of a stable polymeric support by non-covalent interactions. Under these conditions the metal peroxide acts in a specific microenvironment characterized by chemical–physical properties different from that existing in the bulk of the reaction mixture. In this paper we report for the first time that Lewis base adducts of MTO retain their catalytic properties after the microencapsulation with low costing and readily available polystyrene. These novel heterogeneous catalysts were found to be more reactive and selective than their homogeneous parent compounds in the epoxidation of different olefins and monoterpene derivatives. It is worth noting that a large excess of ligand was not necessary to obtain high conversion and yield of epoxide. It is reasonable to suggest that the microenvironment inside the polystyrene capsules shows a beneficial effect on the reactivity of these catalysts probably by increasing their stability with respect to the bulk of the solution. A significant effect of the polymeric support on the reactivity and selectivity of MTO was previously observed during the oxidation of phenolic derivatives. In this latter case, a poly(4-vinylpyridine)-mediated molecular recognition process based on hydrogen-bonding interactions between the pyridinyl moiety and the phenolic group was found to be operative.[21] In accord with the order of stability reported for the Lewis base adducts of MTO in solution, microencapsulated complexes of MTO with bidentate ligands, compounds **mII–mIII**, were more reactive than that with monodentate ligand **mI**. Among the bidentate ligands, aliphatic compounds appear to be more efficient than aromatic compounds. Catalysts **mII–mIII** quantitatively convert olefins to cycloalkene oxides at room temperature using environmental friendly H_2O_2 as oxidant, while a low reaction temperature (−10 °C) was necessary to obtain similar results in the oxidation of monoterpenes. All microencapsulated catalysts were stable systems for at least five recycling experiments. Values of the loading factor higher than 1.0 did not give appreciable increase in the conversion of substrates.

4. Experimental

All commercial products were of the highest grade available and were used as such. Hydrogen peroxide was a 35% aq solution (Aldrich). NMR spectra were recorder on a Bruker (200 MHz). Gas chromatography and gas chromatography–mass spectroscopy (GC–MS) of the reaction products were performed using a SPB column (25 m×0.30 mm and 0.25 mm film thickness) and isothermal temperature profile of 80 °C for the first 2 min, followed by a 10 °C/min temperature gradient to 200 °C for 10 min. The injector temperature was 200 °C. Chromatography grade helium was used as the carrier gas. In GC calculations, all peaks amounting to at least 0.3% of the total products were taken into account. When necessary, chromatographic purification were performed on columns packed with silica gel, 230–400 mesh, for flash technique. Mass spectra were recorded with an electron beam of 70 eV.

4.1. Starting materials

Methyltrioxorhenium, hydrogen peroxide, olefins **2–4** and

monoterpene derivatives **11–13** were obtained from a commercial source (Aldrich).

4.2. Synthesis of Lewis base adduct of MTO, compounds I–III.

Lewis base adducts of MTO **I–III** containing the monodentate ligand 4-methoxyaniline and the bidentate aromatic and aliphatic ligands 2-methyl aminopyridine and *trans*-1,2-diaminocyclohexane, respectively, were prepared as model compounds following a synthetic procedure previously reported in the literature.[27] As a general procedure 1.0 mmol of the appropriate monodentate ligand or 0.5 mmol of bidentate ligands were added to 1.0 mmol of MTO in toluene (10 mL) at room temperature. A yellow precipitate was immediately formed. The reaction mixture was concentrated, cooled to −35 °C and the precipitate isolated by filtration.

4.2.1. [4-(Methoxyaniline)]methyltrioxorhenium (VII) (I). IR [KBr]: ν (Re=O) cm^{-1}: 909, 934, 962. ^1H NMR ($CDCl_3$) δ ppm: 2.56 (s, 3H), 3.39 (br. s, 2H), 3.73 (s, 3H), 6.63 (d, J=9.16 Hz, 2H), 6.73, 6.63 (d, J=8.13 Hz, 2H). $C_8H_{12}NO_4Re$ calcd: C 25.80, H 3.25, N 3.76; Found C 25.93, H 3.15, N 3.74.

4.2.2. [2-(Aminomethyl)pyridine]methyltrioxorhenium (II). IR [KBr]: ν (Re=O) cm^{-1}: 908, 935. ^1H NMR (CD_3CN) δ ppm: 2.12 (s, 3H), 3.53 (br. s, 2H), 5.04 (d, J=22.0 Hz, 1H), 6.09 (d, J=22.0 Hz, 1H), 8.19 (m, 1H), 8.30 (m, 1H), 8.83 (m, 1H), 9.23 (m, 1H). $C_7H_{11}N_2O_3Re$ calcd: C 25.53, H 3.10, N 7.84; Found C 25.41, H 3.08, N 7.78.

4.3. Synthesis of microencapsulated Lewis base adduct of MTO, compounds I–III

Microencapsualted Lewis base adduct of MTO, compounds **mI–mIII**, were prepared following a modified procedure previously reported for the synthesis of polystyrene/MTO catalyst.[19b] In summary, to a suspension of 600 mg of polystirene in 4 mL of tetrahydrofuran (THF) was added 0.3 mmol of the appropriate adduct **I–III**, and the mixture was stirred for 1 h using a magnetic stirrer. Coocervates were found to envelop the solid core dispersed in the medium and 5.0 mL of hexane were added to harden the capsule walls. The solvent was removed by filtration, and the solid residue was washed with ethyl acetate and finally dried under high vacuum. In each case, MTO had completely become bound to the polymer. This result was confirmed by spectroscopic analysis of the residue obtained after evaporation of the organic layers. The catalysts were used without any further purification.

4.4. Epoxidation. General procedure

4.4.1. Epoxidation with MTO and Lewis base adducts of MTO I–III. To the suspension of the appropriate catalyst (**1** or **I–III**, 1.0% in weight) in 5.0 mL of CH_3CN/CH_2Cl_2 (ratio 1/1 v/v) at 25 °C or −10 °C (see Tables 1 and 3) was added the substrate (1.0 mmol) to be oxidised and H_2O_2 (1.5 mmol, 35% water solution). At the end of the reaction MnO_2 (2.0 mg) was added to degrade the excess of primary oxidant (the reaction mixture was found to be unchanged after the MnO_2 addition), the suspension was filtered and the filtrate dried over Na_2SO_4. After the evaporation of the solvent, the crude product was analysed by gas chromatography–mass spectroscopy and when necessary purified by flash-chromatography.

4.4.2. Epoxidation with MTO and microencapsulated Lewis base adducts of MTO mI–mIII. To the suspension of the appropriate catalyst **mI–mIII** (1.0% in weight of MTO adduct, loading factor 1.0) in 5.0 mL of CH_3CN/CH_2Cl_2 (ratio 1/1 v/v) at 25 °C or −10 °C (see Tables 1 and 3) was added the substrate (1.0 mmol) to be oxidised and H_2O_2 (1.5 mmol, 35% aq solution). At the end of the reaction the catalyst was recovered by filtration and washed with CH_2Cl_2. MnO_2 (2.0 mg) was added to degrade the excess of primary oxidant, the suspension was again filtered and the filtrate dried over Na_2SO_4. After the evaporation of the solvent, the crude product was analysed by gas chromatography–mass spectroscopy and when necessary purified by flash-chromatography. Identity of products was confirmed by 200 MHz ^1H and ^{13}C NMR and mass-spectroscopy (EI) analyses. Spectra were compared with those of authentic compounds. Listed data are available for cycloalkene oxides and styrene oxide,[19b] α-pinene oxide,[28] 3-carene oxide[29] and 1,2-limonene oxide.[30]

4.4.3. α-3,4-Epoxycarene 14. Oil, bp 182–184 °C [lit.[31], bp 182 °C], δ_H [$CDCl_3$, 200 MHz] 0.45 (1H, ddd, J=2.2, 8.9, 9.1 Hz, H-1 eq), 0.53 (1H, ddd, J=2.3, 8.9, 9.1 Hz, H-6 eq), 0.73 (3H, s, H-8), 1.01 (3H, s, H-9), 1.26 (3H, s, H-10), 1.49 (1H, dd, J=2.2, 16.2 Hz, H-2 eq), 1.64 (1H, dt, J=2.3, 16.4 Hz, H-5 eq), 2.15 (1H, dd, J=9.1, 16.2 Hz, H-2 ax), 2.30 (1H, ddd, J=1.9, 8.9, 16.4 Hz, H-5 ax), 2.85 (1H, t, J=1.9 Hz, H-4). δ_C [$CDCl_3$, 200 MHz] 13.8 (C-1), 14.6 (C-8), 15.9 (C-6), 16.0 (C-7), 19.1 (C-5), 23.1 (C-10), 23.3 (C-2), 26.7 (C-9), 56.1 (C-3), 58.3 (C-4). MS (EI) m/z 152 (M^+, 2), 137 (42), 109 (62), 91 (24), 81 (45), 67 (82), 43 (100), 39 (56).

4.4.4. α-Pinene oxide 16. Oil, bp 102–104 °C /50 mm [lit.[32], bp 102–103 °C/50 mmHg], δ_H [$CDCl_3$, 200 MHz] 0.91 (3H, s, CH_3), 1.30 (3H, s, CH_3), 1.32 (3H, s, CH_3), 1.59 (1H, m, CH), 1.72 (1H, m, CH), 1.90–2.05 (4H, m, CH_2), 3.08 (1H, m, CH). δ_C [$CDCl_3$, 200 MHz] 60.23 (s, C-1), 56.7 (d, C-2), 44.9 (d, C-6), 40.4 (s, C-10), 39.6 (d, C-4), 27.64 (t, C-5), 26.72 (q, C-9), 25.87 (t, C-3), 22.41 (q, C-8), 20.18 (q, C-7). MS (EI) m/z 152 (M^+).

4.4.5. Limonene oxide 19. Oil, bp 113–114 °C /50 mm [lit.[33], bp 113–114 °C/50 mmHg], δ_H [$CDCl_3$, 200 MHz] 4.65 (2H, m, CH_2), 3.10 (1H, m, CH), 2.97 (1H, m, CH), 2.20–1.40 (6H, 3xm, CH_2), 1.55 (3H, s, CH_3), 1.20 (3H, s, CH_3). δ_C [$CDCl_3$, 200 MHz] 20.19 (q, C-7), 22.05 (q, C-8), 25.81 (t, C-3), 28.53 (t, C-5), 30.66 (t, C-6), 40.68 (d, C-4), 57.35 (s, C-1), 59.24 (d, C-2), 109.0 (d, C-8), 148.78 (s, C-7). MS (EI) m/z 152 (M^+).

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Pd-catalyzed intramolecular cyclization of pyrrolo-2-carboxamides: regiodivergent routes to pyrrolo-pyrazines and pyrrolo-pyridines

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Abstract—Treatment of *N*-alkyl-*N*-allyl-pyrrolo-2-carboxamides with catalytic amounts of palladium derivatives gave regioselectively intramolecular cyclizations to generate bicyclic pyrrolo-fused structures. Pyrrolo[1,2-*a*]pyrazin-1-ones were achieved in high yields by an amination reaction, while pyrrolo[2,3-*c*]pyridin-7-ones and pyrrolo[3,2-*c*]pyridin-4-ones were obtained by an oxidative coupling process.

1. Introduction

Nitrogen-containing heterocycles have always constituted a subject of great interest due to their wide presence in biologically important compounds. Also in this field, the catalysis by palladium has become a powerful arm in the hands of the organic chemists.[1] All typologies of Pd-catalysis have been successfully employed: Heck[2] and Buchwald–Hartwig[3] protocols, cross coupling reactions,[4] alkene and alkyne amination,[5] oxidative coupling.[6]

As a part of an ongoing program directed to the development of palladium-catalyzed intramolecular cyclizations, we already reported efficient methods for the construction of β- and γ-carbolinones,[7–9] pyrazino[1,2-*a*]indoles,[9] quinazolinones and 1,4-benzodiazepin-5-ones,[10] dibenzodiazepinones and pyridobenzodiazepinones.[11]

In the wide range of Pd-catalyzed reactions known today, aryl- and vinyl-halides have been employed more than unhalogenated substrates despite them suffering from a general difficulty of synthesis. In an effort to expand the access to new nitrogenated heteropolycycles, we studied the behavior of *N*-alkyl-*N*-allyl-pyrrolo-2-carboxamides towards Pd-catalyzed intramolecular cyclizations. Particular interest came from the regioselective aspect of the process in the light of the possibility of reaction at the 1- and 3-positions of the pyrrole nucleus.

2. Results and discussion

As a model substrate, the unknown *N*-allyl-*N*-methyl-2-carboxamide **2a** was easily prepared starting from the pyrrole-2-carboxylic acid (Scheme 1). The first cyclization path, involving the pyrrolic nitrogen so giving the pyrrolo[1,2-*a*]pyrazine skeleton, was attained in 62% with 10 mol% of $Pd(OAc)_2$ as catalyst and DMSO as solvent at 100 °C, in presence of AcONa and tetrabutylammonium chloride. This latter, as well as a polar aprotic solvent, was essential to attain a satisfactory yield.

This amination process involves Pd(0) species as confirmed by its inhibition when operating in presence of *p*-benzoquinone as reoxidant agent. In this case, only unreacted starting material was recovered. However, the use of *p*-benzoquinone in different reaction conditions led to a new outcome involving the C-3 position of the pyrrolic ring to give a pyrrolo-pyridine skeleton by way of an oxidative coupling. More precisely, operating with $PdCl_2(CH_3CN)_2$ (10 mol%) as catalyst and a stoichiometric amount of *p*-benzoquinone in a mixture DMF/THF as solvent, the compound **2a** was totally converted in a 1:1 mixture of two products, isolated in 30 and 35% yields, respectively. The isomeric structures **4a** and **5a** were assigned on the base of the analytical and spectroscopic data. The diagnostic evidence to distinguish between the

Keywords: Amination; Fused-pyrrole system; Cyclization reactions; Palladium; Regioselectivity.
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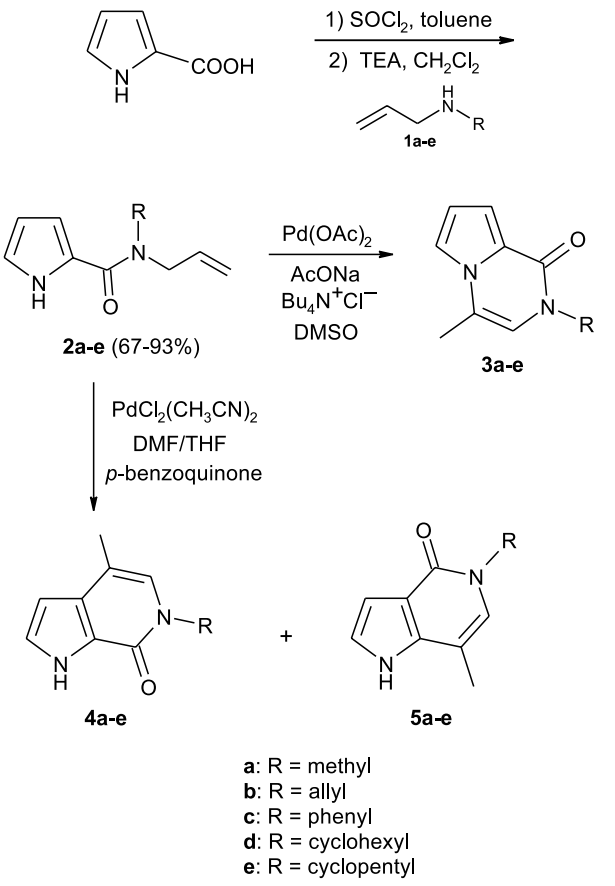
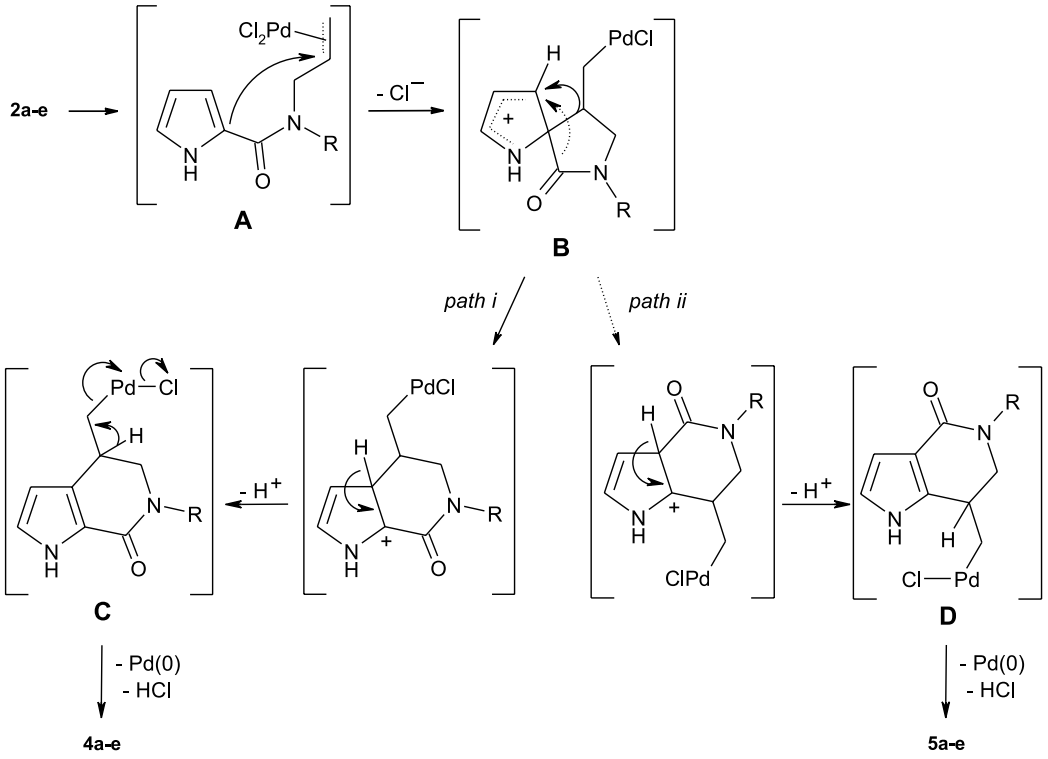


Scheme 1.

pyrrolo[2,3-*c*]pyridin-7-one (**4a**) and the pyrrolo[3,2-*c*]-pyridine-4-one (**5a**) resulted from the ^{1}H NMR and IR spectra. The chemical shift of the NH proton resonates at 10.21 δ in the former suffering of the deshielding effect of the carbonyl group, in comparison with the NH signal at 9.08 δ in the latter. On the other hand, the infrared frequency of the carbonyl group stretch is greater in compound **4a** with respect to **5a** according to analogue structures reported in the literature.[12]

A plausible mechanism, although highly speculative, is shown in Scheme 2. The olefin–palladium complex **A** would undergo the nucleophilic attack by the 2-carbon of the electron-rich pyrrole nucleus to give the transient spiro-derivative **B**. The latter would rearomatize through an anionotropic shift and subsequent loss of a proton. However, both σ bonds at the spiranic center are able to migrate so that two different skeleton types are formed, namely the Pd-σ-complexes **C** (path (i)) and **D** (path (ii)). The subsequent β-elimination afforded unisolable exo-methylenic compounds by loss of hydrochloride acid and Pd(0). Double bond migration inside the six-membered ring originated the thermodynamically more stable structures **4a** or **5a**. Finally, it must be underlined as the palladium can go back to the catalytic cycle after reoxidation due to the presence of the *p*-benzoquinone. The alternative pathway assuming a Heck type mechanism with aromatic palladation,[6j] though consistent with compound **4a**, does not justify the isomeric compound **5a**. In any case, we do not rule out both the mechanisms may be operating.

Given these results, both the reactions of amination and oxidative coupling were carried out with various substrates accessible from commercial alkyl–allyl-amines **1b–e**. The



Scheme 2.

Table 1. Yields (%) of the intramolecular cyclization products **3–5a–e**

Entry	R	**3**[a]	**4**[b]	**5**[b]
a	Methyl	62	30	35
b	Allyl	85	33	31
c	Phenyl	57	27	41
d	Cyclohexyl	89	38	45
e	Cyclopentyl	82	29	48

[a] Reaction conditions: $Pd(OAc)_2$, AcONa, Bu_4NCl, DMSO.
[b] Reaction conditions: $PdCl_2(CH_3CN)_2$, *p*-benzoquinone, DMF/THF.

latter gave the amides **2b–e** in 67–93% yields, the behavior of which resulted analogue to the model **2a**. The cyclization yields (collected in Table 1) were not significantly affected by the *N*-substituents.

In summary, using catalytic amount of palladium, we have developed regioselective cyclization conditions of *N*-allyl-pyrrolo-2-carboxamides to access to different pyrrolo-fused heterocycles. Pyrrolo[1,2-*a*]pyrazin-1-ones were generated in very high yields by an amination process when the Pd(0) species is at work. Conversely, pyrrolo[2,3-*c*]pyridin-7-ones and pyrrolo[3,2-*c*]pyridin-4-ones were formed by an oxidative coupling when using Pd(II) in the presence of an oxidant.

3. Experimental

3.1. General

Preparative column chromatography was carried out on silica gel 60 (Merck) (mesh size 63–200 μm). Melting points were measured on a Büchi B-540 heating unit and are not corrected. NMR spectra were recorded on an AVANCE 400 Bruker. IR spectra were taken on a Jasco FT/IR 5300 spectrophotometer.

3.2. General procedure for the preparation of allylamides 2a–e

A solution of 2-pyrrole-carboxylic acid (1.07 g, 9.6 mmol) and $SOCl_2$ (3.49 ml, 48 mmol) in toluene (30 ml) was refluxed for 4 h. After evaporation of the solvent, the crude mixture was taken up with CH_2Cl_2 (10 ml), then a solution of **1a–e** (14.4 mmol) and TEA (1.35 ml, 9.6 mmol) in CH_2Cl_2 (6 ml) was dropped at 0 °C. The resultant solution was stirred at room temperature for 2 h, then washed with 5% HCl (2×25 ml) and 5% aqueous NaOH (2×25 ml). The organic layer was dried over Na_2SO_4 and the solvent evaporated under reduced pressure. The crude product was chromatographed on a silica gel column to give compounds **2a–e**.

3.2.1. *N*-Allyl-*N*-methyl-pyrrolo-2-carboxamide (2a). Eluent: Et_2O/light petroleum 1:4. Yield: 93%. Mp 55–56 °C (from diisopropyl ether). IR (nujol): 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=3.20$ (3H, s), 4.23 (2H, d, $J=4.4$ Hz), 5.24 (1H, d, $J=10.5$ Hz), 5.26 (1H, d, $J=17.1$ Hz), 5.91 (1H, tdd, $J=4.4$, 10.5, 17.1 Hz), 6.24–6.29 (1H, m), 6.61 (1H, br.s), 6.95 (1H, br.s), 9.57 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=34.6$ (q), 46.2 (t), 109.9 (d), 113.0 (d), 117.5 (t), 121.8 (d), 125.1 (s), 133.4 (d), 160.3 (s). Anal. calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found C, 65.92; H, 7.25; N, 16.87.

3.2.2. *N*,*N*-Diallyl-pyrrolo-2-carboxamide (2b). Eluent: AcOEt/light petroleum 1:4. Yield: 69%. Mp 63–64 °C (from diisopropyl ether). IR (nujol): 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.19$ (4H, br.s), 5.16–5.24 (4H, overlapping), 5.86–5.95 (2H, overlapping), 6.24 (1H, dd, $J=2.3$, 2.6 Hz), 6.60 (1H, d, $J=2.3$ Hz), 6.93 (1H, d, $J=2.6$ Hz), 9.80 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=50.0$ (t), 109.6 (d), 112.9 (d), 117.5 (t), 122.5 (d), 124.6 (s), 133.7 (d), 163.6 (s). Anal. calcd for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.72. Found C, 69.56; H, 7.25; N, 14.80.

3.2.3. *N*-Allyl-*N*-phenyl-pyrrolo-2-carboxamide (2c). Eluent: AcOEt/light petroleum 4:1. Yield: 81%. Mp 117–118 °C (from diisopropyl ether). IR (nujol): 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=4.45$ (2H, d, $J=6.2$ Hz), 4.90 (1H, br.s), 5.15 (1H, d, $J=16.9$ Hz), 5.18 (1H, d, $J=10.3$ Hz), 5.90–6.12 (2H, overlapping), 6.83 (1H, br.s), 7.25–7.31 (2H, overlapping), 7.43–7.53 (3H, overlapping), 9.75 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=53.8$ (t), 110.0 (d), 114.3 (d), 118.3 (t), 121.5 (d), 125.4 (s), 128.7 (d), 129.5 (d), 130.0 (d), 133.6 (d), 143.2 (s), 161.5 (s). Anal. calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found C, 74.22; H, 6.43; N, 12.29.

3.2.4. *N*-Allyl-*N*-cyclohexyl-pyrrolo-2-carboxamide (2d). Eluent: AcOEt/light petroleum 1:5. Yield: 68%. Mp 109–110 °C (from diisopropyl ether). IR (nujol): 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.09$–1.20 (1H, m), 1.27–1.48 (2H, overlapping), 1.50–1.62 (2H, overlapping), 1.65–1.75 (1H, m), 1.78–1.85 (4H, overlapping), 4.18 (2H, d, $J=5.2$ Hz), 4.43 (1H, tt, $J=3.1$, 11.9 Hz), 5.19 (1H, d, $J=10.0$ Hz) 5.26 (1H, d, $J=17.4$ Hz), 5.92 (1H, tdd, $J=5.2$, 10.0, 17.4 Hz), 6.24 (1H, d, $J=2.9$ Hz), 6.56 (1H, br.s), 6.93 (1H br.s), 10.34 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=26.0$ (t), 26.4 (t), 31.5 (t), 46.7 (d), 56.8 (t), 109.6 (d), 112.3 (d), 116.3 (t), 121.7 (d), 125.5 (s), 136.6 (d), 163.1 (s). Anal. calcd for $C_{14}H_{20}N_2O$: C, 72.38; H, 8.68; N, 12.06. Found C, 74.41; H, 8.52; N, 12.12.

3.2.5. *N*-Allyl-*N*-cyclopenthyl-pyrrolo-2-carboxamide (2e). Eluent: AcOEt/light petroleum 1:6. Yield: 67%. Mp 94–95 °C (from diisopropyl ether). IR (nujol): 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.53$–1.82 (6H, overlapping), 1.85–2.09 (2H, overlapping), 4.16 (2H, d, $J=4.5$ Hz), 4.78–4.89 (1H, m), 5.23 (1H, d, $J=12.3$ Hz), 5.27 (1H, d, $J=18.4$ Hz), 5.94 (1H, tdd, $J=4.5$, 12.3, 18.4 Hz), 6.22 (1H, ddd, $J=2.6$, 2.7, 2.9 Hz), 6.60 (1H, br.s), 6.92 (1H, br.s), 10.50 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=24.2$ (t), 24.3 (t), 47.2 (d), 58.8 (t), 109.6 (d), 112.3 (d), 116.3 (t), 121.7 (d), 125.5 (s), 136.1 (d), 163.6 (s). Anal.

calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found C, 71.39; H, 8.51; N, 12.92.

3.3. General procedure for the cyclization to give pyrrolo[1,2-*a*]pyrazin-1-ones 3a–e

To a solution of **2a–e** (1 mmol) in DMSO (5 ml), AcONa (82 mg, 1 mmol), Bu_4NCl (277 mg, 1 mmol) and $Pd(OAc)_2$ (22.4 mg, 0.1 mmol) were added. The mixture was stirred for 72 h at 120 °C. The solution was washed with brine (50 ml) and extracted with Et_2O (2×50 ml). The organic layer was dried over Na_2SO_4 and taken to dryness under reduced pressure. The residue was chromatographed on a silica gel column to give **3a–e**.

3.3.1. 2,4-Dimethyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3a). Eluent: Et_2O/light petroleum 1:4. Yield: 62%. Oil. IR (nujol): 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 2.31 (3H, s), 3.46 (3H, s), 6.20 (1H, s), 6.62 (1H, dd, J=2.7, 3.9 Hz), 7.08 (1H, dd, J=1.6, 2.7 Hz), 7.18 (1H, dd, J=1.6, 3.9 Hz). ^{13}C NMR (100 MHz, $CHCl_3$): δ=14.9 (q), 41.2 (q), 110.6 (d), 112.8 (d), 115.8 (s), 115.9 (d), 116.1 (d), 124.7 (s), 156.4 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.60; H, 6.45; N, 17.32.

3.3.2. 2-Allyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3b). Eluent: Et_2O/light petroleum 1:4. Yield: 85%. Oil. IR (nujol): 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 2.30 (3H, s), 4.49 (2H, d, J=5.8 Hz), 5.21 (1H, d, J= 16.5 Hz), 5.25 (1H, d, J=11.3 Hz), 5.93 (1H, tdd, J=5.8, 11.3, 16.5 Hz), 6.17 (1H, s), 6.61 (1H, dd, J=2.4, 2.9 Hz), 7.08 (1H, dd, J=1.8, 2.4 Hz) 7.18 (1H, dd, J=1.8, 2.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1 (q), 48.9 (t), 111.7 (d), 112.9 (d), 114.4 (d), 116.3 (d), 116.1 (s), 118.4 (t), 124.6 (s), 133.4 (d), 155.9 (s). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.29; H, 6.25; N, 14.97.

3.3.3. 4-Methyl-2-phenyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3c). Eluent: AcOEt/light petroleum 1:4. Yield: 57%. Oil. IR (nujol): 1645 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.36 (3H, s), 6.42 (1H, s), 6.68 (1H, dd, J=3.6, 2.8 Hz), 7.16 (1H, d, J=2.8 Hz), 7.28 (1H, d, J=3.6 Hz), 7.33–7.55 (5H, overlapping). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.1 (q), 112.4 (d), 113.2 (d), 116.0 (d), 116.1 (s), 116.7 (d), 124.7 (s), 127.1 (d), 128.1 (d), 129.7 (d), 140.6 (s), 155.6 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 74.87; H, 5.59; N, 12.57.

3.3.4. 2-Cyclohexyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3d). Eluent: AcOEt/light petroleum 1:4. Yield: 89%. Oil. IR (nujol): 1624 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.10–1.35 (1H, m), 1.42–1.65 (4H, overlapping), 1.67–1.79 (1H, m), 1.83–1.95 (4H, overlapping), 2.32 (3H, s), 4.76–4.85 (1H, m), 6.26 (1H, s), 6.61 (1H, dd, J=2.8, 3.7 Hz), 7.07 (1H, dd, J=1.1, 2.8 Hz), 7.17 (1H, dd, J=1.1, 3.7 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.4 (q), 25.7 (t), 26.1 (t), 32.4 (t), 52.1 (d), 110.7 (d), 110.9 (d), 112.8 (d), 115.6 (d), 115.7 (s) 124.8 (s) 155.7 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 72.93; H, 8.02; N, 12.12.

3.3.5. 2-Cyclopenthyl-4-methyl-2*H*-pyrrolo[1,2-*a*]pyrazin-1-one (3e). Eluent: AcOEt/light petroleum 1:7. Yield: 82%. Oil. IR (nujol): 1638 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=1.55–1.94 (6H, overlapping), 2.03–2.19 (2H, overlapping), 2.34 (3H, s), 5.37 (1H, dddd, J=8.2, 8.2, 8.2, 8.2 Hz), 6.21 (1H, s), 6.61 (1H, dd, J=3.2, 3.8 Hz), 7.07 (1H, br.s), 7.16 (1H, d, J=3.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.5 (q), 25.0 (t), 31.8 (t), 54.0 (d), 110.7 (d), 111.0 (d), 112.9 (d), 115.7 (d), 116.3 (s), 124.7 (s), 156.2 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.11; H, 7.53; N, 12.83.

3.4. General procedure for the cyclization to give pyrrolo[2,3-*c*]pyridin-7-ones (4a–e) and pyrrolo[3,2-*c*]-pyridin-4-ones (5a–e)

To a solution of **2a–e** (1 mmol) in DMF (6 ml) and THF (12 ml), $PdCl_2(CH_3CN)_2$ (389 mg, 0.15 mmol) and *p*-benzoquinone (108, 1 mmol) were added under N_2. The mixture was stirred for 18 h at 100 °C, then poured into brine (30 ml) and extracted with Et_2O (2×25 ml). The solvent evaporated to give a residue that was chromatographed on silica gel column to give the compounds **4a–e** and **5a–e**.

Entry a. Elution with CH_2Cl_2/MeOH 10:1 gave **4a** (30%) and **5a** (35%).

3.4.1. 4,6-Dimethyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4a). Mp 238–239 °C (from diisopropyl ether). IR (nujol): 3394, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.26 (3H, s), 3.67 (3H, s), 6.41 (1H, dd, J=2.3, 2.5 Hz), 6.74 (1H, s), 7.31 (1H, d, J=2.3 Hz), 10.21 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): δ=15.6 (q), 36.4 (q), 102.0 (d), 112.0 (s), 123.8 (s), 126.3 (d), 127.5 (d), 132.5 (s), 155.6 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.49; H, 6.35; N, 17.13.

3.4.2. 5,7-Dimethyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5a). Mp 243–245 °C (from diisopropyl ether). IR (nujol): 3260, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.27 (3H, s), 3.62 (3H, s), 6.85 (1H, s), 6.88 (1H, dd, J= 2.5, 2.6 Hz), 7.03 (1H, dd, J=2.6, 2.6 Hz), 9.08 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): δ=13.7 (q), 36.9 (q), 105.3 (s), 106.1 (d), 115.3 (s), 122.2 (d), 129.7 (d), 139.7 (s), 160.0 (s). Anal. calcd for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found C, 66.47; H, 6.38; N, 17.12.

Entry b. Elution with CH_2Cl_2/MeOH 10:1 gave **4b** (33%) and **5b** (31%).

3.4.3. 6-Allyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4b). Mp 211–212 °C (from diisopropyl ether). IR (nujol): 3389, 1657 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ=2.27 (3H, s), 4.72 (2H, d, J=5.6 Hz), 5.17 (1H, d, J= 17.1 Hz), 5.24 (1H, d, J=10.2 Hz), 6.02 (1H, ddd, J=5.6, 10.2, 17.1 Hz), 6.37 (1H, br.s), 6.70 (1H, s), 7.30 (1H, br.s), 10.48 (1H, br.s). ^{13}C NMR (100 MHz, $CHCl_3$): δ=15.7 (q), 50.3 (t), 102.1 (d), 112.3 (s), 117.6 (t), 123.8 (s), 125.1 (d), 127.5 (d), 132.5 (s), 134.1 (d), 155.0 (s). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.24; H, 6.33; N, 15.00.

3.4.4. 5-Allyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5b). Mp 86–87 °C (from diisopropyl ether).

IR (nujol): 3270, 1649 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.26$ (3H, s), 4.67 (2H, d, $J=5.6$ Hz), 5.16 (1H, d, $J=17.1$ Hz), 5.21 (1H, d, $J=10.3$ Hz), 5.99 (1H, ddd, $J=5.6$, 10.3, 17.1 Hz), 6.81 (1H, s), 6.88 (1H, dd, $J=2.6$, 2.6 Hz), 7.01 (1H, dd, $J=2.6$, 2.7 Hz), 8.80 (1H, br.s); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.7$ (q), 50.4 (t), 105.1 (s), 106.5 (d), 115.7 (s), 117.7 (t), 121.9 (d), 128.5 (d), 134.3 (d), 139.4 (s), 159.7 (s). MS: *m/z* 188 (M^+). Anal. calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found C, 70.16; H, 6.55; N, 14.73.

Entry c. Elution with CH_2Cl_2/MeOH 15:1 gave **4c** (27%) and **5c** (41%).

3.4.5. 4-Methyl-6-phenyl-1,6-dihydro-pyrrolo[2,3-*c*]-pyridin-7-ones (4c). Mp 128–129 °C (from diisopropyl ether). IR (nujol): 3385, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.30$ (3H, s), 6.43 (1H, br.s), 6.84 (1H, s), 7.28 (1H, br.s), 7.35–7.55 (5H, overlapping), 10.75 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=15.5$ (q), 102.7 (d), 107.9 (s), 123.6 (s), 126.6 (d), 127.6 (d), 127.7 (d), 128.3 (d), 129.5 (d), 132.7 (s), 141.7 (s), 155.1 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 74.89; H, 5.43; N, 12.52.

3.4.6. 7-Methyl-5-phenyl-1,5-dihydro-pyrrolo[3,2-*c*]-pyridin-4-ones (5c). Mp 83–84 °C (from diisopropyl ether). IR (nujol): 3268, 1651 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=2.23$ (3H, s), 6.87 (1H, dd, $J=2.6$, 2.6 Hz), 6.90 (1H, br.s), 6.97 (1H, dd, $J=2.6$, 2.8 Hz), 7.32–7.54 (5H, overlapping), 9.27 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=13.7$ (q), 106.1 (d), 106.3 (s), 115.3 (s), 123.0 (d), 127.8 (d), 128.2 (d), 129.3 (d), 129.4 (d), 140.0 (s), 142.2 (s), 160.1 (s). Anal. calcd for $C_{14}H_{12}N_2O$: C, 74.98; H, 5.39; N, 12.49. Found C, 75.03; H, 5.25; N, 12.52.

Entry d. Elution with CH_2Cl_2/MeOH 20:1 gave **4d** (38%) and **5d** (45%).

3.4.7. 6-Cyclohexyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4d). Mp 120–121 °C (from diisopropyl ether). IR (nujol): 3396, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.15$–1.40 (1H, m), 1.42–1.67 (4H, overlapping), 1.74–1.83 (1H, m), 1.91–2.01 (4H, overlapping), 2.30 (3H, s), 5.03 (1H, tt, $J=3.2$, 11.6 Hz), 6.39 (1H, dd $J=2.4$, 2.7 Hz,), 6.82 (1H, s), 7.29 (1H, dd $J=2.7$, 2.7 Hz), 10.35 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.9 (t), 30.1 (t), 33.3 (t), 53.9 (d), 102.3 (d), 112.3 (s), 121.4 (d), 127.4 (s), 127.6 (d), 130.7 (s), 150.5 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 73.13; H, 7.72; N, 12.25.

3.4.8. 5-Cyclohexyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5d). Mp 251–255 °C (from diisopropyl ether). IR (nujol): 3261, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.15$–1.42 (1H, m), 1.44–1.63 (4H, overlapping), 1.70–1.78 (1H, m), 1.84–2.01 (4H, overlapping), 2.27 (3H, s), 5.01–5.15 (1H, m), 6.88 (1H, dd, $J=2.5$, 2.7 Hz), 6.90 (1H, s), 7.00 (1H, dd, $J=2.7$, 2.6 Hz), 8.85 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.9 (t), 26.4 (t), 33.3 (t), 53.2 (d), 102.3 (d), 111.6 (s), 121.4 (d), 123.8 (s), 126.7 (d), 131.4 (s), 154.6 (s). Anal. calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found C, 72.98; H, 7.95; N, 12.13.

Entry e. Elution with CH_2Cl_2/MeOH 27:1 gave **4e** (29%) and **5e** (48%).

3.4.9. 6-Cyclopentyl-4-methyl-1,6-dihydro-pyrrolo[2,3-*c*]pyridin-7-ones (4e). Mp 119–120 °C (from diisopropyl ether). IR (nujol): 3385, 1653 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.66$–1.82 (4H, overlapping), 1.83–2.00 (2H, overlapping), 2.14–2.28 (2H, overlapping), 2.29 (3H, s), 5.53 (1H, dddd, $J=8.1$ Hz), 6.37 (1H, br.s), 6.77 (1H, s), 7.27 (1H, br.s), 10.66 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=16.0$ (q), 25.1 (t), 32.8 (t), 55.2 (d), 102.2 (d), 112.2 (s), 121.4 (d), 123.7 (s), 127.0 (d), 131.5 (s), 155.2 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.02; H, 7.53; N, 12.99.

3.4.10. 5-Cyclopentyl-7-methyl-1,5-dihydro-pyrrolo[3,2-*c*]pyridin-4-ones (5e). Mp 135–136 °C (from diisopropyl ether). IR (nujol): 3256, 1641 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta=1.52$–1.83 (4H, overlapping), 1.84–2.01 (2H, overlapping), 2.10–2.28 (2H, overlapping), 2.29 (3H, s), 5.53 (1H, dddd, $J=8.0$ Hz), 6.88 (1H, dd, $J=2.3$, 2.6 Hz), 6.90 (1H, s), 7.01 (1H, dd, $J=2.6$, 2.7 Hz), 9.22 (1H, br.s). ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=14.2$ (q), 25.0 (t), 32.9 (t), 55.4 (d), 106.5 (d), 115.1 (s), 116.6 (d), 124.9 (d), 139.1 (s), 150.1 (s), 159.9 (s). Anal. calcd for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found C, 72.05; H, 7.56; N, 12.97.

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Constructing the CF_3 group; unique trifluorodecarboxylation induced by BrF_3

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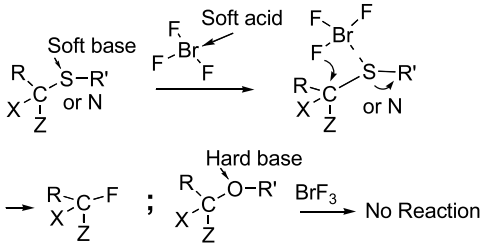
Abstract—A variety of 2-alkyl-1,3-dithiane-2-carboxylic acids was prepared from the appropriate alkyl halides, 1,3-dithiane and CO_2. These acids were reacted with BrF_3 to form the trifluoromethylalkyl derivatives via a combination of ionic and radical trifluorodecarboxylation in about 50–60% yield.

1. Introduction

The trifluoromethyl group has a great impact on a wide range of man-made chemicals such as dyes, polymers, agrochemicals, pharmaceuticals. Incorporating this group into a molecule can often modify the biological activity and physiological properties. These modifications are associated with increased stability and lipophilicity, while the steric distortion, compared to the parent compound, is relatively small. Quite a few methods for trifluoromethylation have been developed using trifluoromethyl trimethylsilane (Ruppert's reagent-CF_3SiMe_3),[1] fluoroform or trifluoromethyl halides,[2] (trifluoromethyl) dibenzothiophenium triflate salt,[3] and more.[4]

In recent years, we and others have devised several methods for incorporating fluorine atom(s) into organic molecules by employing bromine trifluoride. The synthesis of α-trifluoromethyl carboxylic acids,[5] transformation of carbonyls to the CF_2 group,[6] forming alkyltrifluoromethyl ethers,[7] synthesizing modern anaesthetics[8] and converting RX to $RCHF_2$ derivatives,[9] are only a few examples. These works have already established the conditions for selective reactions of BrF_3 with organic substrates. Such substrates should possess soft bases such as nitrogen or sulfur atoms, in order to complex the soft acidic bromine in BrF_3 and place the naked nucleophilic fluorides close to the electrophilic carbon positioned α to the heteroatom (Scheme 1).

The Hunsdiecker reaction is one of the oldest and most well known reactions in organic chemistry dealing with halodecarboxylation of carboxylic acids. Chlorine, bromine or iodine are brought in contact with the acids' salt (usually silver) forming the corresponding alkyl halides.[10] Fluorine, however, was conspicuously missing from this list of halogens. Fluorodecarboxylation reactions are very rare and the few described required xenon difluoride. These reactions proceeded through the RCOOXeF intermediate characterized by the very weak bonds around the Xe atom.[11] We now report a new method for transforming alkyl halides to the trifluoromethyl moiety via a crucial Hunsdiecker-like trifluorodecarboxylation, using BrF_3.



Scheme 1. General mechanism for selective reactions with BrF_3.

2. Results and discussion

Following a known procedure,[12] the lithium salt of dithiane (**1**) was reacted with decyl bromide (**2a**) followed by reaction with carbon dioxide to produce 2-decyl-1,3-dithiane-2-carboxylic acid (**3a**). Reacting **3a** with BrF_3 resulted in a fast trifluorodecarboxylation producing 1,1,1-trifluoroundecane (**4a**)[13] in 60% yield (Scheme 2). The reaction with the disubstituted 1,10-dibromodecane (**2b**)

Keywords: Bromine trifluoride; Trifluoromethyl; Trifluorodecarboxylation; Dithiane.
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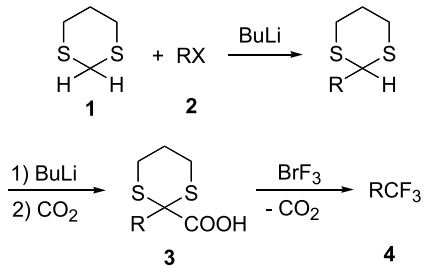


	X	2	3	4 (%)*
a	Br	R = $CH_3(CH_2)_9$		(60 %)#
b	Br	R = $Br(CH_2)_{10}$	R = HOOC $(CH_2)_{10}$	R = $CF_3(CH_2)_{10}$ (40 %)
c	Cl	R = $(CH_2)_3$		(60 %)
d	Br	R = $(CH_2)_2$		(60 %)
e	Br	R = C_6H_{13}, CH_3		(35 %)#
f	Cl	R = $Cl(CH_2)_{10}$		(55 %)#
g	Cl	R = $HO(CH_2)_8$		
h	Cl	R = $THPO(CH_2)_8$	R = $THPO(CH_2)_8$	
i			AcCl/AcOH → R = $AcO(CH_2)_8$	R = $AcO(CH_2)_8$ (50 %)

Scheme 2. Formation of trifluoromethyl derivatives. (*) Yield of the trifluorodecarboxylation step; (#) these compounds could not be fully analyzed by conventional MS (no molecular ion could be detected). However, we have successfully used the Amirav's supersonic GC–MS developed in our department. The main feature of this method is to provide electron ionization while the sample is vibrationally cooled in a supersonic molecular beam. This considerably enhances the relative abundance of molecular ions.[20]

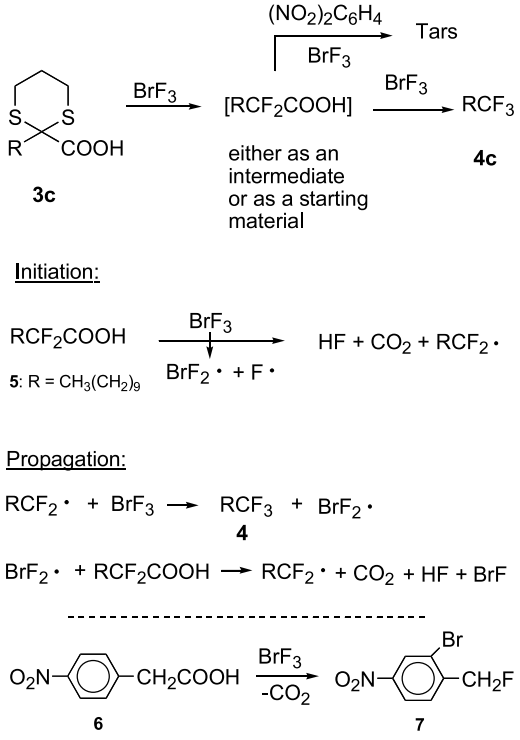
also proceeded as expected and 1,1,1,12,12,12-hexafluorododecane (**4b**)[14] was obtained in 40% yield.

While the fluorine atoms in BrF_3 can act in some cases as electrophiles,[15] substituting tertiary hydrogens in a similar way to F_2,[16] the reaction with the dithiane moiety seems to be much faster. Thus, 2-(3-cyclohexylpropyl)-1,3-dithiane-2-carboxylic acid (**3c**) and 2-(2-norbonylethyl)-1,3-dithiane-2-carboxylic acid (**3d**), made correspondingly from 1-chloro-3-cyclohexylpropane (**2c**) and 1-bromo-2-(2-norbornyl)ethane (**2d**), were reacted with BrF_3 forming the by now expected 4-cyclohexyl-1,1,1-trifluorobutane (**4c**)[17] and 2-(3,3,3-trifluoropropyl)norbornane (**4d**)[13] in 50 and 55% yields, respectively.

In many cases the chemistry of a functional group attached to a primary carbon differs from the chemistry of the same group bonded to a secondary site. The present chemistry, however, is applicable for both primary and secondary carbons. Thus, 2-bromooctane (**2e**) was eventually converted to 1,1,1-trifluoro-2-methyloctane (**4e**) although in a somewhat lower yield of 35%.

Bromine trifluoride is known to substitute chlorine atoms for fluorine ones as demonstrated in the syntheses of modern anaesthetics such as sevoflurane.[18] Here again, the reaction with the dithiane moiety is much faster, and hence chlorine atoms can be tolerated in this reaction. 1,10-Dichlorodecane (**2f**) was easily converted to 2-(10-chlorodecyl)-1,3-dithiane-2-carboxylic acid (**3f**) and when reacted with BrF_3, the previously unknown 11-chloro-1,1,1-trifluoroundecane (**4f**) was obtained in 55% yield. Despite the fact that alcohols are easily oxidized by BrF_3 to acyl fluorides,[19] the presence of an hydroxyl group in a molecule is not a reason for excluding it from the list of materials which can participate in this reaction. Protecting the hydroxyl group of 1-chloro-8-hydroxyoctane (**2g**) as a tetrahydropyranyl (THP) (**2h**) enabled the clean formation of **3h** under the strong basic conditions characteristic to BuLi. The protecting THP was then replaced by acetyl to form 2-(8-acetoxyoctyl)-1,3-dithiane-2-carboxylic acid (**3i**) suitable for the fast reaction with BrF_3 forming eventually 9,9,9-trifluorononyl acetate (**4i**) in 50% yield.

We believe that the first step of the reaction is ionic in nature. First, the sulfur atoms serve as a coordinating site for the BrF_3 and when the complexation is completed these atoms are substituted by the nucleophilic fluorides which by now are in suitable close proximity.[9,21] As a result of this substitution, however, BrF_3 can no longer complex itself around any particular site of the reactant. Consequently, radical reactions, which are always option for this reagent, become dominant and a process with a chain radical decarboxylation (Scheme 3) takes place. Indeed, when the



Scheme 3. Radical chain trifluorodecarboxylation.

reaction of **3c** with bromine trifluoride was carried under either oxygen-rich atmosphere or in the presence of dinitrobenzene, the radical chain process was interrupted and the yields of **4c** dropped to 15 and 0%, respectively. Additional support for this mechanism was found in reactions with α,α-difluoro acids. Thus, for example, α,α-difluorododecanoic acid (**5**) was reacted with BrF_3 resulting in a fast fluorodecarboxylation forming 1,1,1-trifluoroundecane (**4a**) in 60% yield. For comparison, no such reaction takes place with the corresponding dodecanoic acid itself. The fluorodecarboxylation can be explained by pointing out that the difluoromethylene radical is more stable than the methylene counterpart and better sustains a chain reaction with BrF_3 to form the CF_3 group. This hypothesis was also confirmed by reacting BrF_3 with 4-nitrophenylacetic acid (**6**). Since the benzylic radical is relatively stable, fluorodecarboxylation occurs producing 2-bromo-4-nitrobenzylfluoride (**7**) in 50% yield. The ring bromination is unavoidable as BrF_3 is a very powerful brominating agent.[22]

In conclusion, this paper widens the scope of reactions with bromine trifluoride, especially when the construction of the important trifluoromethyl group is concerned. We hope that this work will be an additional step in demonstrating that BrF_3, like F_2 some years ago, can and should be used, as a powerful fluorinating agent in organic chemistry.

3. Experimental

^1H and ^{13}C NMR were obtained at 200 and 50.2 MHz, respectively, with $CDCl_3$ as solvent and Me_4Si as an internal standard. The ^{19}F NMR spectra were measured at 188.1 MHz and are reported upfield from $CFCl_3$, serving as an internal standard. IR spectra were recorded in $CHCl_3$ solution on a FTIR spectrophotometer. HRMS spectra were measured under CI conditions. In extreme cases where the CI method could not detect the molecular ion, we have successfully used the Amirav's supersonic GC–MS developed in our department. The main feature of this method is to provide electron ionization while the sample is vibrationally cooled in a supersonic molecular beam. This considerably enhances the relative abundance of molecular ions.[20]

3.1. Preparing and handling BrF_3

Although commercially available, we usually prepare our own BrF_3 by simply passing 0.6 mol of pure fluorine through 0.2 mol of bromine placed in a copper reactor and cooled to 0–10 °C. Under these conditions, the higher oxidation state, BrF_5, will not form in any appreciable amount. The product can be stored in Teflon containers indefinitely. *Caution*: BrF_3 is a strong oxidizer and tends to react exothermically with water and oxygenated organic solvents such as acetone or THF. Any work using BrF_3 should be conducted in a well-ventilated area, and caution and common sense should be exercised.

3.2. General procedure for preparing 2-alkyl-1,3-dithiane-2-carboxylic acid derivatives.[12]

To a cold (−45 °C) THF solution of 10 mmol of 2-alkyl-1,3-dithiane was added 10.5 mmol of *n*-butyllithium (1.6 M in *n*-hexane) under nitrogen. The mixture was stirred for 1.5 h and poured on to freshly chopped dry ice. After stirring for another hour at room temperature, 10% NaOH was added. The organic layer was extracted twice with the NaOH solution and the combined alkaline layers were acidified with concentrated HCl. The aqueous layer was extracted three times with ether and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the crude product was purified by flash chromatography (using petroleum ether/ethyl acetate as eluent) or recrystallization. The main characteristic features are as follows: ^1H NMR: 3.3 (2H, td, $J_1=13$ Hz, $J_2=2.5$ Hz), 2.7 ppm (2H, dt, $J_1=13$ Hz, $J_2=3.5$ Hz); ^{13}C NMR: 177.0, 52.9 ppm; IR: 1697 cm^{-1}.

3.3. General procedure for reaction of 2-alkyl-1,3-dithiane-2-carboxylic acid derivatives with BrF_3

The 2-alkyl-1,3-dithiane-2-carboxylic acid (usually 2 mmol) was dissolved in 10–15 mL of $CFCl_3$. About 6 mmol of BrF_3 was dissolved in 10 mL the same solvent, and the resulting solution was cooled to 0 °C and added dropwise during 1–2 min to the dithiane derivative solution. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ till colorless. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography (using petroleum ether as eluent) gave the target trifluoromethyl derivatives.

3.3.1. 1,1,1-Trifluoroundecane.[13] (4a) Compound was prepared from **3a** as described above, resulting in 60% yield of an oil. ^1H NMR: 2.06–2.00 (2H, m), 1.59–1.51 (2H, m), 1.27 (14H, br s), 0.89 ppm (3H, t, $J=6.8$ Hz). ^{13}C NMR: 127.2 (q, $J=276$ Hz), 33.6 (q, $J=28$ Hz), 31.8, 29.4, 29.3, 29.2, 29.1, 28.6, 22.6, 21.8, 14.0 ppm. ^{19}F NMR: −67.0 ppm (t, $J=11$ Hz). MS (supersonic molecular beam): m/z 210 $(M)^+$.

3.3.2. 1,1,1,12,12,12-Hexafluorododecane.[14] (4b) Compound was prepared from **3b** as described above, resulting in 40% yield of an oil. ^1H NMR: 2.2–2.0 (4H, m), 1.62–1.51 (4H, m), 1.4–1.3 ppm (12H, br s). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 33.7 (q, $J=28$ Hz), 29.2, 29.1, 28.7, 21.8 ppm. ^{19}F NMR: −66.9 ppm (t, $J=11$ Hz).

3.3.3. 4-Cyclohexyl-1,1,1-trifluorobutane.[17] (4c) Compound was prepared from **3c** as described above, resulting in 55% yield of an oil. ^1H NMR: 2.06–2.00 (2H, m), 1.71–1.68 (6H, m), 1.55 (2H, m), 1.27–1.25 ppm (7H, m). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 37.8, 36.4, 34.0 (q, $J=28$ Hz), 31.1, 26.6, 26.3 ppm. ^{19}F NMR: −66.9 ppm (t, $J=11$ Hz).

3.3.4. 2-(3,3,3-Trifluoropropyl)norbornane.[13] (4d) Compound was prepared from **3d** as described above, resulting in 55% yield of an oil. ^1H NMR: 2.22 (1H, br s), 2.06–2.00 (2H, m), 1.96 (1H, br s), 1.53–1.26 (7H, m) 1.15–1.00 ppm (4H, m). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 41.7, 40.8, 37.8, 36.4, 35.1, 32.2 (q, $J=28$ Hz), 29.9, 29.6, 28.5 ppm. ^{19}F NMR: −66.8 ppm (t, $J=11$ Hz).

3.3.5. 1,1,1-Trifluoro-2-methyloctane (4e). Compound

was prepared from **3e** as described above, resulting in 35% yield of an oil. ^{1}H NMR: 2.0–2.2 (1H, m), 1.8–1.6 (2H, m), 1.3 ppm (8H, br s), 1.05 (3H, d, $J=7$ Hz), 0.89 ppm (3H, t, $J=7$ Hz). ^{13}C NMR: 128.3 (q, $J=279$ Hz), 37.6 (q, $J=26$ Hz), 31.6, 29.4, 28.7, 26.5, 22.3, 13.8 ppm. ^{19}F NMR: -73.8 ppm (d, $J=9$ Hz). MS: *m/z* 182 $(M)^+$, 162 $(M-HF)^+$, 142 $(M-2\,HF)^+$, 113 $(M-CF_3)^+$.

3.3.6. 11-Chloro-1,1,1-trifluoroundecane (4f). Compound was prepared from **3f** as described above, resulting in 55% yield of an oil. ^{1}H NMR: 3.53 (2H, t, $J=6.7$ Hz), 2.06–2.00 (2H, m), 1.77 (4H, quin, $J=6.7$ Hz), 1.30 ppm (12H, br s). ^{13}C NMR: 127.3 (q, $J=276$ Hz), 45.1, 33.7 (q, $J=28$ Hz), 32.6, 29.3, 29.2, 29.1, 28.8, 28.7, 26.7, 22.7 ppm. ^{19}F NMR: -66.9 ppm (t, $J=11$ Hz). MS (supersonic molecular beam): *m/z* 244 $(M)^+$. Anal. Calcd for $C_{11}H_{20}ClF_3$: C, 53.99; H, 8.24; Cl, 14.49. Found: C, 54.59; H, 8.45; Cl, 14.30.

3.3.7. 9,9,9-Trifluorononyl acetate (4i). Compound was prepared from **3i** as described above, resulting in 50% yield of an oil. ^{1}H NMR: 4.04 (2 H, t, $J=6.7$ Hz), 2.03 (3 H, s), 2.07–2.00 (2 H, m), 1.60–1.46 (4H, m), 1.32 ppm (8H, br s). ^{13}C NMR: 171.1, 127.2 (q, $J=276$ Hz), 64.4, 33.6 (q, $J=28$ Hz), 28.9, 28.8, 28.5, 28.4, 25.7, 21.7, 20.8 ppm. ^{19}F NMR: -67.0 ppm (t, $J=11$ Hz). IR: 1720 cm^{-1}. HRMS (CI) (*m/z*): $(MH)^+$ calcd for $C_{11}H_{19}F_3O_2$, 241.1425; found, 241.1454. Anal. Calcd for $C_{11}H_{19}F_3O_2$: C, 54.99; H, 7.97. Found: C, 54.98; H, 8.08.

3.3.8. 2-Bromo-4-nitrobenzylfluoride (7). About 18 mmol of BrF_3 was dissolved in 25 mL of $CFCl_3$, and the resulting solution was cooled to 0 °C and added dropwise during 1–2 min to a solution of 4-nitrophenylacetic acid (**6**) (10 mmol) in 40 mL of $CFCl_3$. The reaction mixture was quenched with aqueous $Na_2S_2O_3$ till colorless. The aqueous layer was extracted twice with CH_2Cl_2 and the organic layer was dried over $MgSO_4$. Evaporation of the solvent followed by purification by flash chromatography (using petroleum ether/ethyl acetate as eluent) gave **7** in 50% yield. ^{1}H NMR: 8.42 (1 H, d, $J=2$ Hz), 8.24 (1 H, dd, $J=8.5$, 2 Hz), 7.67 (1 H, d, $J=8.5$ Hz) 5.53 (2H, d, $J=47$ Hz). ^{13}C NMR: 148.0, 143.1 (d, $J=18$ Hz), 127.6 (d, $J=11$ Hz), 127.5, 122.5, 120.3 (d, $J=6$ Hz) 82.7 (d, $J=174$ Hz) ppm. ^{19}F NMR: -222.4 ppm (t, $J=46$ Hz). HRMS (CI) (*m/z*): $(MH)^+$ calcd for $C_7H_5BrFNO_2$, 233.9559; found, 233.9566. Anal. Calcd for $C_7H_5BrFNO_2$: C, 35.93; H, 2.15; F, 8.12; Br, 34.14; N, 5.99. Found: C, 35.55; H, 2.05; F, 7.67; Br, 34.21; N, 5.68.

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Synthesis of novel 2,5-dihydro-1,5,2-diazaphosphinines from primary enamine phosphonates and from alkyl phosphonates

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Abstract—A simple method for the preparation of phosphorus-containing pyrimidine analogues such as 2,5-dihydro-2-ethoxy-1,5,2-diazaphosphinine 2-oxides **9**, **12–15** and adducts **3**, **10** is described. Dihydrophosphinines **9**, **12–15** are prepared from primary enamine phosphonates and nitriles or from phosphonates and nitriles in the presence of base, while highly stable hydrogen-bonded amine-dihydro-diazaphosphinine adducts **3**, **10** are obtained by the addition of amine to dihydrophosphinines **9** or by reaction of alkylphosphonates with nitriles in the presence of LDA.

1. Introduction

Pyrimidine derivatives (**I**, X=CH_2, CO, Fig. 1) are widely used in organic and medicinal chemistry.[1,2] Furthermore, the incorporation of phosphorus into organic molecules could increase their biological activity,[3] For these reasons, we aimed to incorporate a phosphorus atom into the pyrimidine ring systems **I**. However, very few examples of synthesis of 1,5,2-diazaphosphinine derivatives have been reported[4,5] and, as far as we know, no examples of 2,5-dihydro-1,5,2-diazaphosphinines (**II** Fig. 1) have been described. Moreover, in recent years special interest has been focused on developing synthetic methods for the preparation of fluorine-containing molecules with biological activity and commercial applications.[6]

In this context, we have described new methods for the preparation of phosphorus substituted nitrogen heterocycles[7] from functionalized phosphine oxides and phosphonates and the synthetic uses of amino phosphorus derivatives as starting materials for the preparation of phosphorus-containing heterocycles.[5a,8]

Continuing with our interest in the synthesis of new phosphorus heterocycles and in the reactivity of functionalized enamines,[9] we report here simple syntheses of 2,5-dihydro-1,5,2-diazaphosphinines **II** from nitriles **IV** and primary β-enamine phosphonates **III** (Fig. 2, route a) and/or alkyl phosphonates **V** (Fig. 1, route b).

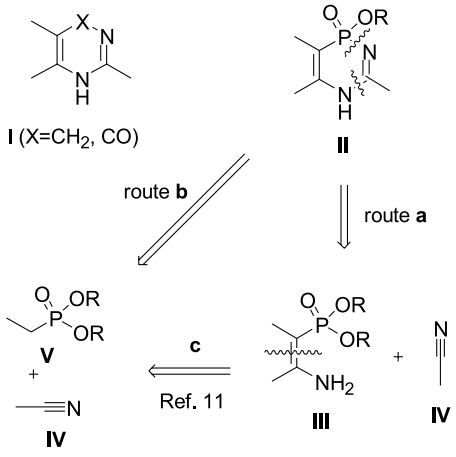

Figure 1.

2. Results and discussion

2.1. Reaction of alkylphosphonates 1 with fluoroalkylated nitriles 2

In the course of our studies for the development of new

Keywords: 1,5,2-Diazaphosphinine; Enamine; Phosphonate; Fluorinated compounds.
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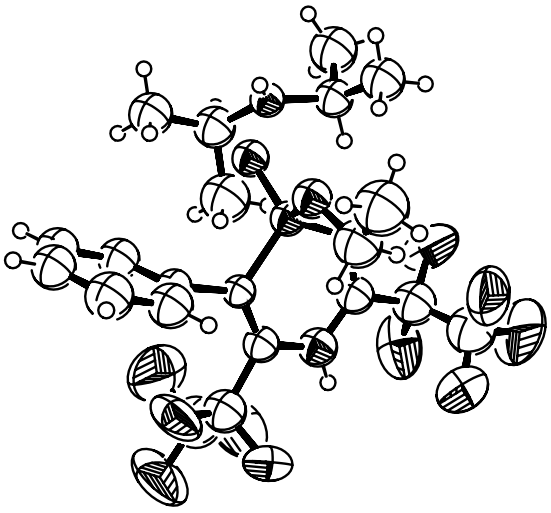
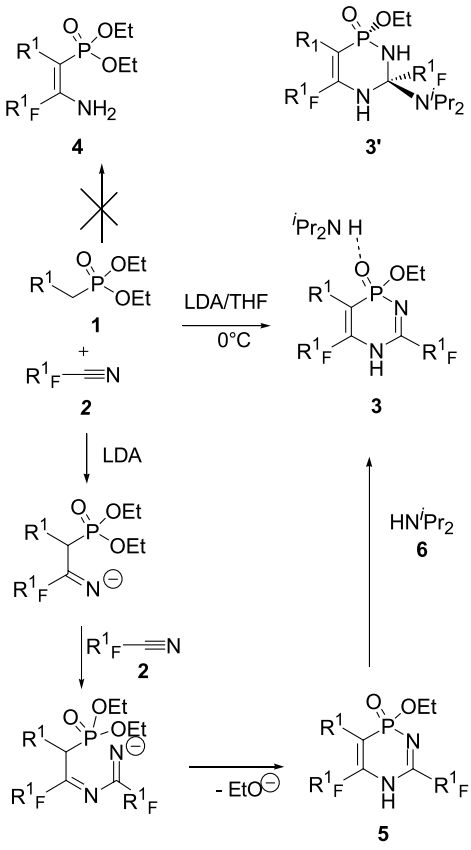


Figure 2.

building blocks containing fluoroalkyl substituents[10] and given the interest gained over recent years in organofluorine compounds,[6] we tried to explore the preparation of fluorinated enamines **III** (Fig. 1), considering that these compounds could be prepared through a similar strategy to that reported for β-enaminophosphonates by reaction of metallated alkylphosphonates and nitriles (Fig. 1, route c).[11] However, when 2,2,3,3,3-pentafluoropropionitrile[12] gas **2** ($R_F^1=C_2F_5$) was bubbled at 0 °C through a solution of diethyl methylphoshonate **1a** ($R^1=H$) in the presence of Lithium Diisopropylamine (LDA), and in an inert atmosphere, after work-up an adduct of diisopropylamine and 2,5-dihydro-1,5,2-diazaphosphinine **3a** ($R^1=H$; $R_F^1=C_2F_5$) was obtained in very high yield (Scheme 1, Table 1, entry 1), instead of the expected primary enamine **4**. The scope of the reaction was not limited to diethyl methylphosphonate **1a** ($R^1=H$), given that ethylphosphonate **1b** ($R^1=CH_3$) and benzylphosphonate **1c** ($R^1=C_6H_5$) also reacted with nitrile **2** ($R_F^1=C_2F_5$) to give similar adducts **3b**, **3c** (Scheme 1) in good yields (see Table 1, entries 2 and 3).

Spectroscopic data were initially consistent not only with 1,2,5,6-tetrahydro-1,5,2-diazaphosphinines **3′** but also with the structure of adducts **3**. Thus, for compound **3c**, in ^{19}F NMR these appeared four signals at $\delta_F=-59.1$, $-68,4$. $-95,0$ and -95.5 ppm for both pentafluoroethyl groups, while ^{31}P NMR spectrum showed only an absorption at $\delta_P=$ 21.8 ppm. Likewise, in the ^1H NMR spectrum signals for methyl groups of diisopropylamine at $\delta_H=0.94$ and



Scheme 1.

0.96 ppm, while the ^{13}C NMR spectrum showed absorptions at $\delta_C=110.3$ ppm ($^1J_{PC}=133.4$ Hz), $\delta_C=148.7$ ppm ($^2J_{FC}=24.3$ Hz, $^2J_{PC}=10.0$ Hz) and at $\delta_C=156.0$ ppm ($^2J_{FC}=25.2$ Hz) for C-3, C-4 and C-6. The X-ray diffraction analysis of compound **3c** confirms the structure of hydrogen-bonded amine-1,5,2-diaza-phosphinine adduct. The corresponding ORTEP drawing is shown in Figure 2. Hydrogen-bonded amine-phosphine oxide[13a–c] and amine-phosphonate[13d,e] adducts have been described; however, as far as we know, this process represent the first example of stable hydrogen-bonded amine-1,5,2-diaza-phosphinine derivatives.

The exclusive formation of hydrogen-bonded adducts **3** suggests the presence of an excess of nitrile, since the nitrile is gas and was bubbled through the reaction mixture, hindering the estequiometric control of the reagent. Therefore, as is illustrated in Scheme 1 the formation of these

Table 1. Fluoroalkyl substituted 2,5-dihydro-1,5,2-phosphinines **3**, **9**, and **10**

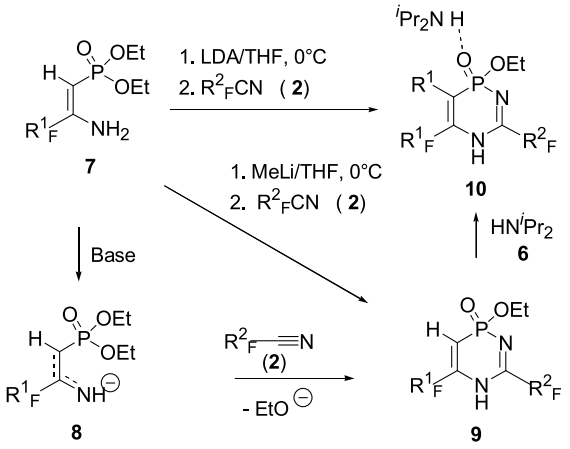
Entry	Compound	R^1	R_F^1	R_F^2	Yield (%)[a]
1	**3a**	H	C_2F_5		92[b]
2	**3b**	CH_3	C_2F_5		81[b]
3	**3c**	C_6H_5	C_2F_5		95[b]
4	**9a**		CF_3	CF_3	30[c]
5	**9b**		CF_3	C_7F_{15}	47[c]
6	**10a**		CF_3	C_2F_5	80[c]
7	**10b**		CF_3	C_7F_{15}	49[c] (99)[d]

[a] Yield of isolated purified compounds.
[b] Yield from phosphonates **1**.
[c] Yield from enaminophosphonates **7**.
[d] Yield from dihydrophosphine **9b**.

amine–diazaphosphine adducts **3** could be explained by nucleophilic addition of 2 equiv of fluorinated nitrile **2** to metallated phosphonate followed by cyclocondensation reaction with the loss of ethanol to give 2,5-dihydrophosphinines **5**, in a similar manner to that reported for 1,4,2-benzodiazaphosphepin-5-ones.[14] Subsequent reaction of diisopropylamine (from LDA) with heterocycles **5** could afford stable solid adducts **3**. In order to test whether proposed unknown heterocycles **5**[9] could be formed, we tried to prepare and isolate this type of phosphorus heterocycles **5**.

2.2. Reaction of fluoroalkylated enaminophosphonates 7 with fluoroalkylated nitriles 2

Primary enamines **7**,[10a] were used as starting materials for the preparation of heterocycles **9**. Initially, the reaction of primary enamine **7** ($R^1_F=CF_3$) with perfluoro propanonitrile **2** ($R^2_F=C_2F_5$) and octanenitrile **2** ($R^2_F=C_7F_{15}$)[12] in the presence of LDA at 0 °C was explored. However, dihydrophosphinine **9** was not isolated and hydrogen-bonded diisopropylamine-2,5-dihydro-phosphinine **10a** ($R^1_F=CF_3$, $R^2_F=C_2F_5$) and **10b** ($R^1_F=CF_3$, $R^2_F=C_7F_{15}$) were obtained, instead (Scheme 2, Table 1, entries 6 and 7). As before, the formation of these crystalline adducts **10** could be explained by addition of diisopropylamine (from LDA) to dihydrophosphinines **9** initially generated (Scheme 2).



Scheme 2.

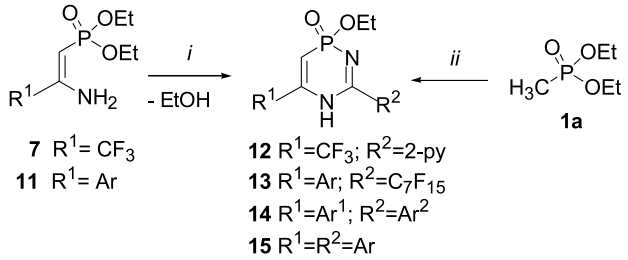
In order to avoid the presence of the amine (Diisopropylamine) in the reaction mixture, and therefore to hinder its addition to heterocycles **9**, we changed the base from LDA to Methyl Lithium (MeLi). Thus, the addition of perfluoronitriles[12] **2** ($R^2_F=CF_3$) and **2** ($R^2_F=C_7F_{15}$) to a solution of enamine **7** ($R^1_F=CF_3$) in the presence of MeLi at 0 °C and subsequent work-up gave 4,6-perfluoro disubstituted 2-ethoxy-2,5-dihydro-1,5,2-diaza-phosphinine 2-oxides **9** (Scheme 2) with the same fluoroalkyl substituents **9a** ($R^1_F=R^2_F=CF_3$) or different **9b** ($R^1_F=CF_3$; $R^2_F=C_7F_{15}$) in moderate yields (see Table 1, entries 4 and 5). Spectroscopic data were consistent with the structure of compounds **9**. The ^{1}H NMR spectrum of **9a** showed a doublet at $\delta=5{,}65$ ppm ($^2J_{PH}=4.6$ Hz) for H-3, and in the ^{13}C NMR spectrum there appeared a doublet at $\delta_C=94.0$ ppm ($^1J_{PC}=147.5$ Hz) for C-3, as well as two quadruplets at $\delta_C=155.6$ ppm ($^2J_{FC}=36.2$ Hz) and at $\delta_C=159.5$ ppm ($^2J_{FC}=35.2$ Hz) for C-4 and C-6. ^{31}P NMR spectrum showed only an absorption at $\delta_P=20.0$ ppm while in ^{19}F NMR two signals appeared at $\delta_F=-73.4$ and -74.5 ppm for both non-equivalent trifluoromethyl groups.

Formation of compounds **9** can be explained by nucleophilic addition of metallated enamines **8** to nitriles **2**, followed by cyclocondensation reaction with the loss of ethanol, in a similar manner to that described before in Scheme 1. As far as we know, with the exception of our previous communication,[9] this process represent the first synthesis of 2,5-dihydrophosphinine derivatives.

Then, in order to confirm the proposed mechanism for the formation of hydrogen-bonded amine-2,5-dihydrophosphinine adducts **10**, we studied the addition of diisopropylamine to heterocycles **9**. The reaction of diisopropylamine **6** (1 equiv) with 2,5-dihydro-1,5,2-diazaphosphinine **9b** gave stable solid adduct **10b** (Scheme 2, in almost quantitative yield (see Table 1, entry 7).

2.3. Reaction of enaminophosphonates 7 and 11 with nitriles

Next, we tried to generalize the process and to extend the strategy for the preparation of 4- or 6-perfluoroalkyl diazaphosphinines and to explore whether fluorinated **7** and simple primary β-enamino-phosphonates **11** could also be useful intermediates for the preparation of 2,5-dihydro-1,5,2-diaza-phosphinines containing only a fluoroalkyl group. Treatment of primary enamine **7** ($R^1=CF_3$) with methyllithium, followed by the addition of 2-pyridylnitrile ($R^2=$2-pyridyl) afforded 2-ethoxy-2-oxo-6-(2-pyridyl)-4-trifluoromethyl-2,5-dihydro-1,5,2-diazaphosphinine **12** ($R^1=CF_3$, $R^2=$2-pyridyl) (Scheme 3) in good yield (see Table 2, entry 1).



Scheme 3.

Similarly, primary β-enamino-phosphonates derived from aromatic **11a** ($R^1=C_6H_5$) and heteroaromatic **11b** ($R^1=$2-furyl) nitriles[11] reacted with perfluoro-octanenitrile ($R^2=C_7F_{13}$) to give 2-ethoxy-2-oxo-4-phenyl- **13a** ($R^1=C_6H_5$, $R^2=C_7F_{13}$) and 2-ethoxy-4-(2-furyl)-2-oxo-6-(perfluoro-heptyl)-2,5-dihydro-1,5,2-diazaphosphinine **13b** ($R^1=$2-furyl, $R^2=C_7F_{13}$) (see Table 2, entries 2 and 3). The

Table 2. 2,5-Dihydro-1,5,2-diazaphosphinines **12–15**

Entry	Compound	R^1	R^2	Yield (%)[a]
1	**12**	CF_3	2-Pyridyl	76
2	**13a**	C_6H_5	C_7F_{15}	52
3	**13b**	2-Furyl	C_7F_{15}	45
4	**14a**	2-Furyl	2-Pyridyl	48
5	**14b**	C_6H_5	2-Furyl	46
6	**14c**	C_6H_5	2-Pyridyl	54
7	**15a**	2-Furyl	2-Furyl	62[b]
8	**15b**	2-Pyridyl	2-Pyridyl	74[b]

[a] Yield of isolated purified compounds.
[b] One-pot procedure from methyl phosphonate diethyl ester **1a**.

process was extended to the preparation of 2,5-dihydro-1,5,2-diazaphosphinine **14** without fluoroalkyl substituents, when primary β-enamino-phosphonates **11a** ($R^1=C_6H_5$), **11b** ($R^1=$2-furyl) were treated with butyllithium followed by the addition of heteroaromatic nitriles ($R^1=$2-furyl, 2-pyridyl) and after work-up 2,5-dihydro-1,5,2-diaza-phosphinines **14** (Scheme 3) were obtained (see Table 2, entries 4–6).

From a synthetic point of view, it is noteworthy that these phosphorus analogues of 1,4-dihydropyrimidines **15**, can also be obtained 'one pot' from phosphonate **1a**. Reaction of phosphonate **1a** with butyllithium followed by the addition of excess of nitriles ($R^1=$2-furyl, 2-pyridyl) and subsequent work-up gave 2,5-dihydro-1,5,2-diaza-phosphinines **15** (Scheme 3) in good yields (see Table 2, entries 7 and 8). Therefore, the scope of the reaction was not limited to the preparation of 2,5-dihydro-1,5,2-diaza-phosphinine **15** with the same substituents in positions 4 and 6 ($R^1=R^2$) given that 'phospha-dihydro-pyrimidines' **12–14** with different substituents (C4 and C6) can also be obtained.

3. Conclusion

In conclusion, a simple and efficient strategy for the first synthesis of 2,5-dihydro-1,5,2-diazaphosphinines **9**, **12–15** and hydrogen-bonded diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinines **3**, **10** is described. These stable adducts **3**, **10** are obtained either one pot by reaction of fluorinated nitriles **2** to alkyl phosphonates **1** in the presence of LDA or 'step by step' by reaction of metallated primary enamine phosphonates **8** and perfluorated nitriles **2** followed by addition of amine to 2,5-dihydro-1,5,2-diazaphosphinines **9**. These phosphorus-containing pyrimidine analogues **9** are prepared by reaction of primary enamine phosphonates **7** and perfluorated nitriles **2**. The reaction can be extended not only to monofluoro substituted 1,5,2-diazaphosphinines **12**, **13**, but also to non-fluoro substituted 1,5,2-diaza-phosphinines **14**, **15**. 1,4-Dihydro-pyrimidine derivatives,[1,2] their phosphorus-containing pyrimidine analogues[4,5] and fluorinated building blocks[6] are useful compounds not only for their application in organic synthesis but also for their biological activities. These results may expand the scope and potential of phosphorus and fluorine preparative organic synthesis.

4. Experimental

4.1. General

Solvents for extraction and chromatography were of technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use. All other reagents were recrystallized or distilled as necessary. All reactions were performed under an atmosphere of dry nitrogen. Analytical TLC was performed with Merck silica gel 60 F_{254} plates. Visualization was accomplished by UV light. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh ASTM). Melting points were determined with an Electrothermal IA9100 Digital Melting Point Apparatus and are uncorrected. ^{1}H (400, 300 MHz), ^{13}C (100, 75 MHz) and ^{31}P NMR (120 MHz) spectra were recorded on a Bruker Avance 400 MHz and a Varian Unity 300 MHz Plus spectrometer using $CDCl_3$ or CD_3OD solutions with TMS as an internal reference ($\delta=$ 0.00 ppm) for ^{1}H and ^{13}C NMR spectra and phosphoric acid (85%) ($\delta=0.0$ ppm) for ^{31}P NMR spectra. ^{19}F NMR spectra were recorded at 282 MHz with $FCCl_3$ as an external reference ($\delta=0.0$ ppm). Chemical shifts (δ) are reported in ppm. Coupling constants (J) are reported in Hertz. Low-resolution mass spectra (MS) were obtained at 50–70 eV by electron impact (EIMS) on a Hewlett Packard 5971 spectrometer or by chemical ionization (CI) on a Hewlett Packard 1100 MSD spectrometer. Data are reported in the form m/z (intensity relative to base = 100). Infrared spectra (IR) were taken on a Nicolet IRFT Magna 550 spectrometer, and were obtained as solids in KBr or as neat oils. Peaks are reported in cm^{-1}. Elemental analyses were performed in a LECO CHNS-932 apparatus. Enamines **7**[10a] and **11**[11] were prepared according to literature procedures.

4.2. General procedure for the preparation of Diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinine adducts 3

The corresponding diethyl alkylphosphonate **1** (5 mmol) in THF (10 mL) was added to a solution of Lithium Diisopropylamine (LDA) (5 mmol) in THF (10 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, then 2,2,3,3,3-pentafluoro propionitrile[12] **2** ($R_F^1=C_2F_5$) was bubbled and the mixture was stirred at room temperature for 15 h. The crude was extracted with dichloromethane and the organic layer was dried over anhydrous magnesium sulfate. Evaporation of

solvent under reduced pressure and recrystallization from diethyl ether afforded compounds **3**.

4.2.1. Diisopropylamine-2-ethoxy-2-oxo-4,6-bis(pentafluoro ethyl)-2,5-dihydro-1,5,2-diazaphosphinine adduct (3a). The general procedure was followed using diethyl methylphosphonate **1a** (760 mg, 5 mmol). Recrystallization from diethyl ether gave 2290 mg (4.61 mmol) (92%) of compound **3a**; mp 133–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, $^3J_{HH}=6.9$ Hz, 3H), 1.21 (s, 6H), 1.24 (s, 6H), 3.20 (m, 2H), 3.37 (q, $^3J_{HH}=7.0$ Hz, 2H), 5.54 (d, $^2J_{PH}=5.7$ Hz, 1H), 8.27 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.8, 19.1, 47.4, 62.0, 91.4 (d, $^1J_{PC}=144.0$ Hz), 105.4–125.2 (m), 155.3 (dt, $^2J_{FC}=25.2$ Hz, $^2J_{PC}=5.6$ Hz), 157.8 (t, $^2J_{FC}=24.7$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.1, −82.9, −118.1, −119.9 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 22.1 ppm; IR (KBr) ν_{max} 3280, 1219, 1186 cm^{-1}; MS (EI): *m*/*z* 397 ($M^+-N^iPr_2$, 32). Anal. Calcd for $C_{15}H_{22}F_{10}N_3O_2P$: C, 36.21; H, 4.43; N, 8.46. Found: C, 35.87; H, 4.35; N, 8.48.

4.2.2. Diisopropylamine-2-ethoxy-3-methyl-2-oxo-4,6-bis (pentafluoroethyl)-2,5-dihydro-1,5,2-diazaphosphinine adduct (3b). The general procedure was followed using diethyl ethylphosphonate **1b** (830 mg, 5 mmol). Recrystallization from diethyl ether gave 2070 mg (4.06 mmol) (81%) of compound **3b**; mp 112–113 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.15 (t, $^3J_{HH}=6.9$ Hz, 3H), 1.25 (s, 6H), 1.28 (s, 6H), 2.05 (d, $^3J_{PH}=12.9$ Hz, 3H), 3.24 (m, 2H), 3.41 (dq, $^3J_{HH}=7.0$ Hz, $^3J_{PH}=26.5$ Hz, 2H), 7.74 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.3, 15.8, 19.1, 47.1, 61.5, 105.2 (d, $^1J_{PC}=133.9$ Hz), 106.1–124.8 (m), 148.7 (dt, $^2J_{FC}=23.7$ Hz, $^2J_{PC}=9.0$ Hz), 154.7 (t, $^2J_{FC}=24.6$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.7, −65.6, −94.7, −95.2 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 26.3 ppm; IR (KBr) ν_{max} 3240, 1215, 1170 cm^{-1}; MS (EI): *m*/*z* 411 ($M^+-N^iPr_2$, 41). Anal. Calcd for $C_{16}H_{24}F_{10}N_3O_2P$: C, 37.57; H, 4.69; N, 8.21. Found: C, 37.33; H, 4.55; N, 7.93.

4.2.3. Diisopropylamine-2-ethoxy-2-oxo-3-phenyl-4,6-bis (pentafluoroethyl)-2,5-dihydro-1,5,2-diazaphosphinine adduct (3c). The general procedure was followed using diethyl benzylphosphonate **1c** (1140 mg, 5 mmol). Recrystallization from diethyl ether gave 2270 mg (4.75 mmol) (95%) of compound **3c**; mp 137–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 6H), 0.96 (s, 6H), 1.14 (t, $^3J_{HH}=7.2$ Hz, 3H), 2.89 (s, 2H), 3.45 (s, 2H), 7.08–7.21 (m, 5H), 7.80 (s, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.7, 18.7, 46.9, 61.5, 108.9–127.4, 110.3 (d, $^1J_{PC}=133.4$ Hz), 127.6–133.3 (m), 148.7 (dt, $^2J_{FC}=24.3$ Hz, $^2J_{PC}=10.0$ Hz), 156.0 (t, $^2J_{FC}=25.2$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.1, −68.4, −95.0, −95.5 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 21.8 ppm; IR (KBr) ν_{max} 3211, 1220, 1157 cm^{-1}; MS (EI): *m*/*z* 473 ($M^+-N^iPr_2$, 45). Anal. Calcd for $C_{21}H_{26}F_{10}N_3O_2P$: C, 43.97; H, 4.53; N, 7.33. Found: C, 43.75; H, 4.21; N, 7.49.

4.3. X-ray analysis of compound 3c

A colourless prismatic crystal of $C_{21}H_{26}F_{10}N_3O_2P$ having approximate dimensions of $0.17\times0.14\times0.08$ mm^3 was mounted on a glass fiber. All measurements were carried out by means of a STOE IPDS diffractometer with graphite monochromated Mo Kα radiation. Crystal data: $C_{21}H_{26}F_{10}N_3O_2P$, $T=293$ K, monoclinic, space group $P2_1/n$, with $a=10.6750(10)$ Å, $b=23.164(2)$ Å, $c=12.1390(10)$ Å, $\beta=115.970(10)°$, $V=2698.6(4)$ Å^3 and $Z=4$ ($d_{calc}=1.414$ g cm^{-3}), μ(Mo Kα)$=0.194$ mm^{-1}, no absorption correction; 8138 unique reflections, but only 669 with $I>2\sigma(I)$; $R=6.0\%$, $R_w=13.5\%$ for reflections with $I>2\sigma(I)$. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 256027.

4.3.1. Procedure for the preparation of 2-ethoxy-2-oxo-4,6-bis(trifluoromethyl)-2,5-dihydro-1,5,2-diazaphosphinine (9a). To diethyl 2-amino-3,3,3-trifluoro-1-propenylphosphonate **7** (494 mg, 2 mmol) in THF (10 mL) was added a solution of MeLi 1.6 M in diethyl ether (1.25 mL, 2 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, then the mixture was cooled at −78 °C and the trifluoroacetonitrile.[12] **2** was bubbled. The reaction was allowed to room temperature and stirred until TLC showed the disappearance of enamine **7**. Saturated NH_4Cl solution was added and the organic layer was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and chromatographic purification gave 178 mg (0.6 mmol) (30%) of compound **9a** as an oil; R_f 0.12 (hexane/ethyl acetate, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.14 (t, $^3J_{HH}=7.0$ Hz, 3H), 3.46–3.57 (m, 2H), 5.65 (d, $^2J_{PH}=4.6$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.4, 63.7, 94.0 (d, $^1J_{PC}=147.5$ Hz), 121.2 (dq, $^3J_{PC}=24.2$ Hz, $^1J_{FC}=277.5$ Hz), 123.2 (dq, $^3J_{PC}=19.1$ Hz, $^1J_{FC}=274.5$ Hz), 155.6 (q, $^2J_{FC}=36.2$ Hz) 159.5 (q, $^2J_{FC}=35.2$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.4, −74.5 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 20.0 ppm; IR (KBr) ν_{max} 3390, 2990, 1580, 1486, 1385 cm^{-1}; MS (EI): *m*/*z* 297 ($M^+ + 1$, 10). Anal. Calcd for $C_7H_7F_6N_2O_2P$: C, 28.39; H, 2.38; N, 9.46. Found: C, 28.17; H, 2.45; N, 9.61.

4.3.2. Procedure for the preparation of 2-ethoxy-2-oxo-6-perfluorohepthyl-4-trifluoromethyl-2,5-dihydro-1,5,2-diazaphosphinine (9b). To diethyl 2-amino-3,3,3-trifluoro-1-propenylphosphonate **7** (494 mg, 2 mmol) in THF (6 mL) was added a solution of MeLi 1.6 M in diethyl ether (1.25 mL, 2 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, then a solution of the perfluorooctanonitrile[12] **2** in THF (6 mL) was added. The reaction was allowed to room temperature and stirred until TLC showed the disappearance of enamine **7**. Saturated NH_4Cl solution was added and the organic layer was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and purification by recrystallization from diethyl ether gave 560 mg (0.94 mmol) (47%) of compound **9b**; mp 113–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (t, $^3J_{HH}=7.0$ Hz, 3H), 3.56–3.66 (m, 2H), 5.80 (d, $^2J_{PH}=4.6$ Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 65.5, 95.6 (d, $^1J_{PC}=149.1$ Hz), 110.4–119.8 (m), 125.1 (dq, $^3J_{PC}=19.6$ Hz, $^1J_{FC}=274.5$ Hz), 158.1 (q, $^2J_{FC}=28.7$ Hz) 161.5 (t, $^2J_{FC}=24.7$ Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.0, −82.2, −115.7,

−115.8, −121.9, −122.7, −123.5, −127.1 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 19.6 ppm; IR (KBr) ν_{max} 3417, 2994, 1575, 1488, 1255, 1209,1147 cm^{-1}; MS (EI): *m/z* 597 ($M^+ + 1$, 100). Anal. Calcd for $C_{13}H_7F_{18}N_2O_2P$: C, 26.19; H, 1.18; N, 4.70. Found: C, 26.37; H, 1.07; N, 4.61.

4.4. General procedure for the preparation of Diisopropylamine-2,5-dihydro-1,5,2-diazaphosphinine adducts 10

To the β enaminephosphonate **7** (2 mmol) in THF (6 mL) was added a solution of Lithium Diisopropylamine (LDA) (2 mmol) in THF (6 mL) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, then the corresponding nitrile **2** (2 mmol) was added. The reaction was allowed to room temperature and stirred until TLC showed the disappearance of enamine **7**. Saturated NH_4Cl solution was added and the organic layer was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and purification by crystallization or column chromatography afforded compounds **10**.

4.4.1. Diisopropylamine-2-ethoxy-2-oxo-6-pentafluoroethyl-4-trifluromethyl-2,5-dihydro-1,5,2-diazaphosphinine adduct (10a). The general procedure was followed using diethyl 2-amino-2-trifluoromethyl etenylphosphonate **7a** (494 mg, 2 mmol) and pentafluoropropionitrile[12] (290 mg, 2 mmol). Recrystallization from diethyl ether gave 715 mg 1.6 mmol) (80%) of compound **10a**; mp 139–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.10 (t, $^3J_{HH}$= 7.1 Hz, 3H), 1.20 (d, $^3J_{HH}$=6.6 Hz, 12H), 3.31–3.49 (m, 4H), 5.57 (d, $^2J_{PH}$=4.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 19.3, 48.4, 62.7, 92.6 (d, $^1J_{PC}$=146.0 Hz), 106.7–126.7, 122.4 (dq, $^3J_{PC}$=19.3 Hz, $^1J_{FC}$=274.0 Hz), 155.1 (q, $^2J_{FC}$=32.7 Hz), 158.7 (t, $^2J_{FC}$=24.2 Hz) 159.5 (q, $^2J_{FC}$=35.2 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.0, −83.2, −119.0 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 20.7 ppm; IR (KBr) ν_{max} 3480, 2994, 1568, 1483, 1255 cm^{-1}; MS (EI): *m/z* 347 ($M^+ - N^iPr_2$, 40). Anal. Calcd for $C_{14}H_{22}F_8N_3O_2P$: C, 37.59; H, 4.96; N, 9.39. Found: C, 37.79; H, 5.09; N, 9.21.

4.4.2. Diisopropylamine-2-ethoxy-2-oxo-6-perfluorohepthyl-4-trifluromethyl-2,5-dihydro-1,5,2-diazaphosphinine adduct (10b). The general procedure was followed using diethyl 2-amino-3,3,3-trifluoro-1-propenylphosphonate **7** (494 mg, 2 mmol). Chromatographic purification with ethyl acetate/*n*-hexane (2/1) gave 683 mg (0.98 mmol) (49%) of compound **10b** as an oil; R_f 0.11 (ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.28 (t, $^3J_{HH}$=7.0 Hz, 3H), 1.38 (d, $^3J_{HH}$=6.6 Hz, 12H), 3.46–3.54 (m, 2H),3.59–3.68 (m, 2H), 5.79 (d, $^2J_{PH}$=4.7 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 22.0, 51.1, 65.5, 95.5 (d, $^1J_{PC}$=148.1 Hz), 108.8–119.8, 121.2 (dq, $^3J_{PC}$= 19.6 Hz, $^1J_{FC}$=274.0 Hz), 158.0 (q, $^2J_{FC}$=32.2 Hz), 161.6 (t, $^2J_{FC}$=23.7 Hz) ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −73.0, −82.3, −115.7, −122.0, −122.8, −123.6, −127.2 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 23.0 ppm; IR (KBr) ν_{max} 3373, 2992, 1573, 1487, 1205 cm^{-1}; MS (EI): *m/z* 698 ($M^+ + 1$, 40). Anal. Calcd for $C_{19}H_{22}F_{18}N_3O_2P$: C, 32.73; H, 3.18; N, 6.03. Found: C, 32.99; H, 3.23; N, 5.90.

4.5. Preparation of adduct 10b

To a solution of 2,5-dihydrophosphinimine **9b** (596 mg, 1 mmol) in THF (3 mL) was added diisopropylamine (1 mmol) at room temperature under a nitrogen atmosphere. The mixture was stirred at the same temperature until ^{31}P NMR spectrum showed the disappearance of compound **9b**. Evaporation of solvent under reduced pressure and purification by flash column chromatography with ethyl acetate afforded 690 mg (99%) of compound **10b**.

4.5.1. Procedure for the preparation of 2-ethoxy-2-oxo-6-(2-pyridyl)-4-trifluorometyl-2,5-dihydro-1,5,2-diazaphosphinine (12). To the diethyl 2-amino-3,3,3-trifluoro-1-propenylphosphonate **7** (494 mg, 2 mmol) in THF (6 mL) was added a solution of MeLi 1.6 M in diethyl ether (1.25 mL, 2 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at the same temperature for 1 h, then a solution of 2-pyridylnitrile **2** (208 mg, 2 mmol) in THF (6 mL) was added. The reaction was allowed to room temperature and stirred until TLC showed the disappearance of enamine **7**. Saturated NH_4Cl solution was added and the organic layer was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and purification by recrystallization from diethyl ether afforded 463.5 mg (1.52 mmol) (76%) of compound **12**; mp 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, $^3J_{HH}$=7.2 Hz, 3H), 4.20–4.25 (m, 2H), 6.04 (s, 1H), 7.54 (dd, $^3J_{HH}$=6.9 Hz, $^3J_{HH}$=6.9 Hz, 1H), 7.93 (dd, $^3J_{HH}$=6.6 Hz, $^3J_{HH}$=6.6 Hz, 1H), 8.43 (d, $^3J_{HH}$=7.8 Hz), 8.63 (d, $^3J_{HH}$=4.7 Hz, 1H), 10.5 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3, 62.4, 95.8 (d, $^1J_{PC}$=150.1 Hz), 117.0–120.9, 122.3, 127.2, 137.7, 147.2, 147.4, 148.1, 152.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −71.4 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 6.5 ppm; IR (KBr) ν_{max} 3070, 2995, 1555, 1405, 1186 cm^{-1}; MS (EI): *m/z* 306 ($M^+ + 1$, 100). Anal. Calcd for $C_{11}H_{11}F_3N_3O_2P$: C, 43.29; H, 3.63; N, 13.77. Found: C, 43.00; H, 3.78; N, 13.89.

4.6. General procedure for the preparation of 2,5-dihydro-1,5,2-diazaphosphinines 13, 14

To a solution of β-enaminophosphonates **11** (1 mmol) in THF (5 mL) at 0 °C under a nitrogen atmosphere was added a solution of butyllithium (2 mmol) in THF (3 mL). The mixture was stirred at the same temperature for 1 h, then the corresponding nitrile **2** (3 mmol) was added. The reaction was allowed to room temperature and stirred until TLC showed the disappearance of enaminephosphonates **11** (3 days). Evaporation of solvent under reduced pressure then was washed with water and was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and purification by column chromatography with ethyl acetate/*n*-hexane (3/1) afforded the corresponding compound.

4.6.1. 2-Ethoxy-2-oxo-4-phenyl-6-perfluorohepthyl-2,5,-dihydro-1,5,2-diazaphosphinine (13a). The general procedure was followed using β-enaminophosphonate (R^1= C_6H_5) **11a** (255 mg, 1 mmol) and perfluorooctanenitrile (R^2=C_7F_{15}) **2** (1185 mg, 3 mmol). Chromatographic purification gave 314 mg (1.56 mmol) (52%) of compound **13a**

as an oil; R_f 0.69 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, $^3J_{HH}$=7.0 Hz, 3H), 4.11–4.22 (m, 2H), 5.71 (d, $^2J_{PH}$=4.8 Hz, 1H), 7.20–7.52 (m, 5H), 8.64 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.7 (d, $^3J_{PC}$=6.6 Hz), 63.8 (d, $^2J_{PC}$=6.5 Hz), 95.5 (d, $^1J_{PC}$=151.5 Hz), 128.5–131.7 (m), 135.8 (d, $^3J_{PC}$=13.1 Hz), 154.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −82.6, −122.3, −122.5, −123.2, −123.9, −127.5 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.5 ppm; IR (KBr) ν_{max} 3405, 1580, 1255, 1147 cm^{-1}. Anal. Calcd for $C_{18}H_{12}F_{15}N_2O_2P$: C, 35.76; H, 1.98; N, 4.63. Found: C, 35.97; H, 1.77; N, 4.71.

4.6.2. 2-Ethoxy-4-(2-furyl)-2-oxo-6-perfluoroheptyl-2,5,-dihydro-1,5,2-diazaphosphinine (13b). The general procedure was followed using β-enaminophosphonate (R^1=2-furyl) **11b** (245 mg, 1 mmol) and perfluorooctanenitrile (R^2=C_7F_{15}) **2** (1185 mg, 3 mmol). Chromatographic purification gave 267 mg (1.35 mmol) (45%) of compound **13b** as an oil; R_f 0.68 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (t, $^3J_{HH}$=7.0 Hz, 3H), 4.16–4.21 (m, 2H), 5.84 (d, $^2J_{PH}$=3.7 Hz, 1H), 6.91 (s, 1H) 6.93 (s, 1H), 7.56 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.3 (d, $^3J_{PC}$=6.6 Hz), 62.6, 90.5 (d, $^1J_{PC}$=150.5 Hz), 11.6, 112.5, 144.8, 145.9 ppm; ^{19}F NMR (282 MHz, $CDCl_3$) δ −81.9, −119.5, −122.2, −123.0, −123.7, −127.2 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 5.46 ppm; IR (KBr) ν_{max} 3427, 1580, 1272, 1123 cm^{-1}; Anal. Calcd for $C_{16}H_{10}F_{15}N_2O_3P$: C, 32.33; H, 1.68; N, 4.71. Found: C, 32.57; H, 1.74; N, 4.83.

4.6.3. 2-Ethoxy-4-(2-furyl)-2-oxo-6-(2-pyridyl)-1,4-dihydro-1,5,2-diazaphosphinine (14a). The general procedure was followed using β-enaminophosphonate (R^1=2-furyl) **11b** (245 mg, 1 mmol) and 2-pyridylnitrile **2** (312 mg, 3 mmol). Chromatographic purification gave 153 mg (1.44 mmol) (48%) of compound **14a** as an oil; R_f 0.74 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.32 (t, $^3J_{HH}$=7.0 Hz, 3H), 4.09 (q, $^3J_{HH}$=7.0 Hz, 2H), 5.73 (d, $^2J_{PH}$=3.9 Hz, 1H), 6.50–8.59 (m, 7H), 10.75 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 61.8, 88.5 (d, $^1J_{PC}$=153.6 Hz), 109.7–148.2, 139.5, 146.8 (d, $^3J_{PC}$=17.1 Hz), 148.9 (d, $^3J_{PC}$=19.1 Hz), 153.1 (d, $^2J_{PC}$=3.6 Hz) ppm; ^{31}P NMR (120 MHz, $CDCl_3$): δ 10.96 ppm; IR (KBr) ν_{max} 3386, 3323, 1643, 1222 cm^{-1}. Anal. Calcd for $C_{14}H_{14}N_3O_4P$: C, 55.45; H, 4.65; N, 13.86. Found: C, 55.34; H, 4.78; N, 13.96.

4.6.4. 2-Ethoxy-6-(2-furyl)-2-oxo-4-phenyl-1,4-dihydro-1,5,2-diazaphosphinine (14b). The general procedure was followed using β-enaminophosphonate (R^1=C_6H_5) **11a** (255 mg, 1 mmol) and 2-furylnitrile **2** (276 mg, 3 mmol). Chromatographic purification gave 139 mg (1.38 mmol) (46%) of compound **14b** as an oil; R_f 0.70 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, $^3J_{HH}$=6.9 Hz, 3H), 4.16 (q, $^3J_{HH}$=6.9 Hz, 2H), 5.65 (d, $^2J_{PH}$=4.7 Hz, 1H), 6.59–7.55 (m, 8H), 8.61 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 61.8, 92.2 (d, $^1J_{PC}$=148.5 Hz), 110.0–144.9, 150.0 (d, $^3J_{PC}$=19.2 Hz), 149.5 (d, $^3J_{PC}$=15.6 Hz), 155.5 (d, $^2J_{PC}$=3.6 Hz) ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.25 ppm; IR (KBr) ν_{max} 3250, 1473, 1228 cm^{-1}. Anal. Calcd for $C_{15}H_{15}N_2O_3P$: C, 59.60; H, 5.00; N, 9.27. Found: C, 59.46; H, 5.11; N, 9.39.

4.6.5. 2-Ethoxy-2-oxo-4-phenyl-6-(2-pyridyl)-1,4-dihydro-1,5,2-diazaphosphinine (14c). The general procedure was followed using β-enaminophosphonate (R^1=C_6H_5) **11a** (255 mg, 1 mmol) and 2-pyridylnitrile **2** (312 mg, 3 mmol). Chromatographic purification gave 169 mg (1.62 mmol) (54%) of compound **14c** as an oil; R_f 0.75 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (t, $^3J_{HH}$=7.0 Hz, 3H), 4.12 (q, $^3J_{HH}$=7.0 Hz, 2H), 5.67 (d, $^2J_{PH}$=4.1 Hz, 1H), 7.42–8.55 (m, 9H), 10.56 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.8, 61.8, 92.6 (d, $^1J_{PC}$=148.6 Hz), 122.7–148.2, 135.1 (d, $^3J_{PC}$=12.6 Hz), 148.9 (d, $^3J_{PC}$=20.6 Hz), 149.6, 153.3 (d, $^2J_{PC}$=3.5 Hz) ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 12.33 ppm; IR (KBr) ν_{max} 3343, 1623, 1218 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_3O_2P$: C, 61.34; H, 5.15; N, 13.41. Found: C, 61.22; H, 5.01; N, 13.59.

4.7. General procedure for the preparation of 2,5-dihydro-1,5,2-diazaphosphinines 15

Buthyllithium (1.6 M in hexanes, 2.4 mmol) was added to a stirred solution of methylphosphonate **1** (1 mmol) in THF (5 mL) at −78 °C and under a nitrogen atmosphere. After 1 h, this solution was added to a solution of the corresponding nitrile **2** (3 mmol). The reaction was allowed to room temperature and stirred until TLC showed the disappearance of phosphonate (2 days). Saturated NH_4Cl solution was added and the organic layer was extracted with dichloromethane and dried over anhydrous magnesium sulfate. Evaporation of solvent under reduced pressure and purification by flash column chromatography with ethyl acetate afforded the corresponding compound.

4.7.1. 2-Ethoxy-4,6-bis-(2-furyl)-2-oxo-1,4-dihydro-1,5,2-diazaphosphinine (15a). The general procedure was followed using diethyl methylphosphonate (R^1=H) **1a** (152 mg, 1 mmol) and 2-furylnitrile **2** (276 mg, 3 mmol). Chromatographic purification gave 181 mg (1.86 mmol) (62%) of compound **15a** as an oil; R_f 0.73 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.29 (t, $^3J_{HH}$=7.0 Hz, 3H), 4.07 (q, $^3J_{HH}$=7.0 Hz, 2H), 5.66 (d, $^2J_{PH}$=2.0 Hz, 1H), 6.49–7.52 (m, 6H), 8.90 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 61.7, 88.6 (d, $^1J_{PC}$=153.1 Hz), 109.8–145.1, 139.2, 146.3 (d, $^3J_{PC}$=18.2 Hz), 146.7, 147.0 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 7.71 ppm; IR (KBr) ν_{max} 3352, 1635, 1220 cm^{-1}; MS (EI): *m/z* 292 (M^+, 49). Anal. Calcd for $C_{13}H_{13}N_2O_4P$: C, 53.43; H, 4.48; N, 9.59. Found: C, 53.27; H, 4.35; N, 9.67.

4.7.2. 2-Ethoxy-2-oxo-4,6-bis-(2-pyridyl)-1,4-dihydro-1,5,2-diazaphosphinine (15b). The general procedure was followed using diethyl methylphosphonate (R^1=H) **1a** (152 mg, 1 mmol) and 2-pyridylnitrile **2** (312 mg, 3 mmol). Chromatographic purification gave 213 mg (2.04 mmol) (68%) of compound **15b** as an oil; R_f 0.75 (chloroform/methanol, 1/1); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (t, $^3J_{HH}$=6.9 Hz, 3H), 4.15 (q, $^3J_{HH}$=6.9 Hz, 2H), 6.08 (d, $^2J_{PH}$=3.4 Hz, 1H), 7.35–8.78 (m, 8H), 12.08 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.6, 61.8, 91.6 (d, $^1J_{PC}$=146.5 Hz), 110.0–144.9, 135.2 (d, $^3J_{PC}$=13.1 Hz), 146.9 (d, $^3J_{PC}$=23.1 Hz), 147.4, 149.6 ppm, ^{31}P NMR (120 MHz, $CDCl_3$): δ 9.25 ppm; IR (KBr) ν_{max} 3396, 3297, 1629, 1228 cm^{-1}; MS (EI): *m/z* 314 (M^+, 59). Anal. Calcd for

$C_{15}H_{15}N_4O_2P$: C, 57.32; H, 4.81; N, 17.83. Found: C, 57.19; H, 5.00; N, 17.67.

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Studies on Wittig rearrangement of furfuryl ethers in steroidal side chain synthesis

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Abstract—Wittig rearrangement of 17(20)-ethylidene-16-furfuryloxy steroids **5**–**8** was examined. Reaction of 17*E*(20)-ethylidene-16α-furfuryloxy steroid **5** with *t*-BuLi in THF afforded (20*S*,22*S*)- and (20*S*,22*R*)-22-hydroxy steroids **9**, **10** and 17*Z*(20)-ethylidene-16α-(2-furyl)hydroxymethyl steroid **11** in 61, 28, and 9% yields, respectively. Base treatment of 17*E*(20)-ethylidene-16β-furfuryloxy steroid **7** gave (20*R*,22*R*)-22-hydroxy steroid **13** and 17*Z*(20)-ethylidene-16β-(2-furyl) hydroxymethyl steroid **14** in 60 and 17% yields. In contrast, 17*Z*(20)-ethylidene-16-furfuryloxy steroids **6**, **8** led to the corresponding 2,3-rearranged products in low yields (25% for (20*R*,22*S*)-22-hydroxy steroid **12**; 31% for (20*S*,22*R*)-22-hydroxy steroid **10**). Both (20*S*,22*S*)- and (20*S*,22*R*)-22-hydroxy steroids **9**, **10** were converted by catalytic hydrogenation into known compounds **16**, **17**, key intermediates for the synthesis of biologically active steroids.

1. Introduction

Wittig rearrangement has been established as one of the most useful synthetic tools in stereocontrolled synthesis.[1] Various variations of Wittig rearrangement have been explored and widely applied to natural product synthesis.[1] Our research efforts in this area have focused on exploiting Wittig rearrangement of furylmethyl ethers.[2] We have found that the Wittig rearrangement of both 2- and 3-furylmethyl ethers provides an efficient method for the preparation of 2-furylmethanol derivatives. As part of our continuing work on the synthesis of naturally occurring compounds employing furan derivatives as versatile synthons, we have succeeded in the synthesis of biologically active steroids with highly oxygenated side chains.[3] In this regard, we have been interested in the application of the Wittig rearrangement of furylmethyl ethers to steroidal side chain synthesis. Chirality transfer from C-16 position to newly created C-20 and C-22 chiral centers through [2,3]-Wittig rearrangement has been successfully applied by Nakai et al.[4] and Koreeda et al.[5] to the construction of steroidal side chains. Wittig–Still rearrangement has also been used for the stereoselective synthesis of steroidal side chains by Castedo et al.[6] In this paper, we describe a new method for construction of the steroidal side chain having furfuryl carbinol moiety at C-22 position based on the Wittig rearrangement of furylmethyl ethers as shown in Scheme 1.

2. Results and discussion

2.1. Preparation of 17(20)-ethylidene-16-furfuryloxy steroids 5–8

We first prepared the requisite furfuryl ethers **5**–**8** from the known 17(20)-ethylidene-16-hydroxy steroids **1**–**4** (Fig. 1). 17*E*(20)-Ethylidene-16α-hydroxy steroid **1**, obtained from the *i*-sterol ether of the commercially available 16α, 17α-epoxypregnenolone,[7a] was isomerized by treatment with benzenethiol and azobisisobutyronitrile in benzene to afford 17*Z*-16α-alcohol **2** as a major product.[4a] 17*E*(20)-Ethylidene-16β-hydroxy steroid **3** was prepared from 17*E*-16α-alcohol **1** by oxidation with manganese dioxide followed by reduction with lithium aluminum hydride.[4a,7b] 17*E*-16β-alcohol **3** was also converted into 17*Z*-16β-alcohol **4** by the same method for **2** from **1**.[4a] Treatment of allyl alcohols **1**–**4** with furfuryl chloride[8] and sodium hydride in DMF gave furfuryl ethers **5**–**8** in 40–67% (74–88% based on the recovery of starting materials) together with the starting materials **1**–**4**. Although we attempted the etherification under various conditions, we could not find more suitable transformation.

2.2. Wittig rearrangement of 16-furfuryloxy steroids 5–8

With furfuryl ethers **5**–**8** in hand, Wittig rearrangement of

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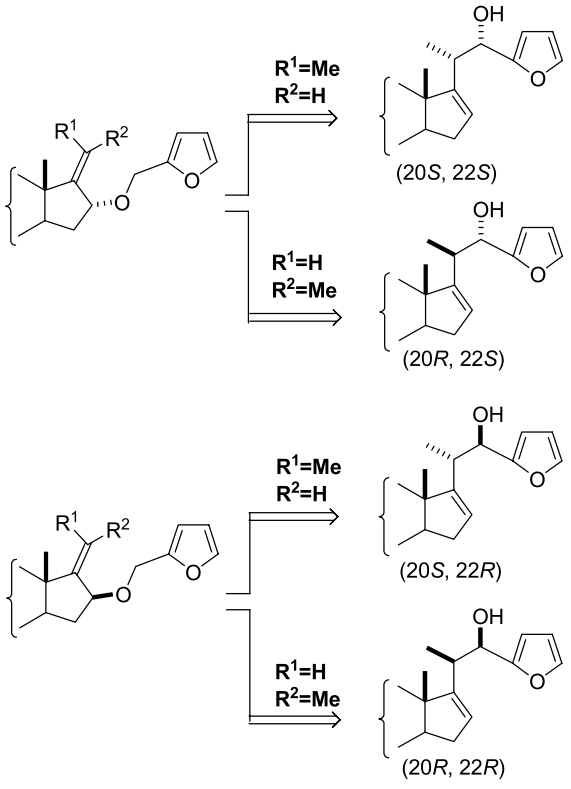
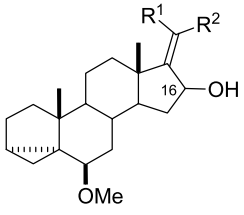
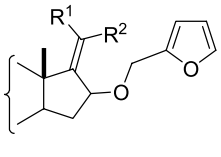


Scheme 1. Wittig rearrangement of 17(20)-ethylidene-16-furfuryloxy steroids.

17*E*(20)-16α-furfuryloxy steroid **5** was first investigated. According to our previous reported studies of the Wittig rearrangement of furfuryl ethers,[2b] furfuryloxy steroid **5** was treated with 10 equiv of *n*-BuLi in THF at −78 °C followed by warming to −20 °C to give none of the desired products. Pleasingly, reaction of **5** with 5 equiv of *t*-BuLi in THF at −78 °C provided [2,3]-rearrangement products **9** and **10** and [1,2]-rearranged product **11** in 61, 28, and 9% yields, respectively (Scheme 2). However, treatment of **5** with 3 equiv of *s*-BuLi in THF at −78 °C did not produce any rearranged products and the starting material was recovered. The moderate diastereoselectivity observed for this [2,3]-Wittig rearrangement of **5** is in accordance with the medium stereoselectivity with the same rearrangement of (*E*)-crotyl furfuryl ether. [2b] In contrast, this observed selectivity is quite different from the high selectivity with the Wittig rearrangement of both α-allyloxycarboxylic acid and

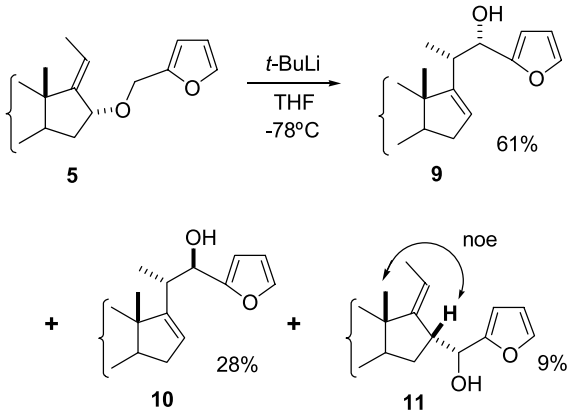


1 R^1=Me, R^2=H, 16-α
2 R^1=H, R^2=Me, 16-α
3 R^1=Me, R^2=H, 16-β
4 R^1=H, R^2=Me, 16-β



5 R^1=Me, R^2=H, 16-α
6 R^1=H, R^2=Me, 16-α
7 R^1=Me, R^2=H, 16-β
8 R^1=H, R^2=Me, 16-β

Figure 1.

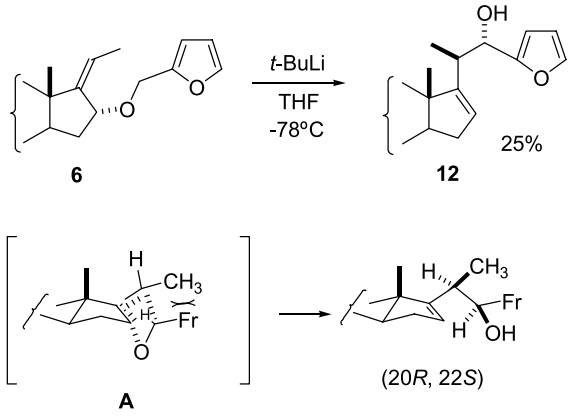


Scheme 2. Wittig rearrangement of 17*E*(20)-ethylidene-16α-furfuryloxy steroids **5**.

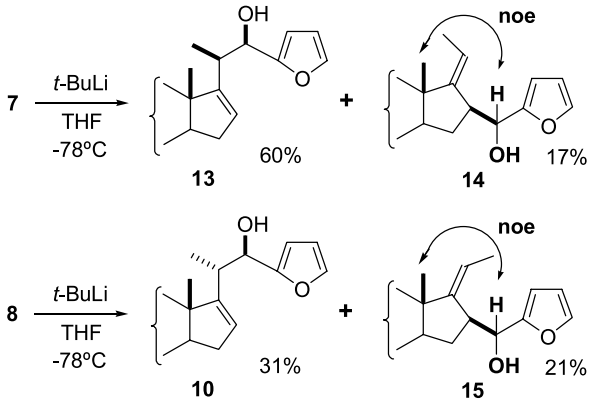
propargyl allyl ether in steroidal side chain construction reported by Nakai et al.[4] and Koreeda et al.[5] Although this discrepancy in stereoselectivity would not be rationally explained, the electronic nature of furan ring may be significant with regard to the overall stereochemical course of the reaction. Recently, Murphy et al. reported that rearrangement of allylic benzyl ether led to both [1,2]- and [2,3]-Wittig products and also suggested a radical mechanism for the formation of these products.[9,10] The stereochemistry at C-16 in [1,2]-rearranged product **11** was assigned by NOE experiment, while the stereocenter at the furfuryl carbinol in **11** could not be determined.

We next examined the Wittig rearrangement of 17*Z*(20)-16α-furfuryloxy steroid **6** (Scheme 3). Reaction of **6** with *t*-BuLi in THF at −78 °C proceeded sluggishly to provide [2,3]-rearranged product **12** as a sole product in 25% yield together with a starting material, while **12** could not be obtained under other conditions. The observed stereoselectivity and low reactivity can be speculated that preferred transition state **A** even suffers from the severe steric repulsion between the furan ring and 21-methyl group.

Wittig rearrangement of 17(20)-16β-furfuryloxy steroids **7** and **8** was carried out under the same condition as above (Scheme 4). Reaction of **7** furnished [2,3]-rearranged product **13** in 60% yield together with [1,2]-rearranged



Scheme 3. Wittig rearrangement of 17*Z*(20)-ethylidene-16α-furfuryloxy steroids **6**.



Scheme 4. Wittig rearrangement of 17(20)-ethylidene-16β-furfuryloxy steroids **7** and **8**.

product **14** in 17% yield, while rearrangement of **8** resulted in the formation of **10** in disappointingly low yield (31%) and **15** in 21% yield, respectively. The observed diastereoselectivities in the [2,3] Wittig rearrangement of 16β-furfuryloxy steroids **7** and **8** are thought to reflect a preference for transition states **B** over **C** with regard to the 1,3-repulsion between the furfuryloxy moiety and 18-methyl group (Fig. 2). The structures including the sterogenic center at C-16 in **14** and **15** were assigned based on NOE experiment as well as **11**.

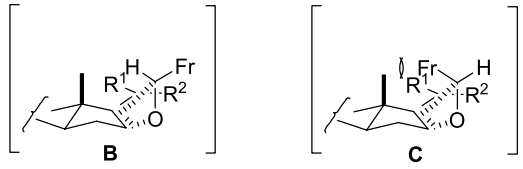


Figure 2.

Configuration at C-20 and C-22 positions in 22-hydroxy steroids **9** and **10** was confirmed as follows (Fig. 3). Hydrogenation of **9** with 10% Pd–C in MeOH under an atmospheric pressure of hydrogen afforded the known compound **16** (88%), whose spectroscopic data are identical with that reported.[3e] Therefore, the configuration of **9** was assigned to (20*S*,22*S*). Reduction of **10** under the same condition as **9** gave the known product **17** (90%),[3e] thus confirming the (20*S*,22*R*) stereochemistry of **10**. Both **16** and **17** could be key intermediates for the synthesis of biologically active steroids, such as ecdysone, withanolide, and brassinolide.

The stereochemistries at C-20 and C-22 positions in **12** and **13** having unnatural side chains were tentatively assigned by

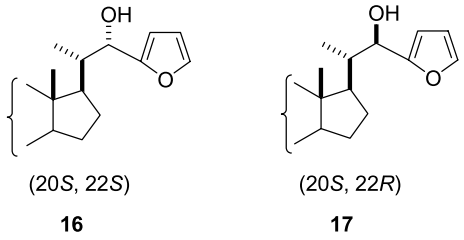


Figure 3.

comparison of ^{1}H NMR spectra of unnatural (20*R*,22*R*)-*threo* **13** and (20*R*,22*S*)-*erythro* **12** with those natural (20*S*,22*S*)-*threo* **9** and (20*S*,22*R*)-*erythro* **10** (Table 1). The ^{1}H NMR signals ascribed to H-16 and Me-18 in *erythro* **10** and **12** are observed further upfield than those *threo* **9** and **13**, while the signals of Me-21 and H-22 in *erythro* **10** and **12** are found further downfield than those *threo* **9** and **13**. The similar relationship between *erythro*- and *threo*-22-hydroxy steroids was also indicated in natural and unnatural brassinosteroids.[11] Based on the discrimination between *erythro*-**10**, **12** and *threo*-**9**, **13** in their ^{1}H NMR spectral data and the preferred transition states **B** over **C**, the stereostructures of unnatural 22-hydroxy steroids **12** and **13** should be (20*R*,22*S*)- and (20*R*,22*R*)-configurations, respectively.

Table 1. Selected ^{1}H NMR spectral data of 22-hydroxy steroids **9**, **10**, **12** and **13**

Position	*erythro*		*threo*	
	10	**12**	**9**	**13**
16	5.50	5.56	5.60	5.57
Me-18	0.68	0.85	0.92	0.88
Me-21	1.09	1.02	0.87	1.00
22	4.78	4.72	4.62	4.59

3. Conclusion

We have disclosed a new method for the synthesis of natural and unnatural 22-hydroxy steroids **9**, **10**, **12**, and **13** employing the Wittig rearrangement of 17(20)-ethylidene-16-furfuryloxy steroids **5**–**8** as a key step. Although the yields are moderate, this method provides a facile access to versatile 22-furyl-22-hydroxy steroids. Both furfuryl carbinols **9** and **10**, natural-type steroidal side chains, could be key intermediates for the synthesis of ecdysone, withanolide, brassinolide. Recent studies toward the synthesis of potent antitumor steroids, OSW-1 and cephalostatin family, have shown the importance of 16-dehydro-22-oxygenated steroids as highly versatile intermediates.[12,13] Further investigation directed toward the synthesis of OSW-1 and cephalostatin is underway in our laboratory.

4. Experimental

4.1. General

IR spectra were obtained using a JASCO FT/IR-200 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-LA270 (^{1}H NMR: 270 MHz, ^{13}C NMR: 67.8 MHz) or a JEOL JNM-LA500 (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz) instrument for solutions in $CDCl_3$, and chemical shifts are reported on the δ scale using TMS as an internal standard of δ 0.00 for ^{1}H NMR spectra and $CDCl_3$ as an internal standard of δ 77.00 for ^{13}C NMR spectra, respectively. MS spectra were measured with a JEOL JMS-D300 spectrometer. Optical rotations were taken with a JASCO DIP-360 polarimeter. Elemental analyses were performed on a Yanaco-MT5.

4.2. General procedure for etherification

To a stirred solution of the steroidal alcohol **1**–**4** (330 mg, 1 mmol) and sodium hydride (ca. 60% purity, 200 mg, 5 mmol) in dry DMF (15 mL) was added freshly distilled furfuryl chloride (583 mg, 5 mmol) at 0 °C and stirring was continued overnight at rt. The reaction was carefully quenched with saturated aqueous NH_4Cl solution in ice bath. The reaction mixture was extracted with Et_2O and CH_2Cl_2 (v/v, 2:1), and the combined organic layer was washed with brine. The organic layer was dried over Na_2SO_4 and evaporated to give a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 95:5) to afford 16-furfuryloxy steroid. Further elution (*n*-hexane/AcOEt = 85:15) gave the recovered steroidal alcohol. In parentheses the yields of 16-furfuryloxy steroid **5**–**8** based on the recovery of the starting material are shown.

4.2.1. (17*E*)-16α-Furfuryloxy-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 5. Yield 40% (85%). A colorless glass; $[\alpha]_D^{24}$ −15.4° (*c* 2.31, $CHCl_3$); IR: 2930, 1505, 1455, 1375, 1095 cm^{-1}; ^1H NMR (270 MHz) δ 0.45 (1H, dd, J = 7.9, 5.3 Hz, 4α-H), 0.66 (1H, t, J = 5.3 Hz, 4β-H), 0.91 (3H, s, 18-H_3), 1.03 (3H, s, 19-H_3), 1.73 (3H, d, J = 7.3 Hz, 21-H_3), 2.80 (1H, br s, 6-H), 3.34 (3H, s, OCH_3), 4.19 (1H, d, J = 5.9 Hz, 16-H), 4.40 and 4.52 (each 1H, each d, J = 12.8 Hz, CH_2O), 5.51 (1H, q, J = 7.3 Hz, 20-H), 6.28–6.35 (2H, m, 3′- and 4′-H), 7.39 (1H, br s, 5′-H); ^{13}C NMR (67.8 MHz) δ 13.1, 13.3, 17.9, 19.1, 21.3, 22.7, 24.9, 29.5, 31.1, 33.2, 34.9, 35.0, 37.2, 43.3, 44.2, 47.8, 52.7, 56.5, 62.8, 80.7, 82.2, 108.8, 110.1, 120.3, 142.4, 151.1, 152.4; MS (EI) (rel. int.): 252 (100, base), 410 (1.0, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2824. Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.63. Found: C, 78.97; H, 9.63.

4.2.2. (17*Z*)-16α-Furfuryloxy-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 6. Yield 43% (81%). A colorless glass; $[\alpha]_D^{26}$ −13.6° (*c* 1.36, $CHCl_3$); IR: 2930, 1455, 1375, 1150, 1095 cm^{-1}; ^1H NMR (270 MHz) δ 0.45 (1H, dd, J = 7.9, 4.9 Hz, 4α-H), 0.66 (1H, t, J = 4.9 Hz, 4β-H), 0.77 (3H, s, 18-H_3), 1.03 (3H, s, 19-H_3), 1.60 (3H, dd, J = 6.9, 0.9 Hz, 21-H_3), 2.80 (1H, t, J = 2.8 Hz, 6-H), 3.35 (3H, s, OCH_3), 4.37 and 4.53 (each 1H, each d, J = 12.7 Hz, CH_2O), 4.53 (1H, br s, 16-H), 5.34 (1H, dq, J = 6.9, 1.8 Hz, 20-H), 6.30–6.35 (2H, m, 3′- and 4′-H), 7.39 (1H, br s, 5′-H); ^{13}C NMR (67.8 MHz) δ 13.1, 14.2, 19.3, 20.9, 21.4, 22.7, 24.9, 29.8, 31.0, 33.3, 35.1, 35.2, 36.6, 43.5, 43.9, 48.3, 51.9, 56.6, 62.7, 78.1, 82.3, 109.3, 110.2, 118.5, 142.5, 152.3, 152.6; MS (EI) (rel. int.): 81 (100, base), 410 (2.3, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2823. Anal. Calcd for $C_{27}H_{38}O_3 \cdot 1/4H_2O$: C, 78.13; H, 9.35. Found: C, 78.30; H, 9.04.

4.2.3. (17*E*)-16β-Furfuryloxy-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 7. Yield 62% (88%). A colorless glass; $[\alpha]_D^{28}$ +91.3° (*c* 0.80, $CHCl_3$); IR: 2930, 1455, 1260, 1100 cm^{-1}; ^1H NMR (270 MHz) δ 0.44 (1H, dd, J = 7.9, 4.6 Hz, 4α-H), 0.66 (1H, t, J = 4.6 Hz, 4β-H), 1.04 (3H, s, 18-H_3), 1.07 (3H, s, 19-H_3), 1.72 (3H, dd, J = 7.3, 1.3 Hz, 21-H_3), 2.79 (1H, br s, 6-H), 3.34 (3H, s, OCH_3), 4.14 (1H, br t, J = 7.6 Hz, 16-H), 4.43 and 4.52 (each 1H, each d, J = 12.8 Hz, CH_2O), 5.46 (1H, dq, J = 7.1, 1.6 Hz, 20-H), 6.25–6.35 (2H, m, 3′- and 4′-H), 7.39 (1H, br s, 5′-H); ^{13}C NMR (67.8 MHz) δ 13.0, 13.2, 17.6, 19.2, 21.4, 22.5, 24.9, 29.5, 31.3, 33.2, 34.9, 35.2, 37.4, 43.4, 43.8, 48.0, 51.7, 56.5, 62.6, 81.6, 82.1, 108.8, 110.1, 119.5, 142.4, 150.5, 152.4; MS (EI) (rel. int.): 81 (100, base), 410 (5.6, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2798. Anal. Calcd for $C_{27}H_{38}O_3$: C, 78.98; H, 9.63. Found: C, 78.50; H, 9.34.

4.2.4. (17*Z*)-16β-Furfuryloxy-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 8. Yield 67% (74%). A colorless glass; $[\alpha]_D^{28}$ +102.8° (*c* 1.67, $CHCl_3$); IR: 2930, 1455, 1095 cm^{-1}; ^1H NMR (270 MHz) δ 0.44 (1H, dd, J = 7.9, 5.1 Hz, 4α-H), 0.66 (1H, t, J = 5.1 Hz, 4β-H), 0.97 (3H, s, 18-H_3), 1.04 (3H, s, 19-H_3), 1.59 (3H, dd, J = 6.9, 0.7 Hz, 21-H_3), 2.78 (1H, t, J = 2.8 Hz, 6-H), 3.34 (3H, s, OCH_3), 4.40 and 4.55 (each 1H, each d, J = 12.8 Hz, CH_2O), 4.44 (1H, br t, J = 6.8 Hz, 16-H), 5.27 (1H, dq, J = 6.9, 2.0 Hz, 20-H), 6.30–6.35 (2H, m, 3′- and 4′-H), 7.39–7.41 (1H, m, 5′-H); ^{13}C NMR (67.8 MHz) δ 13.1, 13.2, 19.2, 19.3, 21.4, 22.4, 24.9, 29.9, 31.9, 33.2, 34.9, 35.3, 36.5, 43.2, 43.5, 48.4, 51.2, 56.6, 62.4, 77.1, 82.2, 109.2, 110.2, 117.1, 142.5, 152.0, 152.3; MS (EI) (rel. int.): 297 (100, base), 410 (18, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2840. Anal. Calcd for $C_{27}H_{38}O_3 \cdot 1/4H_2O$: C, 78.13; H, 9.35. Found: C, 78.42; H, 9.36.

4.3. General procedure for Wittig rearrangement of 16-furfuryloxy steroid 5–8

To a solution of 16-furfuryloxy steroid **5**–**8** (205 mg, 0.5 mmol) in THF (5 mL) was added dropwise *t*-BuLi (1.6 M in pentane, 1.56 mL, 2.5 mmol) at −78 °C under Ar. After stirring for 1.5 h, the reaction mixture was quenched with saturated aqueous NH_4Cl solution and the solvent was removed under vacuum. The residue was extracted with AcOEt. The extract was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a residue, which was chromatographed on silica gel (50 g, *n*-hexane/AcOEt = 93:7) to afford 22-hydroxy steroid and 16-furylhydroxymethyl steroid, respectively.

4.3.1. (20*S*,22*S*,23*Z*,25*Z*)-23,26-Epoxy-22-hydroxy-6β-methoxy-3α,5-cyclo-27-nor-5α-cholesta-16,23,25-triene 9. Yield 61%, a colorless glass; $[\alpha]_D^{24}$ +8.8° (*c* 0.58, $CHCl_3$); IR: 3430, 2930, 1455, 1375, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 0.46 (1H, dd, J = 7.9, 5.1 Hz, 4α-H), 0.67 (1H, t, J = 5.1 Hz, 4β-H), 0.87 (3H, d, J = 7.0 Hz, 21-H_3), 0.92 (3H, s, 18-H_3), 1.07 (3H, s, 19-H_3), 2.74 (1H, dq, J = 10.1, 7.0 Hz, 20-H), 2.81 (1H, t, J = 2.4 Hz, 6-H), 3.36 (3H, s, OCH_3), 4.62 (1H, d, J = 10.1 Hz, 22-H), 5.60 (1H, br d, J = 1.8 Hz, 16-H), 6.31 (1H, dd, J = 3.0, 0.8 Hz, 24-H), 6.34 (1H, dd, J = 3.0, 1.8 Hz, 25-H), 7.40 (1H, dd, J = 1.8, 0.8 Hz, 26-H); ^{13}C NMR (125 MHz) δ 13.1, 16.7, 18.3, 19.2, 21.3, 22.3, 24.9, 29.2, 31.2, 33.1, 35.0, 35.1, 35.3, 39.8, 43.6, 47.6, 48.6, 56.6, 57.6, 70.5, 82.2, 107.9, 110.0, 124.4, 142.0, 154.6, 157.7; MS (EI) (rel. int.): 173 (100, base), 410 (2.5, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2821.

4.3.2. (20*S*,22*R*,23*Z*,25*Z*)-23,26-Epoxy-22-hydroxy-6β-methoxy-3α,5-cyclo-27-nor-5α-cholesta-16,23,25-triene 10. Yield 28 and 31% by Wittig rearrangement of **5** and **8**,

respectively. A colorless glass; $[\alpha]_D^{23}$ +25.0° (*c* 0.43, $CHCl_3$); IR: 3420, 2930, 1455, 1370, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 0.44 (1H, dd, *J*=7.9, 5.1 Hz, 4α-H), 0.66 (1H, t, *J*=5.1 Hz, 4β-H), 0.68 (3H, s, 18-H_3), 1.04 (3H, s, 19-H_3), 1.09 (3H, d, *J*=6.7 Hz, 21-H_3), 2.70 (1H, quintet, *J*=6.7 Hz, 20-H), 2.78 (1H, t, *J*=2.7 Hz, 6-H), 3.30 (3H, s, OCH_3), 4.78 (1H, d, *J*=6.7 Hz, 22-H), 5.50 (1H, d, *J*=3.0 Hz, 16-H), 6.20 (1H, dd, *J*=3.0, 0.8 Hz, 24-H), 6.30 (1H, dd, *J*=3.0, 1.8 Hz, 25-H), 7.32 (1H, dd, *J*=1.8, 0.8 Hz, 26-H); ^{13}C NMR (125 MHz) δ 13.1, 16.3 16.4, 19.2, 21.4, 22.3, 24.9, 29.0, 31.2, 33.1, 35.0, 35.1, 35.4, 37.5, 43.6, 47.4, 48.6, 56.6, 57.4, 70.8, 82.3, 106.4, 110.1, 124.2, 141.1, 155.9, 157.3; MS (EI) (rel. int.): 97 (100, base), 410 (0.9, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2794.

4.3.3. (17*Z*)-16α-(2′-Furyl)hydroxymethyl-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 11. Yield 9%. A colorless glass; $[\alpha]_D^{26}$ +25.6° (*c* 0.25, $CHCl_3$); IR: 3440, 2930, 1450, 1380, 1095 cm^{-1}; ^1H NMR (500 MHz) δ 0.43 (1H, dd, *J*=7.9, 5.1 Hz, 4α-H), 0.65 (1H, t, *J*=4.9 Hz, 4β-H), 0.98 (3H, s, 18-H_3), 1.02 (3H, s, 19-H_3), 1.74 (3H, dd, *J*=7.0, 1.8 Hz, 21-H_3), 2.76 (1H, t, *J*=1.7 Hz, 6-H), 2.99 (1H, m, 16-H), 3.31 (3H, s, OCH_3), 4.55 (1H, d, *J*=7.0 Hz, C*H*OH), 5.36 (1H, dq, *J*=7.0, 1.8 Hz, 20-H), 6.20 (1H, dd, *J*=3.3, 0.8 Hz, 3′-H), 6.33 (1H, dd, *J*=3.3, 1.8 Hz, 4′-H), 7.37 (1H, dd, *J*=1.8, 0.8 Hz, 5′-H); ^{13}C NMR (125 MHz) δ 13.0, 13.5, 17.8, 19.2, 21.5, 22.8, 24.9, 28.6, 29.5, 33.2, 34.9, 35.3, 37.4, 43.4, 45.4, 47.4, 48.0, 53.7, 56.6, 71.2, 82.3, 106.7, 110.2, 118.5, 141.6, 150.9, 155.8; MS (EI) (rel. int.): 279 (100, base), 410 (0.2, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2840.

4.3.4. (20*R*,22*S*,23*Z*,25*Z*)-23,26-Epoxy-22-hydroxy-6β-methoxy-3α,5-cyclo-27-nor-5α-cholesta-16,23,25-triene 12. Yield 25%. A colorless glass; $[\alpha]_D^{24}$ +32.8° (*c* 0.19, $CHCl_3$); IR: 3430, 2930, 1460, 1375, 1095 cm^{-1}; ^1H NMR (500 MHz) δ 0.46 (1H, dd, *J*=7.9, 4.9 Hz, 4α-H), 0.67 (1H, t, *J*=4.9 Hz, 4β-H), 0.85 (3H, s, 18-H_3), 1.02 (3H, d, *J*=7.0 Hz, 21-H_3), 1.06 (3H, s, 19-H_3), 2.75 (1H, dq, *J*=7.0, 3.7 Hz, 20-H), 2.80 (1H, t, *J*=2.7 Hz, 6-H), 3.36 (3H, s, OCH_3), 4.72 (1H, d, *J*=3.7 Hz, 22-H), 5.56 (1H, br s, 16-H), 6.23 (1H, dd, *J*=3.4, 0.9 Hz, 24-H), 6.34 (1H, dd, *J*=3.4, 1.8 Hz, 25-H), 7.36 (1H, dd, *J*=1.8, 0.9 Hz, 26-H); ^{13}C NMR (125 MHz) δ 13.1, 14.5, 16.5, 19.3, 21.4, 22.4, 24.9, 29.2, 31.5, 33.1, 35.0, 35.2, 35.4, 36.9, 43.6, 48.0, 48.6, 56.7, 56.8, 69.9, 82.3, 105.9, 110.1, 125.3, 141.2, 155.5, 157.3 MS (EI) (rel. int.): 314 (100, base), 410 (2.3, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2830.

4.3.5. (20*R*,22*R*,23*Z*,25*Z*)-23,26-Epoxy-22-hydroxy-6β-methoxy-3α,5-cyclo-27-nor-5α-cholesta-16,23,25-triene 13. Yield 60%. A colorless glass; $[\alpha]_D^{27}$ +73.0° (*c* 0.62, $CHCl_3$); IR: 3430, 2930, 1455, 1375, 1090 cm^{-1}; ^1H NMR (500 MHz) δ 0.46 (1H, dd, *J*=8.2, 4.9 Hz, 4α-H), 0.67 (1H, t, *J*=4.9 Hz, 4β-H), 0.88 (3H, s, 18-H_3), 1.00 (3H, d, *J*=7.0 Hz, 21-H_3), 1.06 (3H, s, 19-H_3), 2.75 (1H, quintet, *J*=7.0 Hz, 20-H), 2.80 (1H, t, *J*=2.7 Hz, 6-H), 3.36 (3H, s, OCH_3), 4.59 (1H, d, *J*=7.9 Hz, 22-H), 5.57 (1H, br s, 16-H), 6.25 (1H, d, *J*=3.0 Hz, 24-H), 6.33 (1H, dd, *J*=3.0, 1.8 Hz, 25-H), 7.38 (1H, d, *J*=1.8 Hz, 26-H); ^{13}C NMR (125 MHz) δ 13.1, 17.2, 19.2, 19.4, 21.3, 22.3, 24.9, 29.0, 31.5, 33.1, 34.8, 35.1, 35.3, 37.8, 43.6, 47.8, 48.6, 56.7, 56.9, 71.9, 82.3, 107.2, 110.1, 124.6, 141.7, 155.2, 157.9; MS (EI) (rel. int.): 97 (100, base), 410 (6.3, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2810.

4.3.6. (17*Z*)-16β-(2′-Furyl)hydroxymethyl-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 14. Yield 17%. A colorless glass; $[\alpha]_D^{25}$ +22.5° (*c* 0.24, $CHCl_3$); IR: 3430, 2930, 1455, 1375, 1100 cm^{-1}; ^1H NMR (500 MHz) δ 0.44 (1H, dd, *J*=7.9, 4.9 Hz, 4α-H), 0.65 (1H, t, *J*=4.9 Hz, 4β-H), 0.87 (3H, s, 18-H_3), 1.02 (3H, s, 19-H_3), 1.73 (3H, dd, *J*=7.3, 1.8 Hz, 21-H_3), 2.76 (1H, t, *J*=2.7 Hz, 6-H), 2.93 (1H, br q, *J*=7.6 Hz, 16-H), 3.32 (3H, s, OCH_3), 4.54 (1H, d, *J*=7.6 Hz, C*H*OH), 5.36 (1H, dq, *J*=7.3, 1.8 Hz, 20-H), 6.21 (1H, d, *J*=3.0 Hz, 3′-H), 6.31 (1H, dd, *J*=3.3, 1.8 Hz, 4′-H), 7.36 (1H, dd, *J*=1.8 Hz, 5′-H); ^{13}C NMR (125 MHz) δ 13.1, 13.5, 17.0, 19.2, 21.2, 22.7, 24.9, 28.4, 29.9, 33.3, 35.0, 35.1, 37.7, 43.4, 45.5, 47.8, 48.6, 54.3, 56.6, 71.9, 82.2, 106.8, 110.0, 117.3, 141.8, 150.7, 155.7; MS (EI) (rel. int.): 97 (100, base), 410 (2.5, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2850.

4.3.7. (17*E*)-16β-(2′-Furyl)hydroxymethyl-6β-methoxy-3α,5-cyclo-5α-pregn-17(20)-ene 15. Yield 21%. A colorless glass; $[\alpha]_D^{25}$ +14.4° (*c* 0.27, $CHCl_3$); IR: 3440, 2925, 1455, 1375, 1095 cm^{-1}; ^1H NMR (500 MHz) δ 0.43 (1H, dd, *J*=7.9, 4.8 Hz, 4α-H), 0.65 (1H, t, *J*=4.8 Hz, 4β-H), 0.72 (3H, s, 18-H_3), 1.03 (3H, s, 19-H_3), 1.77 (3H, d, *J*=6.7 Hz, 21-H_3), 2.76 (1H, t, *J*=2.7 Hz, 6-H), 3.27 (1H, q, *J*=8.8 Hz, 16-H), 3.32 (3H, s, OCH_3), 4.73 (1H, d, *J*=8.8 Hz, C*H*OH), 5.36 (1H, dq, *J*=6.7, 2.1 Hz, 20-H), 6.26 (1H, d, *J*=3.3 Hz, 3′-H), 6.33 (1H, dd, *J*=3.3, 1.8 Hz, 4′-H), 7.38–7.39 (1H, m, 5′-H); ^{13}C NMR (125 MHz) δ 13.1, 14.9, 18.3, 19.3, 21.3, 22.5, 24.9, 28.6, 30.2, 33.3, 35.0, 35.1, 37.1, 43.5, 44.6, 45.1, 48.3, 53.4, 56.7, 72.9, 82.2, 107.0, 110.1, 116.2, 142.0, 151.8, 155.4 MS (EI) (rel. int.): 97 (100, base), 410 (0.6, M^+); HRMS (EI) calcd for $C_{27}H_{38}O_3$: 410.2821; Found: 410.2825.

4.4. Hydrogenation of 9

A mixture of olefin **9** (12.1 mg, 0.03 mmol) and 10% Pd–C (2.3 mg) in MeOH (3 mL) was stirred at rt under an atmospheric pressure of hydrogen for 48 h. An insoluble material was filtered off. The filtrate was concentrated to leave a residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=93:7) to afford 22-hydroxy steroid **16** (10.7 mg, 88%). The ^1H NMR spectrum of **16** was identical with that reported.[3e]

4.5. Hydrogenation of 10

Catalytic hydrogenation of **10** was performed as above to afford 22-hydroxy steroid **17** in 90% yield. The ^1H NMR spectrum of **17** was identical with that reported.[3e]

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Halichonadins A–D, new sesquiterpenoids from a sponge *Halichondria* sp.

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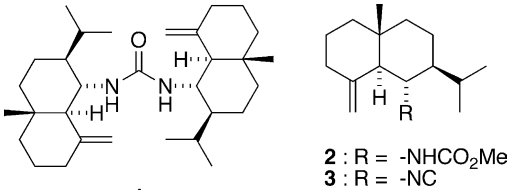
Abstract—A new dimeric sesquiterpenoid with two eudesmane skeletons through a urea linkage, halichonadin A (**1**), as well as three new eudesmane sesquiterpenoids having a carbamate, an isonitrile, or an amino functionality, halichonadins B (**2**), C (**3**), and D (**4**), respectively, have been isolated from a marine sponge *Halichondria* sp., and the gross structures and relative stereochemistry of **1**–**4** were elucidated on the basis of spectral data and chemical means.

A number of sesquiterpene isothiocyanates, isonitriles, and formamides were isolated[1] from marine sponges of the genus *Halichondria*, and these compounds are thought to have any role in maintaining the ecological system, e.g. as an allomon of the browser-prey relationship.[2,3] During our search for bioactive metabolites from Okinawan marine sponges,[4,5] four new sesquiterpenoids, halichonadins A–D (**1**–**4**), have been isolated from a sponge *Halichondria* sp. Here we describe the isolation and structure elucidation of **1**–**4**.



1

2 : R = -NHCO$_2$Me
3 : R = -NC
4 : R = -NH$_2$

The sponge *Halichondria* sp. (SS-1011) collected off Unten Port, Okinawa, was extracted with MeOH, and the extract was partitioned between EtOAc and water. The EtOAc soluble materials were subjected to a silica gel column ($CHCl_3$/MeOH, 95:5, and then petroleum ether/diethyl ether, 9:1) to afford halichonadins A–D (**1**–**4**) (**1**, 0.004%, wet wt; **2**, 0.001%; **3**, 0.01%; **4**, 0.0004%) together with two known related terpenoids, acanthenes B and C.[6]

The molecular formula, $C_{31}H_{52}N_2O$, of halichonadin A (**1**) was established by HREIMS [*m*/*z* 468.4079 (M^+), Δ −0.1 mmu]. IR (1637 cm^{-1}) and ^{13}C NMR (δ_C 158.5) data suggested the presence of urea functionality. The gross structure of **1** was deduced from detailed analysis of the ^1H and ^{13}C NMR data (Table 1) aided with 2D NMR experiments (^1H–^1H COSY, HMQC, and HMBC). The ^{13}C NMR data indicated that **1** possessed one carbonyl, one exomethylene, one sp^3 quaternary carbon, five methylenes, four methines (one of them bearing a nitrogen atom), and three methyl groups. Since 16 of 31 carbons were observed and the remaining 15 carbons were not detected, it was suggested that **1** possessed a symmetrical structure.

The ^1H–^1H COSY spectrum revealed connectivities of C-1–C-8, C-11 to C-12, C-11 to C-13, C-4 to C-14, and C-6 to N-6 (Fig. 1). HMBC correlations of H_3-15 to C-1, C-5, C-9, and C-10, H-8 to C-9, and H-11 to C-7 revealed the presence of a decalin ring with a methyl group (C-15) at C-10, an exomethylene group (C-14) at C-4, and an isopropyl group (C-11–C-13) at C-7 (Fig. 1). The connectivities of N-6 to C-6 and C-16 were deduced from an HMBC correlation of H-6 to C-16. Thus, the gross structure of halichonadin A was elucidated to be **1**, consisting of two eudesmane skeletons linked with urea. EIMS (*m*/*z*, 468, M^+) fragmentation patterns of **1** also supported the structure proposed for **1** (Fig. 2). To confirm the presence of the two

Keywords: Marine sponge; *Halichondria* sp.; Sesquiterpenoid; Halichonadin.
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Table 1. ^{1}H and ^{13}C NMR data of halichonadin A (**1**) in pyridine-d_5

Position	^{1}H[a]	^{13}C[a]	H coupled with C[b]
1α	1.11 (m)	41.7	3β, 15
1β	1.30 (m)		
2α	1.53 (m)	23.9	
2β	1.47 (m)		
3α	1.78 (m)	38.2	1β, 14α, 14β
3β	2.28 (m)		
4		146.7	5
5	1.71 (d, 11.0)	57.1	1β, 3α, 3β, 6, 9β, 14α, 14β, 15
6	4.14 (br dd, 11.0, 11.0)	46.4	5, 8
7	1.04 (m)	51.2	8β, 11, 12, 13
8α	1.36 (m)	18.4	11
8β	1.32 (m)		
9α	1.04 (m)	40.1	2α, 8α
9β	1.36 (m)		
10		37.2	5, 9β, 15
11	2.41 (m)	25.8	12, 13
12	1.19 (d, 6.8)	16.1	7, 8α, 13
13	0.91 (d, 7.0)	21.3	11, 12
14a	5.07 (bs)	107.7	3β, 5
14b	5.32 (bs)		
15	0.76 (s)	16.9	5
16		158.5	6
NH	5.45 (d, 9.3)		

[a] δ in ppm.
[b] HMBC correlations moiety.

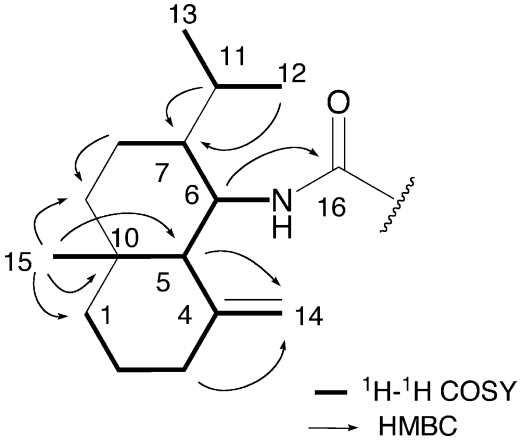

Figure 1. Selected 2D NMR correlations for one half part of halichonadin A (**1**).

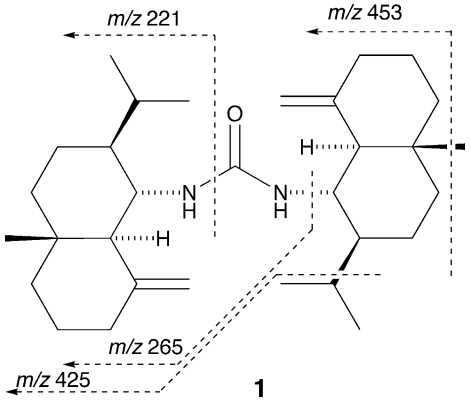

Figure 2. EIMS (M^+, *m/z* 468) fragmentation patterns of halichonadin A (**1**).

eudesmane skeletons, **1** was reduced with rhodium–aluminum to yield compound **5** (Fig. 3), whose EIMS data (M^+, *m/z* 472) indicated reduction of the two exomethylenes in **1**. NOESY correlations of H-11 to H-14′ and H-12 to H-14′ in **1** also suggested the presence of the two eudesmane skeletons. NOESY correlations of H_3-15 to H-2β, H-6 and H-8β, and H-5 to NH and ^{1}H–^{1}H coupling (J=11 Hz, H-5/H-6) in **1** indicated a β-orientation of Me-15, an α-orientation of H-5, a *trans*-fused decalin skeleton, a β-orientation of H-6, and chair conformations of two cyclohexane rings in the decalin ring (Fig. 4). Thus, the relative stereochemistry of halichonadin A was concluded to be **1**.

The molecular formula, $C_{17}H_{29}NO_2$, of halichonadin B (**2**) was established by HREIMS [*m/z* 279.2203 (M^+), Δ −0.5 mmu]. IR (1698 cm^{-1}) and ^{13}C NMR (δ_C 157.4 and 51.0, δ_H 3.67) data suggested the presence of carbamate functionality. The gross structure of **2** was deduced from detailed analysis of ^{1}H and ^{13}C NMR data (Table 2) aided with 2D NMR experiments (^{1}H–^{1}H COSY, HMQC, and HMBC). The ^{13}C NMR data indicated that **2** possessed one carbonyl, one exomethylene, one sp^3 quaternary carbon, five methylenes, four methines (one of them bearing a nitrogen atom), and four methyl groups (one of them bearing an oxygen atom). Since two of four unsaturations were thus accounted for, it was suggested that **2** contained two rings. The ^{1}H–^{1}H COSY spectrum revealed connectivities of C-2 to C-3, C-5–C-7, C-11 to C-12, and C-13, and C-6 to NH (Fig. 5). HMBC correlations (Fig. 5) of H_3-15 to C-1, C-5, C-9, and C-10, H-1α to C-3, H_2-14 to C-3, H-5 to C-4, H-9β to C-7 and C-8, and H_3-12 and H_3-13 to C-7 revealed the presence of a decalin ring with a methyl group at C-10, an exomethylene group at C-4, and an isopropyl group at C-7. The connectivity of NH to C-6 and C-16 was deduced from NOESY correlations of NH to H-7 and H_3-17. Thus, the gross structure of halichonadin B was elucidated to be **2** possessing of an eudesmane skeleton with a carbamate group at C-6. NOESY correlations of H_3-15 to H-2β, H-6 and H-8β, H-3α to H-5, H-3β to H-14a, H-6 to H-14b and H_3-12, and H-7 to NH and the ^{1}H–^{1}H coupling (J=11.2 Hz, H-5/H-6) indicated a β-orientation of Me-15, an α-orientation of H-5, a *trans*-fused decalin skeleton, a β-orientation of H-6, a β-orientation of the isopropyl group, and chair conformations of the two cyclohexane rings in the decalin ring (Fig. 5). Thus, the relative stereochemistry of **2** was assigned as shown in Figure 5.

Halichonadin C (**3**)[7] showed the molecular ion peak at *m/z* 231 (M^+) in EIMS. HREIMS analysis revealed the molecular formula to be $C_{16}H_{25}N$ [*m/z* 231.1987 (M^+), Δ −0.8 mmu]. IR (2135 cm^{-1}) and ^{13}C NMR (δ_C 155.3 (t) and 53.4,(t)) data suggested the presence of isonitrile functionality. The ^{13}C NMR data indicated that **3** possessed one isonitrile, one exomethylene, one sp^3 quaternary carbon, five methylenes, four methines (one of them bearing nitrogen atom), and three methyl groups. Since two of four unsaturations were thus accounted for, it was suggested that **3** contained two rings. The ^{1}H–^{1}H COSY spectrum revealed connectivities of C-1–C-3, C-5–C-9, C-11 to C-12, and C-13 (Fig. 6). HMBC correlations of H_3-15 to C-1, C-5, C-9, and C-10, H-6 to C-16, H_2-14 to C-3, C-4, and C-5, and H_3-12 and H_3-13 to C-7 revealed the presence of a *trans*-

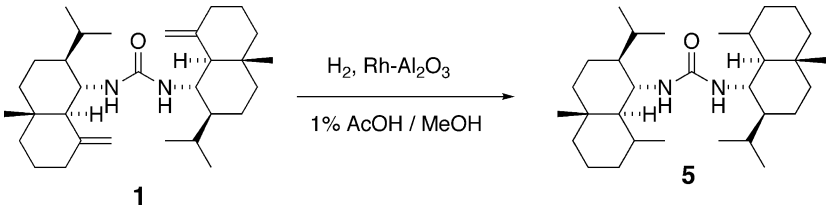

Figure 3. Hydrogenation of halichonadin A (**1**) with Rh–Al_2O_3 and its reductive product **5**.

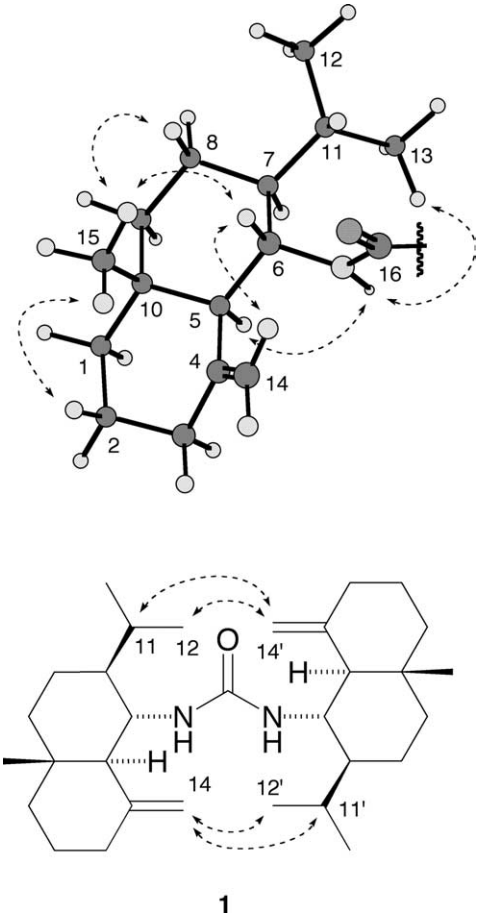

Figure 4. Selected NOESY correlation for halichonadin A (**1**) (lower) and for one half part of **1** (upper).

fused decalin ring with a methyl group at C-10, an exomethylene group at C-4, an isopropyl group at C-7, and an isonitrile group at C-6 (Fig. 6). Thus, the gross structure of halichonadin C was elucidated to be **3** possessing an eudesmane skeleton with an isonitrile group at C-6. NOESY correlations of H_3-15 to H-2β and H-8β, H-1α to H-3α, H-3α to H-5, H-3β to H-14a, H-5 to H-7, and H-6 to H-11 and H-8β, and the ^1H–^1H coupling (J=11 Hz, H-5/H-6) indicated a β-orientation of Me-15, an α-orien-orientation of H-5, a *trans*-fused decalin skeleton, a β-orientation of H-6, a β-orientation of an isopropyl group at C-7 and chair conformations of two cyclohexane rings in the decalin ring (Fig. 6). Thus, the relative stereochemistry of **3** was assigned as shown in Figure 6.

The molecular formula, $C_{15}H_{27}N$, of halichonadin D (**4**) was established by HREIMS [*m/z* 221.2135 (M^+), Δ −0.8 mmu]. IR (3408 cm^{-1}) and ^{13}C NMR (δ_C 48.5, δ_H 3.62) data suggested the presence of amino group. The gross structure of **4** was deduced from detailed analysis of ^1H and ^{13}C NMR data (Table 2) aided with 2D NMR experiments (^1H–^1H COSY, HMQC, and HMBC) as shown in Figure 7. To confirm the presence of an amino group, **4** was acetylated with acetic anhydride to yield compound **6**, whose EIMS data (M^+, *m/z* 263) indicated acetylation of the amino group in **4**. Thus, the gross structure of halichonadin D was elucidated to be **4** possessing of an eudesmane skeleton with an amino group at C-6. NOESY correlations of H_3-15 to H-2β, H-6 and H-8β, H-3β to H-14a, H-5 to H-1α and H-3α, H-7 to H-5, H-9, H-11 and H_3-12, H-6 to H-13, and H-14b to NH and the ^1H–^1H coupling (J=11.1 Hz, H-5/H-6) indicated a β-orientation of Me-15, an α-orientation of H-5, a *trans*-fused decalin skeleton, a β-orientation of H-6, a β-orientation of the isopropyl group, and chair conformations of the two cyclohexane rings in the decalin ring (Fig. 7). Thus, the relative stereochemistry of **4** was assigned as shown in Figure 7.

Halichonadin A (**1**) is a rare dimeric sesquiterpenoid with two eudesman skeletons through a urea linkage, while halichonadins B (**2**) is a rare sesquiterpenoid having a carbamate group, although a dimeric sesquiterpenoid with two germacrane skeletons through a urea linkage[8] and a sesquiterpenoid with a carbamate functionality[9] have been isolated from sponges *Axinyssa* n. sp. and sponge *Geodia exigua*, respectively.

Halichonadins A–D (**1**–**4**) showed antibacterial activity against *Micrococcus luteus*, while halichonadins B (**2**) and C (**3**) exhibited antifungal activity, in which the MIC value of **3** against *Cryptococcus neoformans* was 0.0625 μg/ml (Table 3).

1. Experimental

1.1. General experimental procedures

Optical rotations were recorded on a JASCO DIP-1000 polarimeter. The IR spectrum was taken on a JASCO FT/IR-5300. ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX-600. EI mass spectra were obtained on a DX-303 spectrometer. Antimicrobial activities were determined by a microbroth dilution method using BHI medium.

1.2. Isolation

The sponge *Halichondria* sp. (SS-1011) was collected off Unten Port, Okinawa, and kept frozen until used. The

Table 2. ^{1}H and ^{13}C NMR data of halichonadins B (**2**), C (**3**), and D (**4**)

Position	**2**[a]		**3**[b]		**4**[a]	
	^{1}H[c]	^{13}C[c]	^{1}H[c]	^{13}C[c]	^{1}H[c]	^{13}C[c]
1α	1.16 (m)	41.7	1.27 (m)	41.7	1.17 (m)	40.8
1β	1.31 (m)		1.46 (m)		1.28 (m)	
2α	1.48 (2H, m)	23.9	1.60 (m)	23.9	1.47 (2H, m)	23.5
2β			1.57 (m)			
3α	1.78 (dd, 12.4, 5.6)	38.0	1.97 (ddd, 13.0, 5.7, 5.7)	37.5	1.82 (m)	37.1
3β	2.22 (m)		2.33 (ddd, 13.0. 1.9, 1.9)		2.17 (m)	
4		146.9		145.0		146.0
5	2.01 (d, 11.2)	56.3	2.05 (d, 11.0)	55.4	2.34 (d, 11.1)	54.0
6	3.93 (br dd, 11.2, 11.2)	48.4	3.93 (t, 11.0)	53.4 (t)[d]	3.62 (t, 11.1)	48.5
7	1.33 (m)	50.2	1.49 (m)	48.6	2.18 (d, 10.9)	46.5
8α	1.38 (2H, m)	18.4	1.49 (m)	17.8	1.45 (m)	17.5
8β			1.21 (m)		1.25 (m)	
9α	1.12 (m)	40.1	1.22 (m)	39.6	1.29 (m)	39.1
9β	1.39 (m)		1.47 (m)		1.37 (m)	
10		37.1		37.2		36.9
11	2.24 (m)	26.2	2.27 (m)	26.9	2.74 (m)	26.0
12	1.06 (d, 6.8)	14.6	0.95 (d, 7.1)	21.0	1.03 (d, 4.5)	15.2
13	0.87 (d, 7.1)	21.1	0.83 (d, 6.9)	15.4	0.99 (d, 4.6)	20.6
14a	4.94 (bs)	107.0	4.63 (bs)	108.2	5.06 (bs)	108.1
14b	5.16 (bs)		4.99 (bs)		5.08 (bs)	
15	0.75 (s)	15.3	0.66 (s)	16.7	0.67 (s)	16.4
16		157.4		155.3 (t)[d]		
17	3.67 (s)	51.0				
NH	5.72 (m)					

[a] In pyridine-d_5.
[b] In $CDCl_3$.
[c] δ in ppm.
[d] The signals appear as a 1:1:1 triplet (J=5.8 Hz) due to the coupling with the nitrogen atom.

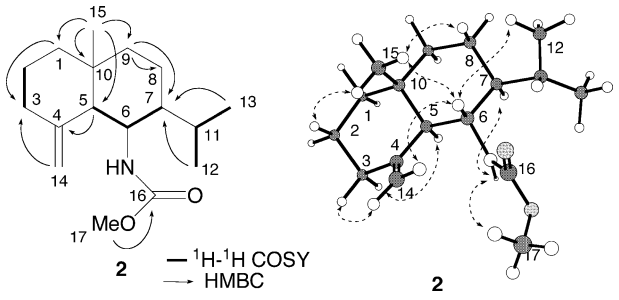

Figure 5. Selected ^{1}H–^{1}H COSY, HMBC (left) and NOESY (right) correlations for halichonadin B (**2**).

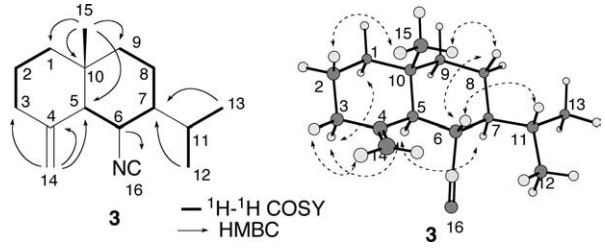

Figure 6. Selected ^{1}H–^{1}H COSY, HMBC (left) and NOESY (right) correlations for halichonadin C (**3**).

sponge (2.5 kg, wet weight) was extracted with methanol (2 L×2). The methanolic extract (115 g) was partitioned between water (400 mL) and ethyl acetate (400 mL×3). The EtOAc soluble material (7.9 g) was subjected to a silica gel column ($CHCl_3$/MeOH, 95:5 and then petroleum ether/diethyl ether, 9:1) to afford halichonadins A–D (**1**–**4**) (**1**, 0.004%, wet wt.; **2**, 0.001%; **3**, 0.01%; **4**, 0.0004%) and acanthenes B and C.

1.2.1. Halichonadin A (1). Colorless needles; mp 114–116 °C; $[\alpha]_D^{24}$ −30° (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3368 and 1637 cm^{-1}; ^{1}H and ^{13}C NMR (Table 1); EIMS (positive) *m/z* 468 (M^+); HREIMS *m/z* 468.4079 (M^+), calcd for $C_{31}H_{52}N_2O$, 468.4080.

1.2.2. Halichonadin B (2). Colorless amorphous solid; $[\alpha]_D^{24}$ −10° (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 3367 and 1698 cm^{-1}; ^{1}H and ^{13}C NMR (Table 2); EIMS (positive) *m/z* 279 (M^+); HREIMS *m/z* 279.2203 (M^+), calcd for $C_{17}H_{29}NO_2$, 279.2208.

1.2.3. Halichonadin C (3). Colorless amorphous solid; $[\alpha]_D^{19}$ −130° (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max} 2135 cm^{-1}; ^{1}H and ^{13}C NMR (Table 2); EIMS (positive) *m/z* 231 (M^+); HREIMS *m/z* 231.1987 (M^+), calcd for $C_{16}H_{25}N$, 231.1995.

1.2.4. Halichonadin D (4). Yellow oil; $[\alpha]_D^{27}$ +18° (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3408 cm^{-1}; ^{1}H and ^{13}C NMR

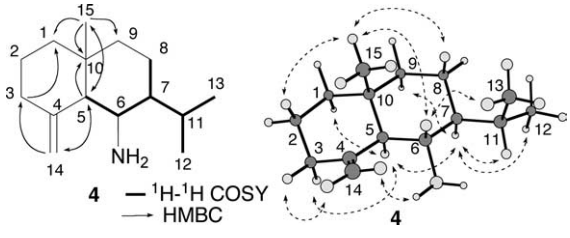

Figure 7. Selected ^{1}H–^{1}H COSY, HMBC (left) and NOESY (right) correlations for halichonadin D (**4**).

Table 3. Antimicrobial activity of halichonadins A–D (**1**–**4**)

Compound	MIC (μg/mL)							
	M. luteus	*B. subtilus*	*E. coli*	*C. neoformans*	*C. albicans*	*P. variotii*	*A. niger*	*A. fumigatus*
Halichonadin A (**1**)	16.7	>33.3	>33.3	16.6	>33.3	>33.3	>33.3	>33.3
Halichonadin B (**2**)	4.18	16.7	>33.3	4.18	16.7	16.7	33.3	33.3
Halichonadin C (**3**)	0.52	>33.3	>33.3	0.0625	2.09	1.04	1.04	1.04
Halichonadin D (**4**)	16.7	>33.3	>33.3	33.3	>33.3	>33.3	>33.3	>33.3

Bacteria: *Micrococcus luteus*, *Bacillus subtilis*, and *Escherichia coli*. Fungi: *Cryptococcus neoformans*, *Candida albicans*, *Paecilomyces variotii*, *Aspergillus niger*, and *Aspergillus fumigatus*.

(Table 2); EIMS (positive) *m/z* 221 (M^+); HREIMS *m/z* 221.2135 (M^+), calcd for $C_{15}H_{27}N$, 221.2143.

1.2.5. Hydrogenation of halichonadin A (1). Halichonadin A (**1**, 0.1 mg) in 1% AcOH/MeOH (50 μL) was treated with 5%Rh–Al_2O_3 (0.2 mg) under an H_2 atmosphere at room temperature for 15 h. The mixture was filtered with Celite and concentrated in vacuo to give compound **5**. **5**: EIMS (positive) *m/z* 472 (M^+); HREIMS *m/z* 472.4385 (M^+), calcd for $C_{31}H_{56}N_2O$, 472.4378.

1.2.6. Acetylation of halichonadin D (4). Halichonadin D (**4**, 0.1 mg) in pyridine (20 μL) was treated with Ac_2O (10 μL) at room temperature for 2 h. The mixture was concentrated to give acetate **6**. **6**: EIMS (positive) *m/z* 263 (M^+); HREIMS *m/z* 263.2241 (M^+), calcd for $C_{17}H_{29}NO$, 263.2250 ^{1}H NMR ($CDCl_3$) δ_H 0.76 (1H, s, H-15), 0.89 (3H, d, J=6.1 Hz, H-12), 0.90 (3H, d, J=5.8 Hz, H-13), 1.04 (1H, m, H-7), 1.19 (1H, m, H-9α), 1.25 (1H, m, H-1α), 1.35 (1H, m, H-8β), 1,44 (2H, m, H-1β, H-8α), 1.51 (1H, m, H-9β), 1.60 (2H, m, H-2), 1.69 (1H, d, J=10.5 Hz, H-5), 1.85 (1H, m, H-11), 1.88 (1H, m, H-3α), 1.91 (3H, s, H-17), 2.29 (1H, m, H-3β), 3.94 (1H, dd, J=10.5 Hz, H-6), 4.62 (1H, br s, H-14a), 4.77 (1H, d, J=9.0 Hz, NH), and 4.80 (1H, br s, H-14b).

Acknowledgements

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Molecular recognition of L-leucyl-L-alanine: enantioselective inclusion of alkyl methyl sulfoxides

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Abstract—A simple aliphatic dipeptide, L-leucyl-L-alanine (Leu-Ala), includes several alkyl methyl sulfoxides enantioselectively to form inclusion crystals. From single-crystal X-ray analyses of three inclusion compounds of dimethyl sulfoxide (DMSO), isobutyl methyl sulfoxide, and benzyl methyl sulfoxide, it was elucidated that Leu-Ala molecules self-assemble to form layer structures and the sulfoxides are included via hydrogen bonding in a cavity between these layers. The inclusion cavity has methyl group and isobutyl group at its each side, and the guest sulfoxide is placed in such a manner that its methyl group faces toward the methyl of the Leu-Ala cavity. When the alkyl group of the sulfoxide is comparably large, it is located in the residual space of the cavity to attain effective crystal packing. Thus, the sulfoxides having a comparably large group such as isobutyl, butyl, and benzyl are included with a high (*R*)-enantioselectivity in Leu-Ala crystals.

1. Introduction

The chemistry of inclusion crystals has a long history, and one important aspect of this chemistry is to recognize the chirality of the included guest: for optical resolution of racemic compounds, enantioselective inclusion has emerged in the field of crystal engineering so that many artificial hosts have been developed for molecular recognition of organic guests.[1,2] For example, several chiral hosts were reported for asymmetric sulfoxides that have a chiral center on their sulfur atom. Toda has reported a practical separation of dialkyl sulfoxides using inclusion phenomena with chiral binaphthol[3a,b] or TADDOL derivatives.[3c] These host molecules have widely spread aromatic parts, which act as the walls of the chiral cavities. We have also demonstrated that a simple dipeptide host, (*R*)-phenylglycyl-(*R*)-phenylglycine, effectively forms inclusion crystals with various sulfoxides in a highly enantioselective manner.[4] The sulfoxides were included in the channel between the layers that were constructed by dipeptide backbones. In addition to hydrogen bonding, π–π interactions[5] and CH/π interactions[6] between the sulfoxide and two phenyl groups of the dipeptide play an essential role in recognizing the chirality of the sulfoxide. In a solution phase, chiral discrimination of sulfoxides has been realized by NMR chiral shift reagents such as binaphthol,[7a,b] α-methoxyphenylacetic acid,[7c] (*R*)-(−)-*N*-(3,5-dinitrophenyl)-α-phenylethylamine.[7d] From the facts mentioned above, the presence of benzene rings in the hosts and/or the guest seems to be crucial to the chiral recognition of the sulfoxides. Is this generally valid? With this question in mind, we started our investigation to realize that a host having no benzene ring can recognize the chirality of aliphatic sulfoxides to form an inclusion compound.

First, our attention was focused on the dipeptides that consisted of aliphatic amino acids. This is mainly because their backbones can be considered from our previous literatures[4,8] to construct a layer structure via salt formation and hydrogen bonding between their terminal amino and carboxyl groups. It is also likely that the inclusion cavities are produced by the alkyl side chains of the dipeptide that stand perpendicular to the layer. We synthesized several aliphatic dipeptides such as Leu-Gly, Leu-Ala, Ala-Leu, and Leu-Leu, which were subjected to a preliminary experiment to evaluate their recognition ability toward aliphatic sulfoxides: the solid dipeptides were simply stirred together with typical aliphatic sulfoxides such as methyl propyl sulfoxide and butyl methyl sulfoxide in hexane for 24 h. The formed inclusion compound was collected by filtration and washed with diethyl ether. Except for Leu-Leu, the aliphatic dipeptides examined here gave the expected inclusion

Keywords: Crystal engineering; Inclusion compounds; Peptides; Sulfoxides; Enantiomeric recognition.
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compound that consists of the dipeptide and the sulfoxide in a ratio of approximatly 1:1. Among them, the inclusion compound of Leu-Ala and butyl methyl sulfoxide showed the highest chiral recognition ability (the enantiomeric excess of the included sulfoxide: 58%. Cf. Leu-Gly/^{n}PrSOMe 32%; Leu-Gly/^{n}BuSOMe 15%; Leu-Ala/^{n}PrSOMe 17%; Ala-Leu/^{n}PrSOMe 10%; Ala-Leu/^{n}BuSOMe 47%). Hence, we selected Leu-Ala as a host aliphatic dipeptide for further detailed investigation. It is noted that the crystal structure of Leu-Ala accompanied with water[9a] or dimethyl sulfoxide (DMSO)[9b] as solvation ligands have been reported from the standpoint of structural interest and conformational information of the dipeptide.

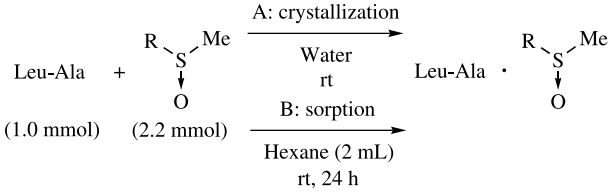
2. Results and discussion

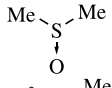
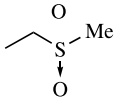
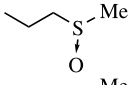
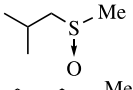
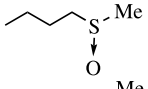
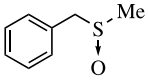
Since the present Leu-Ala shows good solubility in water, an inclusion compound was prepared by two methods: (a) Leu-Ala was crystallized from water in the presence of an alkyl methyl sulfoxide [method A: 'crystallization'] and (b) Leu-Ala and the sulfoxide were simply stirred in hexane for 24 h because Leu-Ala is insoluble in hexane [method B: 'sorption']

The results for enantioselective inclusion of several alkyl methyl sulfoxides are summarized in Table 1. Efficiency (Ef. in Tables 1 and 2) means 'mol percentage' of the guest molecule based on Leu-Ala molecule in the inclusion compound, which was determined by ^{1}H NMR spectra and elemental analyses. Interlayer distances (LD in Table 1) were gained by powder X-ray diffraction (PXRD) of the inclusion compounds, which showed diffraction peaks at lower 2θ range. This assignment of the interlayer distance was confirmed by the single-crystal structure (vide infra). Clearly, these results showed the formation of a 1:1 complex. The included alkyl methyl sulfoxide was recovered from the inclusion crystals and its enantiomeric excess was estimated by its optical rotation and the Kusumi's NMR method that transforms the sulfoxide into a diastereomeric mixture of its *N*-(methoxyphenylacetyl)-sulfoximine derivatives in order to estimate the enantiomeric excess.[10] We also examined the inclusion of benzyl methyl sulfoxide, a typical dialkyl sulfoxide having one phenyl group, whose result is also shown in Table 1 (entry 6).

In all entries of Table 1, both methods A and B gave comparable results for molecular recognition, though method A is often superior to method B in terms of the enantiomeric excess of the included sulfoxide. Small sulfoxides such as dimethyl sulfoxide and ethyl methyl sulfoxide formed the inclusion compounds with narrow interlayer distances (LD=9.3 and 9.4 Å). The stereochemistry of the preferably included enantiomer of ethyl methyl sulfoxide was *S*-form (8% ee by method A and 14% ee by method B in entry 2). In contrast, (*R*)-enantiomer was preferably recognized in the inclusion compound of methyl propyl sulfoxide though its enantioselectivity was low (13% ee by method A and 17% ee by method B in entry 3). Interestingly, other (*R*)-alkyl methyl sulfoxides bearing isobutyl, butyl, and benzyl groups were included with a high enantioselectivity (94, 94, and 93% ee by method A, respectively), and their interlayer distances were similar to each other within the range of 11.0–11.2 Å (entries 4–6). The efficient chiral recognition of benzyl methyl sulfoxide

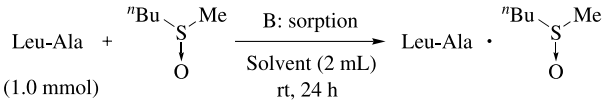
Table 1. Enantioselective inclusion of alkyl methyl sulfoxides by Leu-Ala



Entry	Sulfoxide	A: crystallization		B: sorption		LD[a]/Å
		ee/%	Ef.[b]/%	ee/%	Ef.[b]/%	
1		—	100	—	103	9.4
2		8(*S*)	98	14(*S*)	98	9.3
3		13(*R*)	97	17(*R*)	99	10.4
4		94(*R*)	100	60(*R*)	98	11.2
5		94(*R*)	100	58(*R*)	104	11.2
6		93(*R*)	93	44(*R*)	97	11.0

[a] LD is an interlayer distance measured by PXRD.
[b] Ef. means mol% of the guest based on the dipeptide in the inclusion complex.

Table 2. Enantioselective inclusion of butyl methyl sulfoxide by Leu-Ala



Entry	Solvent	Equiv of guest	ee/%	Ef.[a]/%
1	Hexane	2.2	58 (*R*)	104
2	Hexane	4.0	69 (*R*)	86
3	Hexane	8.0	75 (*R*)	99
4	Diethyl ether	2.2	59 (*R*)	98
5	Toluene	2.2	57 (*R*)	102

[a] Ef. means mol% of the guest based on the dipeptide in the inclusion complex.

by Leu-Ala is in marked contrast with that by (*R*)-phenylglycyl-(*R*)-phenylglycine, which formed the inclusion crystals containing both enantiomers of benzyl methyl sulfoxide to result in the racemic recognition.[4a]

As shown in Table 2, the replacement of hexane with diethyl ether or toluene as a dispersion solvent in method B did not affect the enantioselectivity and the Ef. significantly (entries 4 and 5). As the amount of the guest increased, the enantioselectivity was raised up to 75% ee with 8 equiv of sulfoxide (entries 2 and 3).

Fortunately, we obtained good-quality single crystals for the inclusion compound of isobutyl methyl sulfoxide, DMSO, and benzyl methyl sulfoxide, which could be analyzed by single-crystal X-ray crystallography. Figure 1 shows the top view of the sheet structure of the inclusion compound, where the dipeptide backbones are colored in black, guest sulfoxides in gray, and alkyl groups of Leu-Ala in white. The space-filling models reveal that, in all of these inclusion crystals, the guest molecules are similarly arranged in the cavity of Leu-Ala, though dimethyl sulfoxide is disordered (Fig. 1b). As mentioned previously, the inclusion crystal of DMSO was reported in the literature.[9b] The result obtained here is similar to the literature one: the guest DMSO has the disordered structure of a trigonal-bipyramidal geometry having the sulfur atom that occupies two coordination sites (6:4). Our result is shown in Figure 1b: the ratio (S1/S2= 62:38) is reproducible and the disordered site occupancy is statistic.

In the present inclusion compounds, the dipeptide molecules have a straight glycylglycine backbone to construct a two-dimensional layer. In Figure 2, the intermolecular distances of hydrogen bonding in crystals are summarized. A set of the hydrogen bonding distances is similar to each other in all of the Leu-Ala inclusion compounds. The Leu-Ala backbones are arranged into a parallel motif to construct a sheet by ionic pairing of the carboxyl and amino groups via hydrogen bonding network: one terminal COO^- links two $^+NH_3$ of adjacent dipeptides and the $^+NH_3$ also binds two adjacent COO^- groups. Here, two characteristic distances, the repetition of glycylglycine backbone (*L*) and the distance between dipeptides arranged side by side (*W*), are introduced, and then the area occupied by glycylglycine backbone is estimated by $L\times W$. By comparison of three crystal structures of Leu-Ala, it was found that the values of $L\times W$ increased as the guest sulfoxides became larger.

It is worthy to note that these dipeptide backbone arrangements are quite similar to those of the inclusion compounds of (*R*)-phenylglycyl-(*R*)-phenylglycine.[4] Although the chiral cavity of Leu-Ala possesses no benzene ring, isobutyl methyl sulfoxide is included with a high enantioselectivity. Careful insight into the X-ray structure of the inclusion cavity suggests the reason why the chiral discrimination is achieved. Although the layer structure of Leu-Ala is similar in all of the inclusion compounds mentioned herein, these dipeptide sheets are arranged

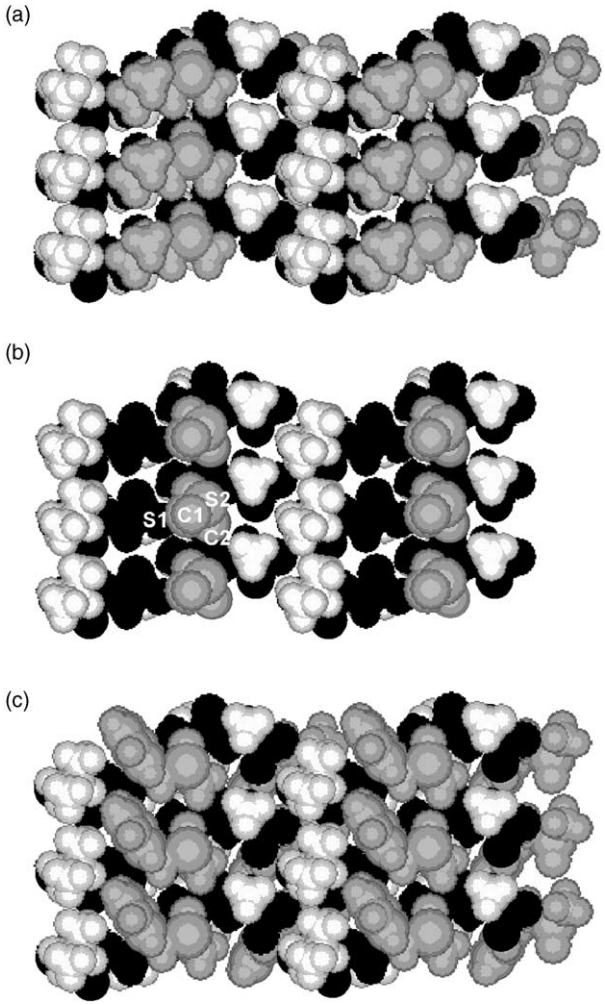
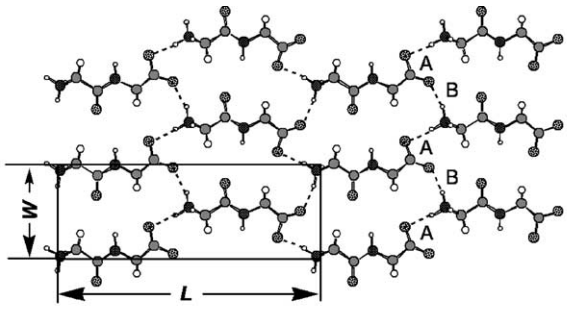


Figure 1. Top views of sheet structure of inclusion crystals (CPK model). (a) Leu-Ala with (*R*)-isobutyl methyl sulfoxide. (b) Leu-Ala with dimethyl sulfoxide. Hydrogens of the sulfoxide were omitted for its disordered structure. (c) Leu-Ala with (*R*)-benzyl methyl sulfoxide.



	host-host / Å		host-guest / Å
	A N---O	B N---O	N---O(G)
Leu-Ala · ^{t}BuSOMe	2.76	2.75	2.84
Leu-Ala · BnSOMe	2.78	2.75	2.81
Leu-Ala · MeSOMe	2.88	2.75	2.79

	L / Å	*W* / Å	*L* X *W* / Å^2
Leu-Ala · ^{t}BuSOMe	15.94	5.40	86.08
Leu-Ala · BnSOMe	15.88	5.57	88.45
Leu-Ala · MeSOMe	16.10	5.21	83.88

Figure 2. Atomic distances of intermolecular hydrogen bonds and dipeptide backbones.

differently depending on the guest structure, as shown in Figure 3.

The guest sulfoxide in Leu-Ala crystals is bound to the dipeptide-backbone layer via hydrogen bonding between the sulfoxide oxygen and the ammonio proton of Leu-Ala with a N···O(G) distance of 2.79–2.84 Å. The inclusion compound of (*R*)-isobutyl methyl sulfoxide has $P2_12_12_1$ space group: the sheets piles up in the opposite direction (arrows in Fig. 3a). In this inclusion compound, the sulfinyl methyl group is faced toward the methyl group of Leu-Ala in the cavity. The larger area in the Leu-Ala cavity is filled with the isobutyl group. The such placement of isobutyl methyl sulfoxide in the inclusion cavity can diminish the space between the layers to make the host–guest packing effective. Consequently, (*R*)-enantiomer of the sulfoxide is recognized as the suitable guest. It should be noted that, in the inclusion compound of benzyl methyl sulfoxide, the sheets stacked in the same direction shown by the arrows to become the space group $P2_1$ (see Fig. 3c). In this case, the phenyl ring of the sulfoxide seems to contact with the Leu-Ala in the neighboring layer. Thus, the terminal proton of the Leu part is located 2.9 Å from the center of the benzene ring. This is within the distance that is capable of CH/π interaction.[6] This interaction would compel the dipeptide sheets to pile up in the same direction.

Since DMSO is too small to fill the inclusion cavity of Leu-Ala (Fig. 3b), another DMSO molecule belonging to the adjacent layer sticks the residual vacant space and, as a result, the layers interdigitate each other so as to make the interlayer distance smaller (9.4 Å). The PXRD pattern of the inclusion crystals with ethyl methyl sulfoxide showed the interlayer distance of 9.3 Å that is comparable with that of the DMSO inclusion crystal. This suggests that these crystals have the interdigitating structure similar to that of the DMSO inclusion compound. If the C1 (methyl) group of the disordered sulfoxide (Fig. 3b) is replaced with ethyl group, the stereochemistry of the included ethyl methyl sulfoxide would be *S*. Indeed, ethyl methyl sulfoxide was recognized with an enantioselectivity of 8–14% ee (*S*). While, methyl propyl sulfoxide and butyl methyl sulfoxide expanded the interlayer distance to 10.4 and 11.2 Å, respectively. From these facts, it seems to be suggested that the sulfoxide molecule itself is large enough to fill the cavity without the aid of another sulfoxide molecule. Since the (*R*)-form of these sulfoxides was preferably recognized by Leu-Ala crystal, it is likely that the structures of these sulfoxide inclusion crystals are analogous to that of (*R*)-isobutyl methyl sulfoxide inclusion crystal.

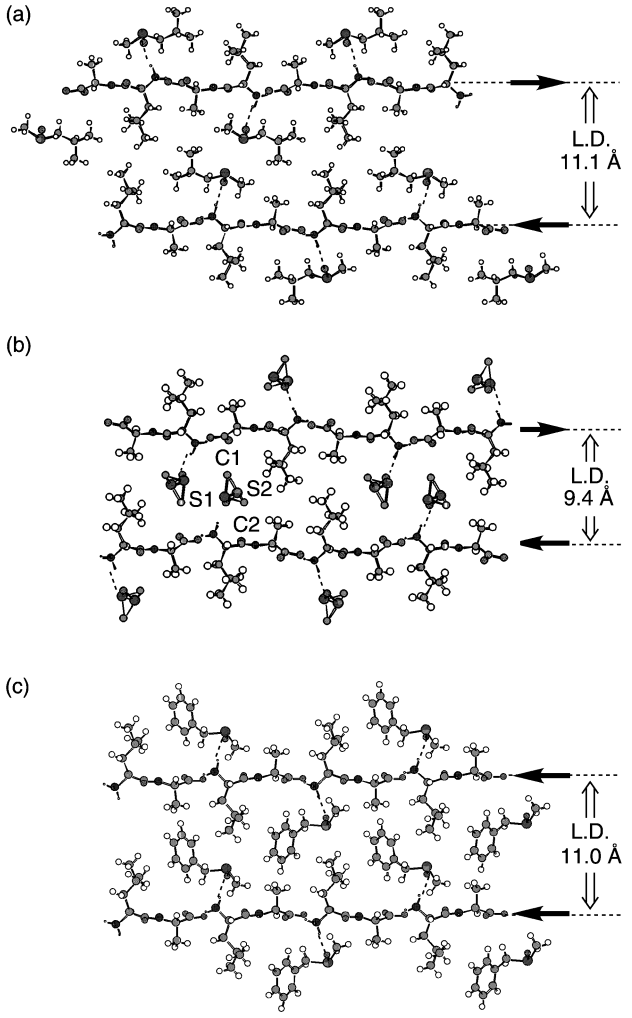


Figure 3. Layer structure of inclusion crystals. The arrows indicate the direction of the sheet from the *C*-terminal to the *N*-terminal. (a) Leu-Ala with (*R*)-isobutyl methyl sulfoxide. (b) Leu-Ala with dimethyl sulfoxide. (c) Leu-Ala with (*R*)-benzyl methyl sulfoxide.

3. Conclusion

L-Leucyl-L-alanine molecules self-assemble by intermolecular salt formation and hydrogen bonding to form a layer structure. In the cavity between the layers, alkyl methyl sulfoxides (alkyl = methyl, ethyl, propyl, isobutyl, butyl, and benzyl) were included by the driving force of hydrogen bonding between the oxygen atom of the sulfinyl group and the ammonio proton of Leu-Ala. The included sulfoxide is placed in such a manner that the sulfinyl methyl group faces toward the methyl group of Ala part. When the sulfoxide such as DMSO or ethyl methyl sulfoxide is too small to fill the cavity, the layers are interdigitated to one another and, as a result, the cavity is filled by two sulfoxide molecules. In the case that the alkyl group is comparably large, it is placed in the residual space and, as a result, one molecule of the sulfoxide itself can fill the cavity. Thus, the alkyl methyl sulfoxide having a comparably large group as the alkyl was included with a high (*R*)-enantioselectivity.

4. Experimental

4.1. General methods

NMR spectra were recorded at 300 MHz for ^{1}H NMR. Elemental analyses were performed at the Chemical Analysis Center, Chiba University, Japan. Inclusion efficiency was determined by NMR measurements and elemental analyses. Melting points (decomposition) were measured on a TG-DTA. As a chiral shift reagent, (*S*)-α-methoxyphenyl acetic acid [(*S*)-MPAA] was purchased from Aldrich Chemical Co.

4.1.1. Synthesis of Leu-Ala. Protected amino acids, *N*-(benzyloxycarbonyl)-L-leucine and L-alanine benzyl ester *p*-toluenesulfonate, were prepared according to literature procedure.[11,12] These were coupled with DCC and HOBt to form the corresponding protected dipeptide.[13] Final deprotection was performed by hydrogenation with Pd black under hydrogen atmosphere. The Leu-Ala was dried over 3 h at 70 °C in vacuo. It contained 2.1 wt% water detected by elemental analysis and TG-DTA.[14] Leu-Ala·0.24H_2O: a colorless solid; dec 143.5 °C; $[\alpha]_D^{25} = +21.7$ (*c* 0.82, methanol); $[\alpha]_D^{25} = +22.9$ (*c* 5, methanol);[15] ^{1}H NMR (300 MHz, D_2O) δ (q, 1.0H, J=7.28 Hz), 4.01 (t, 1.0H, J=7.21 Hz), 1.84–1.68 (m, 3.0H), 1.38 (d, 3.0H, J=7.28 Hz), 0.99 (d, 3.0H, J=6.32 Hz), 0.97 (d, 3.0H, J=6.32 Hz); IR (KBr) 3057, 1664, 1589 1510 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 12.8(1.00), 7.16(0.43), 5.80(0.28), 4.87(0.47), 4.14(0.64). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.24H_2O$: C, 52.33; H, 9.02; N, 13.56. Found: C, 52.31; H, 9.11; N, 13.40.

4.2. Preparation of inclusion compounds of Leu-Ala and alkyl methyl sulfoxide

Method A. To a solution of Leu-Ala (1.0 mmol) in water (2 mL) was added a racemic sulfoxide (2.2 mmol). Inclusion compounds were formed by slow evaporation of a solution of the complex at an ambient temperature, then it was collected by filtration and washed with diethyl ether (20 mL).

Method B. Crystals of Leu-Ala are essentially insoluble in hexane. A suspension of Leu-Ala (1.0 mmol) in hexane (2 mL) was stirred together with a racemic sulfoxide (2.2 mmol) at an ambient temperature for 1 day. The formed inclusion compound was collected by filtration and washed with diethyl ether (20 mL).

4.2.1. Leu-Ala·ethyl methyl sulfoxide. A colorless solid; dec 127.2 °C; IR (KBr) 3350, 1664, 1587, 1510, 1005 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 9.33(0.34), 9.14(0.31), 6.99(0.33), 4.98(1.00), 4.90(0.77), 4.01(0.61). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.98C_3H_8OS$: C, 49.02; H, 8.90; N, 9.57. Found: C, 48.92; H, 9.11; N, 9.53.

4.2.2. Leu-Ala·methyl *n*-propyl sulfoxide. A colorless solid; dec 135.2 °C; IR (KBr) 3352, 1666, 1583, 1510, 1005 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 10.4(0.93), 8.70(0.24), 5.27(0.90), 5.00(1.00), 3.73(0.69), 3.54(0.65). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.97C_3H_8OS$: C, 50.68; H, 9.15; N, 9.18. Found: C, 50.42; H, 9.14; N, 9.03.

4.2.3. Leu-Ala·*n*-butyl methyl sulfoxide. A colorless solid; dec 130.2 °C; IR (KBr) 3354, 1669, 1581, 1507, 1009 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.2(0.34), 10.7(0.38), 7.80(1.00), 5.53(0.18), 4.50(0.23), 3.66(0.79). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 1.0C_5H_{12}SO$: C, 52.15; H, 9.38; N, 8.69. Found: C, 52.05; H, 9.44; N, 8.61.

4.2.4. Leu-Ala·isobutyl methyl sulfoxide. A colorless solid; dec 130.5 °C; IR (KBr) 3353, 1666, 1584, 1508, 1009 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.2(0.65), 10.3(0.84), 5.37(0.47), 4.46(0.34), 3.70(1.00), 3.62(0.81). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 1.0C_5H_{12}SO$: C, 52.15, H, 9.38; N, 8.69. Found: C, 51.78; H, 9.66; N, 8.59.

4.2.5. Leu-Ala·benzyl methyl sulfoxide. A colorless solid; dec 167.2 °C; IR (KBr) 3354, 1671, 1578, 1508, 1018 cm^{-1}. Powder X-ray diffraction [Å(I/I_0)] 11.0(0.10), 10.5(0.10), 8.53(0.33), 4.49(0.47), 4.40(1.00), 3.95(0.52). Anal. Calcd for $C_9H_{18}N_2O_3\cdot 0.93C_8H_{10}SO$: C, 57.12; H, 7.96; N, 8.10. Found: C, 56.85; H, 8.05; N, 7.81.

4.3. Determination of stereochemistry and enantiomeric excess in the inclusion

The included sulfoxide was isolated by dissolution of the inclusion compound in water (5.0 mL) and extraction with $CHCl_3$. In addition to comparison of the optical rotation to the value of the literature, absolute configuration and enantiomeric excess of recognized sulfoxides were determined by a Kusumi's NMR method (chiral sulfoximines), another NMR method with a chiral shift reagent [(*S*)-MPAA], or a chiral HPLC method. According to the Kusumi's methodology,[10] *N*-(methoxyphenylacetyl)-sulfoximines were obtained from sulfoxides by a one pot reaction (alkyl methyl sulfoxide/*O*-(mesitylsulfony)-hydroxylamine[16]/$CHCl_3$ then (*S*)-MPAA/PyBOP/HOBt/pyridine).

4.3.1. Ethyl methyl sulfoxide. $[\alpha]_D^{25} = +7.69$ (*c* 1.26, ethanol). 8.1% ee *S* by NMR;[10] *S*-ethyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.54H, *S*

major), 4.74 (s, 0.46H, *R* minor), 3.47–3.10 (m, 8.0H, *S* major and *R* minor), 1.31 (t, 1.38H, $J=7.42$ Hz, *R* minor), 1.18 (t, 1.62H, $J=7.49$ Hz, *S* major).

4.3.2. Methyl propyl sulfoxide. $[\alpha]_D^{25}=-17.8$ (*c* 0.94, ethanol); 13% ee *R* by [α]; (*R*)-(−)-methyl *n*-propyl sulfoxide: $[\alpha]_D^{25}=-139.0$ (*c* 0.83, EtOH).[17a] *S*-Methyl *n*-propyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 17% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.42H, *S* minor), 4.73 (s, 0.58H, *R* major), 3.41–3.12 (m, 8.0H, *R* major and *S* minor), 1.79–1.55 (m, 2.0H, *R* major and *S* minor), 1.03 (t, 1.74H, $J=$ 7.42 Hz, *R* major), 0.94 (t, 1.26H, $J=7.42$ Hz, *S* minor).

4.3.3. Butyl methyl sulfoxide. $[\alpha]_D^{25}=-103.2$ (*c* 1.12, ethanol); 94% ee *R* by [α]; (*S*)-(+)-*n*-butyl methyl sulfoxide: $[\alpha]_D^{25}=+109.9$ (*c* 1.53, ethanol).[17a,b] *S*-*n*-Butyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 90% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.75 (s, 0.05H, *S* minor), 4.73 (s, 0.95H, *R* major), 3.48–3.12 (m, 8.0H, *R* major and *S* minor), 1.71–1.60 (m, 2.0H, *R* major and *S* minor), 1.40 (sext, 1.90H, $J=7.42$ Hz, *R* major), 1.30 (sext, 0.10H, $J=7.57$ Hz, *S* minor), 0.89 (t, 2.85H, $J=7.28$ Hz, *R* major), 0.81 (t, 0.15H, $J=7.32$ Hz, *S* minor).

4.3.4. Isobutyl methyl sulfoxide. $[\alpha]_D^{25}=-129.2$ (*c* 2.94, ethanol); 94% ee *R* by [α]; (*S*)-(+)-isobutyl methyl sulfoxide: $[\alpha]_D^{25}=+138.0$ (*c* 0.97, ethanol).[17a,b] *S*-Isobutyl methyl *N*-[(*S*)-methoxyphenylacetyl]sulfoximine: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$, 88% ee *R*) δ 7.51–7.27 (m, 5.0H), 4.77 (s, 0.06H, *S* minor), 4.74 (s, 0.94H, *R* major), 3.47–3.00 (m, 8.0H, *R* major and *S* minor), 2.23 (sept, 0.96H, $J=6.71$ Hz, *R* major), 1.99 (sept, 0.04H, $J=$ 6.53 Hz, *S* minor), 1.07 (d, 2.88H, $J=6.73$ Hz, *R* major), 1.02 (d, 2.88H, $J=6.73$ Hz, *R* major), 0.96 (d, 0.12H, $J=$ 6.73 Hz, *S* minor), 0.83 (d, 0.12H, $J=6.87$ Hz, *S* minor).

4.3.5. Benzyl methyl sulfoxide. $[\alpha]_D^{25}=-97.4$ (*c* 0.27, ethanol); 93% ee *R* by [α], (*R*)-(+)-benzyl methyl sulfoxide: $[\alpha]_D^{25}=-105$ (*c* 6.0, ethanol).[17c] HPLC (Daicel Chiralcel OB–H) eluent, hexane/2-propanal=9:1, flow rate=0.9 mL/min, $t_R(S)=31$ min, $t_R(R)=39$ min, 97% ee *R*. ^{1}H NMR (300 MHz, with (*S*)-MPAA (3 mol equiv) in $CDCl_3$, 94% ee *R*) δ 4.17 (d, 1.00H, $J=12.8$ Hz, *R* major and *S* minor), 3.99 (d, 0.03H, $J=13.2$ Hz, *S* minor), 3.98 (d, 0.97H, $J=12.9$ Hz, *R* major), 2.51 (s, 2.91H, *R* major), 2.49 (s, 0.09H, *S* major). Aromatic H could not be identified because of (*S*)-MPAA.

4.4. X-ray analyses

X-ray powder diffractions were obtained with a MAC Science MXP diffractometer using graphite-monochromated Cu Kα radiation (30 kV, 200 mA). The spectra were measured at room temperature between 2 and 50° in the 2θ scan mode with steps of 0.01° in 2θ and 4°/min.

4.5. Crystallographic data for the inclusion compounds

To the solution of Leu-Ala was added the guest (dimethyl sulfoxide, isobutyl methyl sulfoxide and benzyl methyl sulfoxide) directly in a vial, then a lid of the vial was loosely closed for evaporation of the solvent. The samples were allowed to stand for several days to form the desirable single crystals. Data collection was performed on a Mac Science MXC18 four-circle diffractometer with graphite-monochromated Cu Kα ($\lambda=1.54178$) radiation using the $2\theta-\omega$ scan technique, and the X-ray intensities were measured up to $2\theta=140°$ at 298 K. The structures were solved by a direct method SIR97[18] and refined by a computer program package; maXus ver. 4.3.p2 from BrukerAXS. Hydrogen atoms were placed in calculated position with C–H= 0.96 Å. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 250905-250907. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

The inclusion compound of Leu-Ala and isobutyl methyl sulfoxide: $C_{14}H_{30}N_2O_4S$, M_w 322.47, crystal dimensions $0.50\times0.50\times0.10$ mm^3, orthorhombic, $P2_12_12_1$, $a=$ 22.212(7) Å, $b=15.943(5)$ Å, $c=5.401(2)$ Å, $V=$ 1912.7(11) Å^3, $Z=4$, $d_{calcd}=1.120$ g cm^{-3}, 2237 reflections measured, 2157 independent, $R1=0.051$ (1541 reflections with $I>2.00\sigma(I)$), $Rw2=0.174$, $S=1.018$, 190 parameters, with heavy atoms refined anisotropically, residual electron density 0.25/−0.32.

The inclusion compound of Leu-Ala and benzyl methyl sulfoxide: $C_{17}H_{28}N_2O_4S$, M_w 356.49, crystal dimensions $0.40\times0.35\times0.10$ mm^3, monoclinic, $P2_1$, $a=10.983(8)$ Å, $b=15.878$ (12) Å, $c=5.569(4)$ Å, $\beta=96.22(6)°$, $V=$ 965.5(12) Å^3, $Z=2$, $d_{calcd}=1.226$ g cm^{-3}, 2010 reflections measured, 1932 independent, $R1=0.044$ (1746 reflections with $I>2.00\sigma(I)$), $Rw2=0.144$, $S=1.030$, 217 parameters, with heavy atoms refined anisotropically, residual electron density 0.28/−0.32.

The inclusion compound of Leu-Ala and dimethyl sulfoxide: $C_{11}H_{24}N_2O_4S$, M_w 280.39, crystal dimensions $0.45\times0.08\times0.08$ mm^3, orthorhombic, $P2_12_12_1$, $a=$ 5.208(3) Å, $b=16.095(3)$ Å, $c=18.7069(10)$ Å, $V=$ 1568.1(9) Å^3, $Z=4$, $d_{calcd}=1.188$ g cm^{-3}, 1911 reflections measured, 1782 independent, $R1=0.058$ (1120 reflections with $I>2.00\sigma(I)$); $Rw2=0.176$, $S=1.032$, 174 parameters, with heavy atoms refined anisotropically, residual electron density 0.31/−0.28.

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Evaluation of ethyl 2-carbomethoxyethenesulfinates as 2-hydroxymethyl enethiol equivalents in the Diels–Alder reaction

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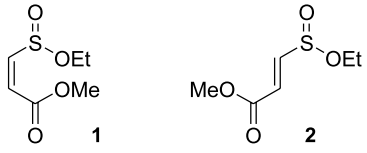
Abstract—*Z*- and *E*-ethyl 2-carbomethoxyethenesulfinates **1** and **2** hold the potential to be enethiol equivalents by way of Diels–Alder cycloaddition chemistry followed by reduction. To pursue this, both dieneophiles were subjected to thermal and Lewis acid mediated [4+2] cycloadditions with a number of dienes. Yields of cycloadduct ranged from 34 to 94%, with cycloadditions of the aromatic dienes proceeding in moderate yields, presumably due to the reversibility of the reactions. Many cycloadducts were obtained as a mixture of sulfur epimers, but these isomers were unified in the subsequent reduction step. Using either LAH or DIBAL, the cycloadducts were reduced providing β-mercapto (or sulfanyl) carbinols in 32–97%. The sequence of two reactions places sulfur and hydroxy functional groups in set relative stereochemistry within a 6-membered ring.

Whereas the Diels–Alder chemistry of vinyl sulfones and sulfoxides has been recognized and utilized for decades,[1–3] the value of vinylic sulfur acid derivatives as dienophiles has only recently come to light.[4,5] The chemistry of α,β-unsaturated sulfonates and sulfonamides has been the subject of a number of studies. Valuable contributions have been made by Metz who demonstrated the intramolecular cycloaddition chemistry of ethenesulfonates and ethenesulfonamides tethered to dienes.[6–19] That chemistry has been elaborated to include syntheses of methyl nonactate[12,10] and ivangulan,[14] and efforts toward the synthesis of pamamycin-607.[8,9] Work from the Lee group[20–24] has focused on intermolecular cycloadditions of acetylenic sulfonates,[22] and on α,β-unsaturated γ-sultones[21,23] and γ-sultams.[20,24] Some of the cycloadducts of sultones and sultams have been adapted for the creation of sultam chiral auxiliaries.[20,24]

The story of sulfinic acid derivatives as dienophiles is more fragmented. The cycloaddition chemistry of some α,β-unsaturated γ-sultims (cyclic sulfinamides) has been investigated.[25–27] Cyclohexyl ethynesulfinates undergo intermolecular cycloadditions with a variety of dieneophiles.[28] Parallel to Metz chemistry, furan tethered esters derived from ethenesulfinyl chloride readily undergo intramolecular cyclizations.[29]

The Schwan group introduced *Z*- and *E*-ethyl 2-carbomethoxyethenesulfinates **1** and **2** as dieneophiles in the thermal and Lewis acid accelerated Diels–Alder reactions with cyclopentadiene.[30] The various isomeric cycloadducts obtained in that investigation were identified with the assistance of X-ray crystallography and electrophilic cyclization chemistry. The advantage of the sulfinate functionality over sulfones and sulfoxides is its potential for facile conversion to thiol in a single reduction step. The sulfinate, as an electron withdrawing group, has the makeup to activate the alkene for normal electron demand Diels–Alder chemistry, yet emerge as a thiol after a reduction treatment. In this regard compounds **1** and **2** can act as masked 2-hydroxymethyl enethiol equivalents.



Although some enethiols have been generated and characterized,[31–33] they tend to have limited stability due to their high reactivity[31–34] and hence have not been evaluated in Diels–Alder chemistry. In any event, if enethiols could be groomed to overcome their inherent instability, they would

Keywords: Diels–Alder cycloadditions; Sulfinate; Reduction; Stereospecific; Lewis acid.
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only be applicable to inverse electron demand cycloadditions. Moreover, their nucleophilic character would be expected to complicate and more likely preclude any cycloaddition attempts.

In this paper we further investigate the general usefulness and reactive character of alkenes **1** and **2** as dienophiles and explore the simultaneous reduction of both the sulfinate and carboxylate ester functionalities of the cycloadducts.

1. Results and discussion

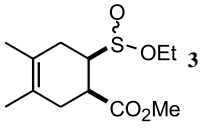
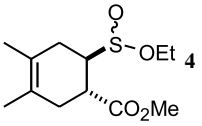
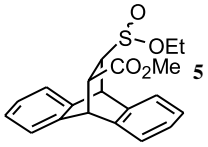
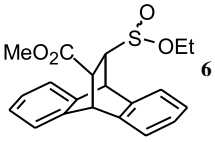
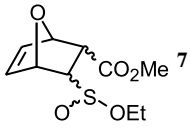
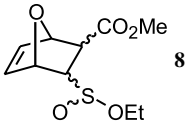
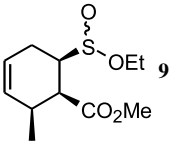
1.1. Cycloadditions

The Diels–Alder reactions of **1** and **2** with a variety of dienophiles was studied under thermal and Lewis acid catalyzed conditions. Among the numerous Lewis acids tried,[30] Et_2AlCl, $ZnCl_2$ and $ZnBr_2$ were found to be most generally applicable. A summary of the results is shown in Table 1.

Cycloaddition yields are greater when the diene is not part of an aromatic system. The ratio of sulfinyl epimers was viewed as unimportant, since the reduction step would eliminate the stereogenicity at sulfur, thereby unifying isomeric cycloadducts. Indeed some of the *exo*/*endo* stereochemistry assignments were only fully finalized after the reduction and product characterization.

When an aromatic diene was employed, the results obtained were not optimized in each individual case (entries 5–11). It was found that subjecting cycloadducts **5–8** to the reaction conditions led to some retro-Diels–Alder chemistry,

Table 1. Cycloadditions of dienophiles **1** and **2**

#	Reactants	Conditions[a]	Cycloadduct	Isomer ratios[b]	% Yield[c]
1	2,3-dimethyl	Toluene/65 °C, 24 h	 **3**	(3.1:1)	60
2	butadiene/**1**	Et_2AlCl/CH_2Cl_2/rt, 10 min		(3.7:1)	85
3	2,3-dimethyl	Toluene/100 °C, 24 h	 **4**	(1.8:1)	91[d]
4	butadiene/**2**	Et_2AlCl/CH_2Cl_2/rt, 10 min		(1.8:1)	94
5	anthracene/**1**	Toluene/80 °C, 24 h	 **5**	—	0
6		Et_2AlCl/CH_2Cl_2/rt, 18 h		(5.6:1)	62[d]
7	anthracene/**2**	Toluene/60 °C, 5 d	 **6**	(2.1:1)	34[d]
8		Et_2AlCl/CH_2Cl_2/rt, 18 h		(2.7:1)	67
9	furan/**1**	Et_2AlCl/CH_2Cl_2/rt, 10 min	 **7**	1.1(2.2:1):1(2.4:1)	46[e]
10	furan/**2**	$ZnBr_2/CH_2Cl_2$/rt, 24 h	 **8**	1.6(1.5:1):1(1.2:1)	45[d,f]
11		Et_2AlCl/CH_2Cl_2/rt, 10 min		1(1.8:1):2.3(1.8:1)	68[f]
12	piperylene/**1**	$ZnCl_2/CH_2Cl_2$/40 °C, 3 d	 **9**	(1.58:1)	78[f,g]

[a] Two different conditions are reported for many of the cycloadditions.
[b] Values in parentheses are sulfur epimer ratios; values not in parentheses are the *endo*/*exo* ratios. The endo/exo assignment is made based on the position of the sulfur containing substituent.
[c] Isomers were separated unless otherwise indicated.
[d] Yield is based on the recovered starting material.
[e] Two of the isomers could be obtained pure.
[f] Isomers could not be separated.
[g] Another unidentified isomer comprising 1/16 of the 78% was also present.

releasing both diene and dienophile. Hence the isolated yields presented in Table 1 represent a balance between the forward cycloaddition and its reverse reaction rather than an optimized yield. The propensity of cycloadducts of furan[35] and of anthracene[36] toward reversion to starting components is well established.

While the ca. 1:1 sulfinyl epimer ratio of the furan cycloadducts was predicted, the *exo*/*endo* ratio, at least compared to the cyclopentadiene cycloadducts, was disappointing particularly in light of the overall goal of efficient synthesis of 1,3 mercapto alcohols. However, there is ample precedent for low *endo*/*exo* selectivities in reactions involving a number of dienophiles with furan;[37–40] especially in comparison with cyclopentadiene cycloadditions.[41–43] The reasons offered for low *endo*/*exo* selectivities include steric obstruction[44,45] and stabilizing polar interactions[45,46] in the transition state. Also, the reversible nature allows adduct isomer interconversions, presumably favoring the *exo* isomers.[40]

Cycloadducts **9** were assigned to be epimers differing in their sulfinyl configuration, as opposed to being a pair of regio or *endo*/*exo* isomers. This conclusion was reached based on the similarity of the ^{1}H NMR resonances of the ring hydrogens and the ^{13}C NMR resonances of all carbons of the isomeric cycloadducts. This assignment was corroborated by a molecular modeling (PC Spartan Pro) exercise, which indicated that the cyclohexene ring of each isomer adopted essentially identical conformations.

The high regioselectivity of the cycloaddition yielding **9** offers insight into the electronic character of **1**. Specifically, the positioning of the methyl group in cycloadducts **9** suggests that the alkene carbon adjacent to the sulfinyl moiety has the larger coefficient of the two alkene carbons in the LUMO of the dienophile. This is consistent with the usual resonance character of the carbonyl and the accompaniment of some electron donation from the sulfinyl sulfur to the carbonyl, as has been recently discussed.[47]

1.2. Reactive character of dienophiles 1 and 2

The structural similarities of **1** and **2** to the esters of maleic and fumaric acids, respectively, are undeniable. Given the pervasiveness of the butene-1,2-doic esters as dienophiles, we compared their reactivity to sulfur analogs **1** and **2**. Simple competitive cycloaddition experiments were performed between **1** and dimethyl maleate (**10**) and between **2** and diethyl fumarate (**11**). Under the reaction conditions, one equivalent of each of the dienophiles, one equivalent of cyclopentadiene and 1.2 equiv of Lewis Acid were used. Reaction times were kept short so that a measure of the relative reactivity of the substrates could be realized. Hence with a 15 min reaction time, the consumption of diene was low. Product ratios were established through gas chromatography and Table 2 shows the results.

Table 2. Competitive cycloaddition reactions of carboxylate and sulfinate dienophiles

#	Diene pair	Conditions[a]/Lewis acid[b]	Ratio of cycloadducts
1	**1/10**	40 °C; no L.a.	188:1
2	**1/10**	$ZnCl_2$	78:1
3	**1/10**	Et_2AlCl	461:1
4	**2/11**	40 °C; no L.a.	0.71:1
5	**2/11**	$ZnCl_2$	1.55:1
6	**2/11**	Et_2AlCl	1.49:1
7	**1/2**	40 °C; no L.a.	2.11:1

[a] Reactions were performed at room temperature unless otherwise noted.
[b] 1.2 equiv of Lewis acid were employed, reaction time was 15 min.

Dienophile **1** undergoes cycloadditions with cyclopentadiene much more rapidly than dicarboxylate **10**, whereas **2** possesses reactivity comparable to **11**. Under thermal conditions, **11** is more reactive than **2**, but **2** is more reactive under Lewis acid conditions, although this latter effect may simply be a reflection of the sulfinyl unit's tighter grip on the available Lewis acid, thereby preferentially activating **2**.

The relative thermal reactivity of **1** versus **2** (entry 7) is probably not determined by steric factors since **1** reacts with almost exclusive *endo* selectivity, an alignment that demands the more sterically encumbered transitions state. Given the electron donation from the sulfinyl sulfur to the ester,[47] and since electronic factors govern the rates of cycloaddition, it can be realized that **2** has the capacity to relay electron density from the sulfinyl lone pair to the ester carbonyl, by imparting stabilizing 'push–pull' character to the double bond.[47] Dienophile **1**, with both groups on the same side of the alkene presumably has reduced electron transmission and consequently, increased reactivity.

To learn more about the Lewis base character of **1** and **2**, spectroscopic studies were performed to learn which of the two ester functionalities of **1** and **2** were complexing the Lewis acid. Solutions of dienophile in $CDCl_3$ were set up

Table 3. Spectroscopic determination of the coordination of selected Lewis acids to dienes **1** and **2**

Solution	^{1}H NMR			^{13}C NMR					IR bands	
	Vinyl H	Vinyl H	OCH_2	Vinyl C	Vinyl C	C=O	OCH_2	OCH_3	C=O	S=O
1/Et_2O	6.69	6.23	4.09	153.26	125.33	163.90	64.40	52.18	1728	1152 (m), 1119 (s)
1/$ZnCl_2$/Et_2O	6.92	6.35	4.24	150.52	127.45	163.69	67.22	52.51	1727	1152 (m), 1117 (s)
1/C_7H_8	6.69	6.20	4.11	153.27	125.44	164.02	64.60	52.34	1727	1157 (m), 1119 (s)
1/Et_2AlCl/C_7H_8	6.83	6.41	4.39	147.05	130.42	163.55	71.16	53.27	1725	1156 (w), 1116 (w), 1030 (br, s)
2/Et_2O	7.32	6.52	4.00	149.03	128.66	163.95	62.57	52.16	1731	1152 (m), 1118 (s)
2/$ZnCl_2$/Et_2O	7.35	6.56	4.07	147.61	129.51	163.72	64.25	52.33	1731	1152 (m), 1116 (s)
2/C_7H_8	7.55	6.76	3.97	149.12	128.78	164.14	62.79	52.35	1730	1154 (m), 1132 (s)
2/Et_2AlCl/C_7H_8	7.53	6.86	4.27	142.28	132.80	162.71	69.28	52.97	1733	1155 (m), 1131 (m), 1030 (br, s)

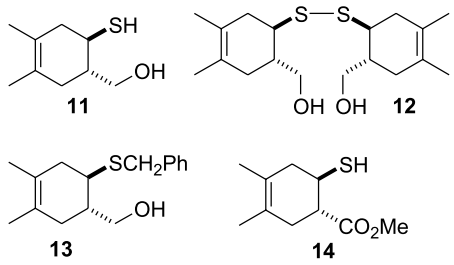


Chart 1.

with and without Lewis acid. The molar concentration of dienophile and makeup (identity) of the solvent were identical in all cases and the relative amount Lewis acid, when present, was one equivalent. With these solutions, ^{1}H and ^{13}C NMR and IR acquisitions were performed and the diagnostic pieces of data are shown in Table 3. An analysis of the C=O stretching frequency, the ^{13}C NMR chemical shift of the ester carbonyl and the ^{1}H NMR shift of the ester methoxy suggest that the carboxylic ester oxygen is not involved significantly in coordination with Et_2AlCl or $ZnCl_2$. Moreover, since both vinyl hydrogens are shifted downfield in the ^{1}H NMR (in every case), one can see further evidence of the lack of significant coordination to the carbonyl oxygen. In that scenario, one would expect an exaggeration of the resonance induced chemical shift changes normally brought on by carbonyl resonance. On the other hand, there is significant change in the chemical shifts of alkene protons and carbons, of the ethoxy methylene group and particularly of the S=O band in the IR spectrum of the dienophile complexes with Et_2AlCl.

Such data is consistent with predominant coordination to the sulfinyl group. These spectroscopic data are consistent with two observations concerning the observed reactivity increase. One, the ^{1}H NMR chemical shift changes suggest a strong withdrawing influence by the coordination, lowering the LUMO of the dienophile. Secondly, the change in ^{13}C NMR chemical shifts of the vinylic carbons of **1** and **2** with either Lewis acid, also provides useful information. The difference in ^{13}C NMR chemical shift values for each carbon in the dienophile is reduced upon Lewis acid coordination, consistent with an attenuation of the 'push–pull' effect in both substrates and an increase in observed Diels–Alder reactivity.

1.3. Reduction chemistry

An advantage of sulfinate esters over sulfoxides and sulfones is their susceptibility to reduction using LAH.[48,49] In this study, the simultaneous reduction of sulfinate and carboxylate esters was required. Based on the applicability of LAH for both types of esters we did a series of trial reductions on cycloadduct **4**. In addition, DIBAL which is well documented for carboxylate reductions,[50] was also examined.

Chart 1 shows the products that were obtained in the reduction trials, while Table 4 outlines the results of the various attempts. In some cases, the complete reduction product was not isolated as the thiol, but was benzylated in order to overcome the difficulties associated with small scale isolation of a low molecular weight thiol. Conveniently, benzyl thioethers can readily be debenzylated.[51–53]

In ether, LAH reductions were hindered by the formation of disulfide, formed presumably by partial reduction followed by intermolecular chemistry of two substrates of different oxidation states. The use of THF provided clean access to mercapto alcohol **11** or its benzylated analog **13**. The use of 6 equiv of DIBAL in THF at −78 °C offered clean formation of thiol **11** and this treatment was selected as the optimal DIBAL reduction protocol. Benzylated **13** could be obtained in moderate yield, a reaction that required the addition of base.

Reductions with DIBAL also proved interesting in that selective reduction was occasionally observed. Specifically, mercapto ester **14** could be obtained in moderate yield. The reaction was attempted on other cycloadducts, and only low yields of partially reduced products from compounds such as **6** and **9** could be obtained. Lacking generality, the reaction was not studied further. However, product **14** can be regarded as equivalent to the product of a cycloaddition of *E*-2-carbomethoxyenethiol.

All of the cycloadducts including previously reported bicyclic adducts **15** and **16**[30] were exposed to the LAH and(or) the DIBAL conditions and reduction products are listed in Chart 2. Bicyclic cycloadducts were not reduced as

Table 4. Trial bifunctional reductions of cycloadducts

#	Reduction reagent/conditions	Products (% yield)
1	1. LAH (4 equiv), ether, rt, 30 min 2. $PhCH_2Br$, rt, 4 h	**12** (13); **13** (22)
2	1. LAH (4 equiv), ether, 35 °C, 30 min 2. $PhCH_2Br$, rt, 4 h	**12** (6); **13** (36)
3	1. LAH (4 equiv), THF, 35 °C, 30 min 2. $PhCH_2Br$, rt, 4 h	**13** (68)
4	LAH (4 equiv), THF, 35 °C, 30 min	**11** (82)
5	DIBAL (3 equiv), THF, −78 °C, 30 min	**4** (12); **14** (62)
6	1. DIBAL (4.4 equiv), CH_2Cl_2, −78 °C, 1.5 h 2. $PhCH_2Br$, −78 °C⇒rt, 2 h	**11** (38)
7	DIBAL (6 equiv), THF, −78 °C, 30 min	**11** (97)
8	1. DIBAL (6 equiv), THF, −78 °C, 30 min 2. $PhCH_2Br$, −78 °C⇒rt, 3 h	**11** (14); **12** (33)
9	1. DIBAL (6 equiv), THF, −78 °C, 30 min 2. $PhCH_2Br$, Et_3N, −78 °C⇒rt, 1.5 h	**13** (61)
10	DIBAL (6 equiv), toluene, −78 °C, 1.5 h	**11** (53); **12** (3)

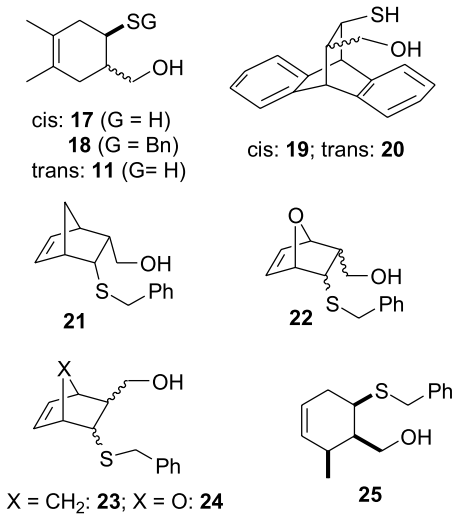


Chart 2.

efficiently as the monocyclic Diels–Alder adducts. When inseparable mixtures of cycloadducts were reduced, a mixture of mercapto carbinols was obtained in most cases. The exception was the mixture of cycloadducts **16** where only *endo* sulfido carbinol **21** was isolated, presumably because the *endo* cycloadduct dominated the constituency of the mixture exposed to reduction.

The reduction of **9** proceeded with high selectivity offering a 17:1:1:1 ratio of isomers in 61% yield. The dominant isomer was assigned to be **25**, based on the COSY and HMQC NMR analyses, while the minor isomers could not be identified. The obtention of primarily a single product in moderate yield is an example of how the cycloaddition/reductions steps exhibited herein can create three contiguous stereocentres in a 6-membered ring (Table 5).

Overall, the yields are good considering the large number of hydride transfers that are required for complete reduction of both esters. Moreover, the benzylation adds another step, one that suggests the thiolates present at the end of the reduction are available for other electrophiles, depending on the synthetic target.

2. Conclusions and future work

The sulfinate ester is a powerful and adaptable functional group for Diels–Alder cycloadditions. In combination with a carboxylic ester, its electronic influence makes it more reactive than the two carboxylic esters of maleates or fumarates under Lewis acid mediation. Moreover, the different electronic influences of the substituents may induce high regioselective cycloadditions of asymmetrically substituted dienophiles.

The reduction chemistry proceeds well forming monocycles, but yields of bicyclic substrates are lower. Selective reduction to the thiol can be achieved but only in isolated examples. Overall the cycloaddition reduction sequence holds promise for the preparation of cyclic compounds possessing thiol and carbinol functionalities in a set stereochemical relationship. Further studies will involve the use of chiral ligands and(or) chiral dienophiles. Chiral compounds possessing mercapto and hydroxy groups in a constrained proximity or derivatives of such compounds are valuable as chiral auxiliaries in organic synthesis.[54–58] Under chiral cycloaddition conditions, the dienophiles would serve as 'chiral' enethiol equivalents.

3. Experimental

3.1. General procedures and instrumentation

Melting points were determined on a MEL-TEMP melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Spectrometer at 400 MHz (or 600 MHz) and 100.6 MHz, respectively, in $CDCl_3$. ^{1}H NMR chemical shifts are reported in parts per million δ (ppm) referenced to internal tetramethylsilane ($\delta=0.00$ ppm) or $CHCl_3$ ($\delta=7.26$ ppm). In some cases

Table 5. Bifunctional reductions of cycloadducts

S.M.[a]	Reduction conditions	Product[b]	Yield (%)
3	LAH, THF, rt, 15 min	**17**	82
	DIBAL (6 equiv), THF, −78 °C, 30 min		97
3	DIBAL (6 equiv), THF, −78 °C, 1 h	**18**[c]	65
4	LAH, THF, rt, 15 min	**11**	97
5	LAH, THF, rt, 15 min	**19**	84
6	LAH, THF, rt, 15 min	**20**	70
15[d]	LAH, THF, 0 °C, 5 h	**21**[c]	52
16[d]	LAH, THF, rt, 15 min	**23** (2.5:1)[c]	55
7[e]	LAH, THF, rt, 15 min	**22** (2.6:1)[c]	32
8[e,f]	LAH, THF, rt, 15 min	**24** (1:3.5)[c,f]	65
9	DIBAL (12 equiv), THF, −78 °C, 30 min	**25**[g]	61

[a] S.M., starting material. Each sulfinate starting material existed as a pair of sulfinyl epimers in addition to any geometric isomers that may have been present.
[b] Ratios are of *endo*/*exo* isomers.
[c] Benzyl bromide was added after the reduction. As indicated in Chart 2, the product is benzylated at sulfur.
[d] Compounds **15** and **16** can be prepared as per Ref. 30. Cycloadduct **15** is methyl 3-[ethoxysulfinyl]bicyclo[2.2.1]hept-5-ene-2-carboxylate with both ester groups predominantly (ca. 20:1) *endo*. Cycloadduct **16** is methyl 3-[ethoxysulfinyl]bicyclo[2.2.1]hept-5-ene-2-carboxylate with both ester groups in a trans relationship. The sample of **16** had an *endo*/*exo* ratio of 2.5:1.
[e] **7** was used as a 1.1:1=*endo*/*exo* mixture; **8** was used as a 1:2.3=*endo*/*exo* mixture.
[f] In either isomer, the carbonyl/carbinol group is always trans to the sulfur containing group.
[g] An inseparable 17:1:1:1 ratio of products was obtained.

where there is an inseparable mixture of isomers, the complete ^{1}H spectrum for the major isomer is reported. For the minor isomer, in some cases, a partial ^{1}H spectrum is reported including only data that could be observed or readily inferred. ^{13}C NMR chemical shifts are reported in parts per million δ (ppm) referenced to $CDCl_3$ (δ= 77.00 ppm). Infrared (IR) spectra were obtained on a Bomen FTIR spectrometer either neat or in a solution cell with CH_2Cl_2 or $CDCl_3$. Mass spectra (MS) were performed by the McMaster Regional Center for Mass Spectrometry, McMaster University, or at the Department of Chemistry, University of Waterloo. Elemental Analyses were performed by M.H.W Laboratories, Phoenix, AZ. Flash chromatography was performed on virgin or recycled 200–245 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on 0.25 mm Merck Kieselgel 60 P_{254} precoated glass-backed silica gel plates and visualized through charring with anisaldehyde/sulfuric acid solution.

3.2. General methods for Diels–Alder reactions of 1 and 2 with dienes

Small scale. A solution of sulfinyl alkene (**1** or **2**) (60.0–348 mg, 0.337–1.95 mmol, 1.0 equiv) and diene (1.3 equiv) in dry CH_2Cl_2 or dry toluene was stirred until TLC showed the disappearance of the sulfinate ester. The mixture was then washed with $NaHCO_3$ (aq), water, and brine and was dried with $MgSO_4$. Concentration under reduced pressure (aspirator) provided crude products. Flash chromatography on silica gel with EtOAc/hexanes as eluent afforded pure cycloadducts. When Lewis acids were employed, 1.2 equiv were introduced to the mixture at the beginning. Yields are listed in Table 1.

Large scale. A solution of sulfinyl alkene (**1** or **2**) (1.21–3.84 g, 6.79–21.6 mmol, 1.0 equiv), diene (1.3 equiv, cyclopentadiene or 2,3-dimethyl-1,3-butadiene) and Et_2-AlCl (1.2 equiv) in dry CH_2Cl_2 was stirred until TLC showed the disappearance of the sulfinate ester. The mixture was then washed with $NaHCO_3$ (aq), water, and brine and was dried with $MgSO_4$. Concentration under reduced pressure (aspirator) provided crude products. Flash chromatography on silica gel with EtOAc/hexanes as eluent afforded pure.

3.2.1. Cycloadduct 3 from the reaction of 1 with 2,3-dimethyl-1,3-butadiene. An inseparable mixture of sulfinyl epimers were obtained as a pale yellow solid, mp=41–43 °C. TLC (25% EtOAc/hexanes) R_f=0.29. *Major isomer*. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.15–3.90 (m, 2H), 3.64 (s, 3H), 3.13 (m, 1H), 3.01 (m), 2.57–2.07 (m, 4H), 1.60 (s, 6H), 1.27 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 172.8, 124.8, 123.5, 65.8, 64.4, 51.6, 39.8, 31.5, 28.3, 18.8, 18.7, 15.7; *Minor isomer*. ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 172.8, 124.6, 123.3, 65.2, 63.5, 51.9, 38.0, 32.6, 28.3, 18.9, 18.8, 16.0. *Mixture of isomers*. IR (cm^{-1}) 2984, 2918, 2860, 1736, 1400, 1386, 1367, 1314, 1266, 1228, 1210, 1177, 1127, 892, 882; Anal. Calcd for $C_{12}H_{20}O_4S$: C, 55.36; H, 7.74. Found: C, 55.51; H, 7.60.

3.2.2. Cycloadduct 4 from the reaction of 2 with 2,3-dimethyl-1,3-butadiene. An inseparable mixture of sulfur epimers were obtained, as a colourless oil: TLC (25% EtOAc/hexanes) R_f=0.33. *Major isomer*. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 4.12 (ABX_3, $\Delta\nu_{AB}$=38.2 Hz, J_{AB}=10.3 Hz, J_{AX}=J_{BX}=7.0 Hz, 2H), 3.72 (s, 3H), 3.28–3.16 (m, 1H), 2.94 (apparent (app) q, J=7.4 Hz, 1H), 2.53–2.20 (m, 4H), 1.66 (s, 3H), 1.64 (s, 3H), 1.34 (t, J=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 173.9, 124.0, 123.1, 65.4, 61.5, 51.9, 39.4, 32.9, 26.4, 18.7, 18.5, 15.7; *Minor isomer*. ^{1}H NMR (400 MHz, $CDCl_3$) (partial spectrum) δ 3.73 (s, 3H), 2.84 (ddd, J=14.5, 7.9, 6.5 Hz, 1H) 1.36 (t, J=7.0 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 173.9, 124.0, 123.3, 65.3, 61.1, 51.9, 39.2, 33.3, 25.3, 18.7, 18.5, 15.8; *Mixture of isomers*. IR (cm^{-1}) 2953, 2917, 2847, 1733, 1386, 1313, 1195, 1117, 1061, 1017 879; Anal. Calcd for $C_{12}H_{20}O_4S$: C, 55.36; H, 7.74. Found: C, 55.16; H, 7.56.

3.2.3. Cycloadduct 5 from the reaction of 1 with anthracene. A mixture of sulfur epimers were obtained and separated by flash chromatography. *Major isomer*. Pale yellow solid, mp=148–149 °C. TLC (25% EtOAc/hexanes) R_f=0.24. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.50–7.10 (m, 8H), 4.87 (d, J=2.2 Hz, 1H), 4.50 (d, J=1.8 Hz, 1H), 4.05–3.93 (m, 1H), 3.85–3.70 (m, 1H), 3.62 (s, 3H), 3.33 (dd, J=9.7, 1.8 Hz, 1H), 3.14 (dd, J=9.7, 2.2 Hz, 1H), 1.19 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.1, 141.9, 141.2, 140.3, 138.8, 126.9, 126.7 (2 C), 126.6, 125.3, 124.8, 124.2, 123.6, 69.7, 65.4, 52.0, 48.2, 47.4, 44.1, 15.6; IR (cm^{-1}) 2979, 2951, 1740, 1612, 1514, 1468, 1460, 1437, 1388, 1357, 1207, 1192, 1175, 1113, 1062, 1019, 910, 878; EIMS, *m/z* (%): 263 (100), 203 (47), 178 (35), 93 (19), 85 (52); Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.18; H, 5.82.

Minor isomer. Pale yellow oil. TLC (25% EtOAc/hexanes) R_f=0.15. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.40–7.10 (m, 8H), 4.73 (d, J=2.3 Hz, 1H), 4.56 (d, J=2.2 Hz, 1H), 4.23–4.09 (m, 2H), 3.65 (s, 3H), 3.37 (dd, J=10.0, 2.2 Hz, 1H), 3.20 (dd, J=10.0, 2.3 Hz, 1H), 1.47 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.6, 141.8, 141.5, 140.4, 139.1, 126.8, 126.7, 126.6, 126.5, 125.6, 124.1, 123.9, 123.8, 69.8, 64.7, 52.3, 47.9, 46.7, 44.9, 16.1; IR (cm^{-1}) 2979, 2952, 1737, 1512, 1468, 1459, 1435, 1386, 1355, 1299, 1208, 1176, 1119, 1017, 884, 763; Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.27; H, 5.80.

3.2.4. Cycloadduct 6 from the reaction of 2 with anthracene. A mixture of sulfur epimers were obtained and isolated by flash chromatography. *Major isomer*. Pale yellow oil. TLC (25% EtOAc/hexanes) R_f=0.25. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.93–7.10 (m, 8H), 4.78 (d, J=2.6 Hz, 1H), 4.68 (d, J=2.6 Hz, 1H), 4.18–4.03 (m, 2H), 3.76 (dd, J=4.5, 2.6 Hz, 1H), 3.65 (s, 3H), 3.28 (dd, J=4.5, 2.6 Hz, 1H), 1.39 (t, J=7.1 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.6, 141.7, 140.8, 140.4, 139.4, 126.9, 126.7, 126.7, 126.5, 124.7, 124.6, 124.1, 123.9, 67.8, 64.7, 52.5, 46.9, 45.4, 44.3, 15.9; IR (cm^{-1}) 3025, 2980, 2952, 1740, 1468, 1459, 1436, 1387, 1362, 1318, 1273, 1215, 1169, 1127, 1114, 1061, 1017, 880; Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.12; H, 5.74.

Minor isomer. Pale yellow solid, mp=141–142 °C. TLC (25% EtOAc/hexanes) R_f=0.14. ^{1}H NMR (400 MHz,

$CDCl_3$), δ: 7.45–7.05 (m, 8H), 4.81 (d, $J=2.7$ Hz, 1H), 4.73 (d, $J=2.6$ Hz), 3.96 (ABX_3, $\Delta\nu_{AB}=16.4$ Hz, $J_{AB}=7.1$ Hz, $J_{AX}=3.1$ Hz, $J_{BX}=3.1$ Hz, 2H, SO_2CH_2), 3.69 (dd, $J=4.5$, 2.8 Hz, 1H, CH), 3.64 (s, 3H), 2.89 (dd, $J=4.5$, 2.6 Hz, 1H), 1.18 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.3, 141.9, 140.7, 140.1, 139.0, 127.0, 126.9, 126.7, 126.7, 125.3, 124.5, 124.1, 123.8, 67.6, 64.6, 52.5, 47.2, 46.2, 43.7, 15.7; IR (cm^{-1}) 3078, 30.27, 2954, 2897, 1739, 1468, 1460, 1437, 1387, 1361, 1318, 1216, 1194, 1117, 1061, 1017, 881; Anal. Calcd for $C_{20}H_{20}O_4S$: C, 67.39; H, 5.66. Found: C, 67.27; H, 5.65.

3.2.5. Cycloadduct 7 from the reaction of 1 with furan. Three products were isolated by flash chromatography; one S-*endo* sulfur epimer, one S-*exo* sulfur epimer, and a mixture of the other S-*endo* and S-*exo* sulfur epimers. S-*endo* epimer: White solid, mp=63–65 °C. TLC (25% EtOAc/hexanes) $R_f=0.21$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.77 (dd, $J=5.8$, 1.4 Hz, 1H), 6.66 (dd, $J=5.8$, 1.4 Hz, 1H), 5.24–5.18 (m, 2H), 4.05 (ABX_3, $\Delta\nu_{AB}=48.9$ Hz, $J_{AB}=10.0$ Hz, $J_{AX}=J_{BX}=7.1$ Hz, 2H), 3.72 (dd, $J=9.2$, 4.4 Hz, 1H), 3.67 (s, 3H), 3.52 (dd, $J=9.1$, 4.4 Hz, 1H), 1.30 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 169.8, 136.3, 135.0, 80.7, 80.0, 69.6, 65.6, 52.1, 46.7, 15.8; IR (cm^{-1}) 3056, 2987, 2958, 1738, 1437, 1423, 1387, 1359, 1320, 1263, 1198, 1171, 1115, 1064, 1020, 879; Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.57; H, 5.89.

Mixture of S-endo and S-exo sulfur epimers. Pale yellow oil. TLC (25% EtOAc/hexanes) $R_f=0.11$. ^{1}H NMR (400 MHz, $CDCl_3$) (S-*endo* epimer), δ: 6.53 (s, 2H), 5.20 (d, $J=4.2$ Hz, 1H), 5.10 (d, $J=4.2$ Hz, 1H), 4.15–3.93 (m, 2H), 3.69 (s, 3H), 3.63 (dd, $J=9.1$, 4.2 Hz, 1H), 3.56 (dd, $J=9.1$, 4.2 Hz, 1H), 1.37 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.2, 136.4, 134.2, 80.7, 80.0, 71.3, 64.6, 52.4, 46.3, 16.0; ^{1}H NMR (400 MHz, $CDCl_3$) (S-*exo* epimer), δ: 6.47 (s, 2H), 5.42 (s, 1H), 5.18 (s, 1H), 4.15–3.93 (m, 2H), 3.74 (s, 3H), 2.90 (d, $J=8.2$ Hz, 1H), 2.83 (d, $J=8.2$ Hz, 1H), 1.30 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.6, 136.8, 135.9, 81.9, 78.9, 69.0, 65.4, 52.3, 45.9, 15.7; *Mixture of isomers*. IR (cm^{-1}) 3057, 2986, 2954, 2898, 1740, 1623, 1571, 1437, 1388, 1356, 1306, 1272, 1171, 1121, 1020, 949, 922, 881, 808.

S-endo epimer. Pale yellow oil. TLC (25% EtOAc/hexanes) $R_f=0.06$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.49 (s, 2H), 5.22 (s, 1H), 5.20 (s, 1H), 4.18 (ABX_3, $\Delta\nu_{AB}=21.8$ Hz, $J_{AB}=10.3$ Hz, $J_{AX}=J_{BX}=7.1$ Hz, 2H), 3.74 (s, 3H), 2.95 (d, $J=8.2$ Hz, 1H), 2.87 (d, $J=8.2$ Hz, 1H), 1.40 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.6, 136.7, 135.8, 82.1, 79.0, 69.4, 65.5, 52.6, 45.4, 16.0; IR (cm^{-1}) 3056, 2987, 2958, 1723, 1428, 1314, 1286, 1256, 1209, 1189, 1120, 1046, 1008, 923, 897, 883, 811; Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.79; H, 5.79.

3.2.6. Cycloadduct 8 from the reaction of 2 with furan. A mixture of 4 inseparable isomers were obtained; 2 S-*endo* epimers and 2 S-*exo* epimers. TLC (25% EtOAc/hexanes) $R_f=0.13$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.70–6.35 (m, 2H), 5.40–5.12 (m, 2H), 4.25–4.05 (m, 2H), 3.79 (s, 3H, CO_2CH_3 of S-*endo* epimer), 3.78 (s, 3H, CO_2CH_3 of S-*endo* epimer), 3.70 (s, 3H, CO_2CH_3 of S-*exo* epimer), 3.69 (s, 3H, CO_2CH_3 of S-*exo* epimer), 3.27–3.18, 3.57–3.50 (m, 1H), 2.82 (d, $J=3.8$ Hz, 1H, *endo* H in S-*endo* isomers), 2.52 (d, $J=4.0$ Hz, 1H, *endo* H in S-*exo* isomers), 1.43–1.29 (m, 3H); *Mixture of four isomers*. ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 171.2, 170.1, 169.9, 137.1, 136.9, 135.9, 135.8, 135.6, 135.4, 134.9, 134.4, 82.5, 82.5, 79.7, 79.6, 79.5, 79.4, 78.6, 78.1, 68.9, 68.2, 68.1, 67.5, 65.0, 64.5, 64.2, 52.7, 52.6, 52.0, 45.3, 45.0, 44.8, 44.6, 15.8, 15.7; IR (cm^{-1}) 3021, 1742, 1650, 1640, 1357, 1315, 1193, 1124, 1016, 867; Anal. Calcd for $C_{10}H_{14}O_5S$: C, 48.77; H, 5.73. Found: C, 48.58; H, 5.52.

3.2.7. Cycloadduct 9 from the reaction of 1 with trans-piperylene. To an oven dried 100 mL sealable chamber was added *cis*-sulfinate ester (599 mg, 3.36 mmol), 30 mL CH_2Cl_2, *trans*-piperylene (4 equiv, 1 g, 13.4 mmol) and $ZnCl_2$ (1.2 equiv, 1.0 M, 4.03 mmol, 4.03 mL). The vessel was sealed and placed into a pre-equilibrated oil bath at 40 °C and stirred for 3 days. The reaction was quenched with $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3×15 mL), washed with brine (15 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was chromatographed twice (silica gel, flash conditions, 15% EtOAc/hexanes) yielding a clear oil 512 mg, 78%, as a mixture of inseparable isomers with a ratio of 16:1. The minor isomer could not be identified, whereas the major isomer was composed of two sulfur epimers (1.56:1, based on NMR analysis). *Major S-epimer*. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.77–5.72 (m, 1H), 5.40 (d, $J=10.0$ Hz, 1H), 4.19 (m, 1H), 3.66 (s, 3H), 3.21 (dd, $J=5.3$, 4.0 Hz, 1H), 3.04–2.96 (m, 1H), 2.65–2.56 (m, 2H), 2.41–2.33 (m, 1H), 1.37 (t, $J=7.1$ Hz, 3H), 1.05 (d, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.0, 131.1, 124.2, 65.6, 63.1, 51.1, 41.9, 32.6, 21.4, 17.6, 15.7. *Minor S-epimer*. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 5.72–7.67 (m, 1H), 5.40 (d, $J=10.0$ Hz, 1H), 4.11 (m, 1H), 3.68 (s, 3H), 3.28 (dd, $J=5.6$, 3.9 Hz, 1H), 3.04–2.96 (m, 1H), 2.65–2.56 (m, 2H), 2.32–2.35 (m, 1H), 1.35 (t, $J=7.1$ Hz, 3H), 1.07 (d, $J=7.3$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 171.0, 130.1, 124.3, 65.4, 63.6, 51.1, 41.4, 32.9, 21.7, 18.1, 15.8. *Mixture of isomers*. IR (cm^{-1}) (neat): 3025, 2977, 2936, 2878, 1738, 1728, 1461, 1452, 1434, 1384, 1227, 1196, 1164, 1127, 1019 cm^{-1}; MS (CI), *m/z* (%): 247.10 ($(M)^+$, 48), 215 (86), 201 (100), 153 (48), 121 (25), 93 (42). HRCIMS: Calc. For $C_{11}H_{19}O_4S$ 247.0998; Found 247.0998.

3.3. Reductions

General procedure for cycloadduct reductions with LAH. The cycloadduct (1.0 equiv) in dry solvent (3 mL) was added dropwise with stirring, to a suspension of LAH (4.0 equiv) in the same solvent (7 mL). The mixture was stirred at rt for 30 min. To the solution was added EtOAc (10 mL) and HCl (10% aq, 10 mL). The layers were separated and the aqueous layer washed with EtOAc (3× 5 mL). The combined organic extracts were washed with water to neutral pH, then washed with brine, dried with anhydrous $MgSO_4$, and concentrated. The products were purified by flash chromatography on silica gel with EtOAc/hexanes.

General procedure for cycloadduct reductions with LAH and capture with benzyl bromide. The cycloadduct (1.0 equiv) in dry solvent (3 mL) was added dropwise,

with stirring, to a suspension of LAH (4.0 equiv) in the same dry solvent (7 mL). The mixture was stirred at room temperature for 30 min. Benzyl bromide (1.1 equiv) was added dropwise. The mixture was stirred at rt until the TLC showed the disappearance of the uncaptured intermediate. To the solution was added EtOAc (10 mL) and HCl (10% aq, 10 mL). Isolation and purification was as indicated above for the thiol.

General procedure for cycloadduct reductions with DIBAL. A solution of cycloadduct (1.0 equiv) in dry solvent (10 mL) was cooled to −78 °C. DIBAL (1.0 M in THF, 3.0–6.0 equiv) was added dropwise and the mixture was allowed to stir at −78 °C until the TLC showed the disappearance of cycloadduct (30 min to 1.5 h). The mixture then was warmed to rt for 30 min and was quenched by adding NH_4Cl (satd aq, 5 mL), followed by HCl (10% aq, 5 mL). Isolation and purification was as indicated above for the LAH reductions.

General procedure for cycloadduct reductions with DIBAL and capture with benzyl bromide. A solution of cycloadduct (1.0 equiv) in dry solvent (10 mL) was cooled to −78 °C. DIBAL (1.0 M in THF, 4.4–6.0 equiv) was added dropwise and the mixture was allowed to stir at −78 °C until the TLC showed the disappearance of cycloadduct (30 min to 1.5 h). Benzyl bromide (1.1 equiv) was added dropwise at −78 °C. The mixture was stirred for 10 min and allowed to warm to rt until the TLC showed the disappearance of the uncaptured thiol intermediate. The mixture was quenched with NH_4Cl (satd aq, 5 mL), followed by HCl (10% aq, 5 mL). Isolation and purification was as indicated above for the LAH reductions.

3.3.1. Reduction of cycloadduct 4 with LAH. The reduction of cycloadduct **4** (70.0 mg, 0.269 mmol) with LAH (40.8 mg, 1.08 mmol) in dry THF yielded mercapto alcohol **11** (37.9 mg, 82%) as an oil after flash chromatography (10% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.74 (ABX, $\Delta\nu_{AB}=17.2$ Hz, $J_{AB}=11.1$ Hz, $J_{AX}=J_{BX}=4.8$ Hz, 2H), 2.90 (app ddt, $J=15.3$, 10.0, 5.2 Hz, 1H), 2.50–1.80 (m, 4H), 1.73 (app ddt, $J=15.3$, 10.2, 5.2 Hz, 1H), 1.59 (s, 6H), 1.52 (d, $J=8.3$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 126.3, 125.7, 67.3, 45.6, 45.2, 39.7, 36.4, 20.1, 19.9; IR (cm^{-1}) 3373, 2916, 2859, 2832, 2560, 1435, 1379, 1261, 1097, 1051, 1020, 931; Anal. Calcd for $C_9H_{16}OS$: C, 62.74; H, 9.36. Found: C, 62.58; H, 9.31.

3.3.2. Reduction of cycloadduct 4 with LAH and capture with benzyl bromide. Cycloadduct **4** (70.0 mg, 0.269 mmol) was reduced with LAH (40.8 mg, 1.08 mmol) in dry THF. Addition of benzyl bromide (35.2 μL, 0.296 mmol) and stirring for 4 h, alcohol **13** (47.7 mg, 68%) was obtained as a white solid after flash chromatography (10% EtOAc/hexanes), mp=46–47 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.38–7.20 (m, 5H), 3.79 (AB, $\Delta\nu_{AB}=16.2$ Hz, $J_{AB}=13.1$ Hz, 2H), 3.63 (ABX, $\Delta\nu_{AB}=55.7$ Hz, $J_{AB}=11.3$ Hz, $J_{AX}=J_{BX}=4.6$ Hz, 2H), 2.68 (dt, $J=9.9$, 5.5 Hz, 1H), 2.38–1.85 (m, 4H), 1.82 (m, 1H), 1.59 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.5, 128.8, 128.6, 127.1, 124.7, 124.1, 65.7, 43.1, 40.8, 39.5, 34.9, 18.6; IR (cm^{-1}) 3390, 3027, 2911, 2831, 1601, 1494, 1452, 1434, 1381, 1236, 1071, 1049, 926; Anal. Calcd for $C_{16}H_{22}OS$: C, 73.23; H, 8.45. Found: C, 73.07; H, 8.19.

3.3.3. Formation of 13 via reduction of cycloadduct 4 with LAH and attempted capture with benzyl bromide. Cycloadduct **4** (70.0 mg, 0.269 mmol) was reduced with LAH (40.8 mg, 1.08 mmol) in dry ether. Addition of benzyl bromide (35.2 μL, 0.296 mmol) and stirring for 2 h afforded sulfide **13** (15.5 mg, 22%) and disulfide **12** (12.0 mg, 13%) after flash chromatography (10–25% EtOAc/hexanes, gradient). Data for **12**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.76 (ABX, $\Delta\nu_{AB}=104.6$ Hz, $J_{AB}=11.2$ Hz, $J_{AX}=J_{BX}=4.6$ Hz, 2H), 3.75 (ABX, $\Delta\nu_{AB}=54.1$ Hz, $J_{AB}=11.3$ Hz, $J_{AX}=J_{BX}=4.8$ Hz, 2H), 3.02 (m, 2H), 2.39 (app dt, $J=4.5$, 17.4 Hz, 2H), 2.26–1.99 (m, 6H), 1.92 (m, 2H), 1.61 (s, 12H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 124.8, 124.8, 123.6, 123.4, 64.6, 64.2, 49.2, 48.6, 40.6, 40.5, 37.6, 37.3, 34.2, 34.0, 18.7, 18.7; IR (cm^{-1}) 3404, 2987, 2915, 2861, 2834, 1463, 1436, 1383, 1252, 1233, 1181, 1122, 1048, 908; EIMS, *m/z* (%): 343 (66, $[M+H]^+$), 171 (45), 139 (80), 121 (100), 113 (19), 107 (49), 93 (54), 91 (47), 83 (14), 77 (20); HRMS: Calcd for $C_{18}H_{31}O_2S_2$: 343.1765. Found: 343.1747.

3.3.4. Reduction of cycloadduct 4 with DIBAL. Cycloadduct **4** (75.0 mg, 0.288 mmol) was reduced with DIBAL (1.0 M in THF, 1.73 mL, 1.73 mmol), in dry THF for 30 min. Mercapto alcohol **11** (48.1 mg, 97%) was obtained after flash chromatography (10% EtOAc/hexanes).

3.3.5. Formation of 14 via reduction of cycloadduct 4 with DIBAL. Cycloadduct **4** (70.0 mg, 0.269 mmol) was reduced with DIBAL (1.0 M in THF, 0.807 mL, 0.807 mmol), in dry THF for 30 min. Thiol **14** (33.5 mg, 62%) was obtained as a pale yellow oil with a very potent stench after flash chromatography (10% EtOAc/hexanes). Starting material was also recovered (8.5 mg, 12% yield), making the chemical reaction yield 69%. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.73 (s, 3H), 3.16 (app ddt, $J=10.8$, 7.5, 5.5 Hz, 1H), 2.60 (dt, $J=10.1$, 6.2 Hz, 1H), 1.75 (d, $J=7.5$ Hz, 1H), 1.60 (s, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 175.0, 124.5, 123.7, 51.7, 50.4, 41.4, 36.3, 35.2, 18.5, 18.4; IR (cm^{-1}) 2915, 2522, 1735, 1437, 1370, 1309, 1261, 1227, 1196, 1173, 1160, 1119, 1069, 1024, 911; EIMS, *m/z* (%): 200 (2, M^+), 166 (29), 107 (91), 91 (22), 84 (100).

3.3.6. Reduction of cycloadduct 4 with DIBAL and capture with benzyl bromide. Cycloadduct **4** (70.0 mg, 0.269 mmol) was reduced with DIBAL (1.0 M in THF, 0.807 mL, 0.807 mmol) in dry THF for 30 min. Addition of benzyl bromide (35 μL, 0.296 mmol), followed by triethylamine (41 μL, 0.296 mmol) with stirring for 4 h, afforded sulfide **13** (43.0 mg, 61%) after flash chromatography (10% EtOAc/hexanes).

3.3.7. Reduction of cycloadduct 3 with LAH, formation of 17. A solution of cycloadduct **3** (62.8 mg, 0.241 mmol) in dry THF (3 mL) was added dropwise with stirring, to a suspension of LAH (36.6 mg, 0.965 mmol) in dry THF (7 mL). After stirring at rt for 15 min and workup, product **17** (40.2 mg, 97%) was obtained as a pale yellow liquid by flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 3.63 (ABX, $\Delta\nu_{AB}=32.9$ Hz,

$J_{AB}=10.7$ Hz, $J_{AX}=J_{BX}=6.6$ Hz, 2H), 3.36 (m, 1H), 2.60 (d(br), $J=17.0$ Hz, 1H), 2.12 (d, $J=17.0$ Hz, 1H), 2.02 (m, 1H), 1.88 (m, 2H), 1.63 (s, 3H), 1.62, (s(br), 1H), 1.61 (s, 3H), 1.43 (d, $J=9.3$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 122.3 (2 C), 63.0, 41.6, 40.4, 36.4, 30.2, 19.1, 18.8; IR (cm^{-1}) 3417, 2959, 2927, 2554, 1727, 1461, 1382, 1277, 1125, 1074, 1048, 908. GCMS, *m/z* (%): 123 ($[M+H]^+$, 35), 155 (32), 139 (100), 138 (99), 121 (50) 107 (39), 95 (13).

3.3.8. Reduction of cycloadduct 3 with DIBAL and capture with benzyl bromide. Cycloadduct **3** (159 mg, 0.613 mmol) was reduced with DIBAL (1.0 M in CH_2Cl_2, 3.68 mmol, 3.68 mL) in dry THF for 1 h. Addition of benzyl bromide (109 μL, 0.920 mmol), followed by triethylamine (128 μL, 0.920 mmol) with stirring with warming for 12 h, afforded sulfide **18** (105 mg, 65%) after flash chromatography (15% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.28–7.16 (m, 5H), 3.67 (AB quart, $\Delta_{AB}=26.23$, $\nu_A=1484$, $\nu_B=1457$, $J=13.5$ Hz, 2H), 3.59 (dd, $J=10.9$, 7.9 Hz, 1H), 3.38 (dd, $J=10.9$, 5.6 Hz, 1H), 2.94 (dt, $J=5.1$, 3.1 Hz, 1H), 2.24–2.22 (m, 1H), 2.07–1.92 (m, 2H), 1.82–1.69 (m, 3H), 1.52 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$), δ: 138.9, 128.8, 128.5, 127.0, 124.4, 123.3, 64.3, 41.8, 39.6, 37.7, 35.5, 32.1, 19.0, 18.9; IR (neat): ν 3387, 3084, 3061, 3027, 2983, 2911, 2828, 1494, 1453, 1353, 1338, 1173, 1144, 1114 cm^{-1}; MS(EI) *m/z* (%): 262 (M^+, 5), 244 (5), 171 (73), 153 (22), 120 (14), 113 (25), 107 (100), 91 (73); HRMS: Calcd for $C_{16}H_{22}OS$: 262.1391 Found: 262.1393.

3.3.9. Reduction of cycloadduct 5 with LAH, formation of 19. The reduction of cycloadduct **5** (82.2 mg, 0.231 mmol) with LAH (35.0 mg, 0.922 mmol) in dry THF yielded mercapto alcohol **19** (52.2 mg, 84%) as a solid after flash chromatography (20% EtOAc/hexanes), mp 128–129 °C. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.36–7.11 (m, 8H), 4.33 (d, $J=1.9$ Hz, 1H), 4.21 (d, $J=1.9$ Hz, 1H), 3.44–3.27 (m, 3H), 2.34 (m, 1H), 1.26 (br s, 1H), 1.22 (d, $J=9.9$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 143.0, 140.2, 126.6, 126.4 (2 C), 126.1, 125.9, 125.1, 123.9, 123.4, 65.1, 54.0, 47.0, 43.8, 40.8, 29.6; IR (cm^{-1}) 3515, 3025, 2929, 2446, 1737, 1608, 1467, 1459, 1193, 1079, 1036, 911; Anal. Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01. Found: C, 76.29; H, 6.04.

3.3.10. Reduction of cycloadduct 6 with LAH, formation of 20. The reduction of cycloadduct **6** (150.0 mg, 0.421 mmol) with LAH (63.9 mg, 1.68 mmol) in dry THF yielded mercapto alcohol **20** (78.5 mg, 69%) as a solid after flash chromatography (20% EtOAc/hexanes), mp 123–124 °C. TLC (25% EtOAc/hexanes) $R_f=0.25$. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.45–7.00 (m, 8H), 4.32 (d, $J=2.2$ Hz, 1H), 4.21 (d, $J=2.2$ Hz, 1H), 3.31 (AMX, $\Delta\nu_{AM}=167.1$ Hz, $J_{AM}=10.7$ Hz, $J_{AX}=5.7$ Hz, $J_{MX}=9.1$ Hz, 2H), 2.49 (ddd. $J=9.6$, 5.2, 2.2 Hz, 1H), 1.93 (m, 1H), 1.70 (br s, 1H, OH), 1.43 (d, $J=9.6$ Hz, 1H, SH); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 143.1, 142.7, 139.4, 139.2, 126.6, 126.6, 126.3 (2 C), 125.8, 125.4, 123.6, 123.5, 64.6, 54.3, 53.5, 45.8, 40.9; IR (cm^{-1}) 3619, 3025, 2927, 2545, 1466, 1458, 1193, 1020, 1011; Anal. Calcd for $C_{17}H_{16}OS$: C, 76.08; H, 6.01. Found: C, 75.98; H, 5.97.

3.3.11. Reduction of cycloadduct 15 with LAH and capture with benzyl bromide, formation of 21. Cycloadduct **15** (102 mg, 0.409 mmol) was reduced with LAH (64.0 mg, 1.64 mmol) in dry THF. Addition of benzyl bromide (120 μL, 1.01 mmol) with stirring for 2 h afforded sulfide **21** (54.2 mg, 52%) as an oil after flash chromatography (20% EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.40–7.20 (m, 5H), 6.17 (dd, $J=5.6$, 3.0 Hz, 1H), 6.12 (dd, $J=5.6$, 3.0 Hz, 1H), 3.77 (s, 2H), 3.42 (ABX, $\Delta\nu_{AB}=35.0$ Hz, $J_{AB}=11.5$ Hz, $J_{AX}=8.7$ Hz, $J_{BX}=5.7$ Hz, 2H), 3.19 (dd, $J=9.0$, 3.3 Hz, 1H), 2.89 (br s, 1H), 2.85 (br s, 1H), 2.51 (app ddt, $J=9.0$, 5.7, 3.3 Hz, 1H), 1.48 (dt, $J=8.5$, 1.6 Hz, 1H), 1.30 (d, $J=8.5$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 135.5, 135.3, 128.7, 128.6, 127.1, 64.1, 48.9, 48.2, 47.9, 47.2, 45.5, 37.6; IR (cm^{-1}) 3402, 2960, 2929, 1724, 1494, 1274, 1123, 1072, 1028, 912; MS (EI), *m/z* (%): 246 (M+, 2), 214 (5), 155 (32), 123 (10), 91 (100). HRMS: Calcd for $C_{15}H_{18}OS$: 246.1078; Found 246.1081.

3.3.12. Reduction of cycloadduct 16 with LAH and capture with benzyl bromide, formation of 23. A mixture of cycloadducts **16** (65.0 mg, 0.266 mmol) was reduced with LAH (40.4 mg, 1.06 mmol) in dry THF. Benzyl bromide (34 μL, 0.293 mmol) was added with stirring for 2 h; An inseparable 2.5:1 mixture of S-*endo*-**23** and S-*exo*-**23** sulfides (36.0 mg, 55%) were obtained as an oil after flash chromatography (20% EtOAc/hexanes).

S-endo-**23**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.38–7.20 (m, 5H), 6.06 (ABX, $J_{AB}=5.6$ Hz, $J_{AX}=J_{BX}=2.7$ Hz, 1H), 3.80 (s, 2H), 3.34 (ABX, $\Delta\nu_{AB}=48.3$ Hz, $J_{AB}=10.7$ Hz, $J_{AX}=8.1$ Hz, $J_{BX}=6.0$ Hz, 2H), 2.89 (br s, 1H), 2.69 (br s, 1H), (2.00 (m, 1H), 1.74 (d, $J=8.6$ Hz, 1H), 1.56 (dd, $J=1.5$, 8.6 Hz, 1H), 1.49 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.5, 136.3, 134.8, 128.8, 128.5, 126.9, 65.6, 50.9, 48.0, 47.1, 46.3, 43.6, 37.2.

S-exo-**23**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 6.29 (dd, $J=5.9$, 3.2 Hz, 1H), 6.09 (dd, $J=5.9$, 3.2 Hz, 1H), 3.77 (s, 2H), 3.61 (ABX, $\Delta\nu_{AB}=72.6$ Hz, $J_{AB}=10.6$ Hz, $J_{AX}=8.2$ Hz, $J_{BX}=6.4$ Hz, 2H), 2.85 (br s, 1H), 2.71 (br s, 1H), 2.65 (dd, $J=3.4$, 4.5 Hz, 1H), 1.98 (m, 1H), 1.52–1.38 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.5, 137.9, 134.7, 128.8, 128.5, 126.9, 65.8, 51.2, 47.4, 46.3, 45.7, 44.1, 37.0; *Mixture of isomers*. IR (cm^{-1}) 3427, 3030, 2969, 2929, 1602, 1494, 1466, 1453, 1383, 1336, 1297, 1072, 1028, 908; Anal. Calcd for $C_{15}H_{18}OS$: C, 73.13; H, 7.36. Found: C, 73.14; H, 7.11.

3.3.13. Reduction of cycloadduct 7 with LAH and capture with benzyl bromide, formation of 22. Cycloadduct **7** (89.7 mg, 0.364 mmol) was reduced with LAH (55.3 mg, 1.46 mmol) in dry THF. Benzyl bromide (47.6 μL, 0.401 mmol) was added with stirring for 2 h. An inseparable 2.6:1 mixture of *endo*-**22** and *exo*-**22** sulfides (30.5 mg, 34%) were obtained as an oil after flash chromatography (20–50% EtOAc/hexanes, gradient).

Endo-**22**. ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.36–7.25 (m, 5H), 6.38 (ABX, $J_{AB}=5.9$ Hz, $J_{AX}=J_{BX}=1.5$ Hz, 2H), 4.91 (d, $J=4.2$ Hz, 1H), 4.65 (d, $J=4.2$ Hz, 1H), 3.76 (m, 2H), 3.37 (d, $J=7.3$ Hz, 2H), 3.23 (dd, $J=9.0$, 4.4 Hz, 1H), 2.65 (m, 1H); *Exo*-**22**: ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.36–7.25 (m, 5H), 6.37 (dd, $J=5.8$, 1.4 Hz, 1H), 6.21 (dd,

$J=5.8$, 1.4 Hz, 1H), 4.77 (br s, 1H), 4.57 (br s, 1H), 3.83 (s, 2H), 3.82–3.71 (m, 2H), 2.70 (d, $J=7.7$ Hz, 1H), 2.00 (m, 1H); *Mixture of isomers*. ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 135.8, 135.7, 134.6, 128.8, 128.8, 128.8, 127.4, 127.4, 80.9, 80.4, 80.4, 62.5, 45.9, 44.8, 38.0; IR (cm^{-1}) 3412, 2925, 1494, 1453, 1320, 1071, 1027, 902; EIMS, *m/z* (%): 180 (14), 91 (100), 65 (89); Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.92; H, 6.20.

3.3.14. Reduction of cycloadduct 8 with LAH and capture with benzyl bromide, formation of 24. Cycloadduct **8** (70.0 mg, 0.284 mmol) was reduced with LAH (43.1 mg, 1.14 mmol) in dry THF. Addition of benzyl bromide (35.2 μL, 0.296 mmol) and stirring for 2 h afforded S-*endo* sulfide **24** (10.6 mg, 15%) and S-*exo* sulfide **24** (35.5 mg, 50%) both as a pale yellow oils after flash chromatography (10–25% EtOAc/hexanes, gradient).

S-endo-**24**. TLC (50% EtOAc/hexanes) $R_f=0.32$. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.39–7.22 (m, 5H), 6.43 (dd, $J=5.8$, 1.6 Hz, 1H), 6.31 (dd, $J=5.8$, 1.4 Hz, 1H), 4.80 (s, 1H), 4.59 (d, $J=3.8$ Hz, 1H), 3.77 (s, 2H), 3.67 (ABX, $\Delta\nu_{AB}=53.4$ Hz, $J_{AB}=10.5$ Hz, $J_{AX}=5.2$ Hz, $J_{BX}=7.6$ Hz, 2H), 2.71 (app t, $J=4.0$ Hz, 1H), 1.56 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.2, 135.7, 134.9, 128.7, 128.7, 127.3, 80.8, 80.4, 63.9, 50.2, 44.2, 37.7; IR (cm^{-1}) 3412, 2919, 1494, 1453, 1078, 1029, 908, 871; EIMS, *m/z* (%): 180 (14), 91 (100), 65 (89).

S-exo-**24**. ^1H NMR (400 MHz, $CDCl_3$), δ: 7.37–7.22 (m, 5H), 6.34 (dd, $J=5.9$, 1.0 Hz, 1H), 6.31 (dd, $J=5.9$, 1.3 Hz, 1H), 5.00 (d, $J=4.3$ Hz, 1H), 4.53 (s, 1H), 3.84 (s, 2H), 3.58 (dd, $J=10.6$, 6.2 Hz, 1H), 3.24 (t, $J=10.6$ Hz, 1H), 2.21 (m, 1H), 2.11 (d, $J=4.3$ Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$), δ: 138.2, 135.7, 134.1, 128.8, 128.6, 127.2, 83.3, 79.5, 64.1, 49.9, 45.5, 36.8; IR (cm^{-1}) 3412, 3027, 2923, 1601, 1494, 1453, 1317, 1257, 1199, 1089, 1027, 1001, 908, 872; Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.58; H, 6.29.

3.3.15. Reduction of cycloadduct 9 with DIBAL and capture with benzyl bromide, formation of 25. Cycloadduct **9** (42.6 mg, 0.173 mmol) was reduced with DIBAL (1.0 M in THF, 2.07 mmol, 2.07 mL) in dry THF for 30 min. Addition of benzyl bromide (35 μL, 0.296 mmol), followed by triethylamine (41 μL, 0.296 mmol) with stirring with warming for 4 h, afforded sulfide **25** (43.0 mg, 61, 86% pure) after flash chromatography (15% EtOAc/hexanes). ^1H NMR (600 MHz, $CDCl_3$), δ: 7.37–7.22 (m, 5H), 5.57–5.52 (m, 1H), 5.40 (dq, $J=9.9$, 1.7 Hz, 1H), 3.78 (dd, $J=11.5$, 7.3 Hz, 1H) 3.74 (ABq, $J=13.5$ Hz, 2H), 3.69 (dd, $J=11.5$, 4.5 Hz, 1H), 2.96 (ddd, $J=8.9$, 5.6, 3.1 Hz, 1H), 2.33 (m, 1H), 2.25–2.19 (m, 2H), 2.10–2.04 (m, 2H), 0.99 (d, $J=7.5$ Hz, 3H); ^{13}C (100 MHz, $CDCl_3$), δ: 138.0, 132.0, 128.9, 128.8, 128.6, 127.1, 124.6, 60.2, 42.5, 42.4, 35.4, 33.7, 29.1, 18.2; IR (neat): 3409, 3084, 3061, 3020, 2960, 2921, 2875, 1494, 1453, 1436, 1373, 1238, 1070, 1030 cm^{-1}; MS (EI), *m/z* (%): 248 ((M^+), 16), 180 (10), 157 (39), 139 (10), 124 (22), 106 (24), 93 (35), 91 (100), 77 (15), 65 (12); HRMS: Calc. for $C_{15}H_{20}OS$ 248.1235. Found: 248.1248.

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On the synthesis of pyrinodemin A. Part 1: The location of the olefin

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Abstract—The elucidation of the structure of the cytotoxic marine sponge alkaloid pyrinodemin A by synthesis is described. Based on the ^{13}C NMR spectra of three double bond positional isomers and the natural product, it is concluded the C14′–C15′ isomer best represents the true structure of pyrinodemin A. In addition, the structural assignment of pyrinodemin C is evaluated.

1. Introduction

The bioassay-guided isolation of new compounds from marine sponges has led to the discovery of a diverse array of important biologically active alkaloids.[1] They are usually obtained in very small quantities, which makes accurate structural determination challenging, as attested by the instances of structural revisions in the literature.[2] With the unfeasible or unacceptable possibility of harvesting significant quantities from the natural source, it often falls to the synthetic chemist to confirm or revise the structure of these natural products.[3]

Pyrinodemin A was isolated from an unidentified marine sponge *Amphimedon* sp. collected off Nakijin, Okinawa, Japan by Kobayashi and co-workers.[4] The natural product exhibited cytotoxicity against murine leukaemia L1210 ($IC_{50}=0.058$ μg/mL) and KB epidermoid carcinoma cells ($IC_{50}=0.5$ μg/mL) in vitro, and the structure was proposed to be **1** based on electron impact mass spectrometry (EIMS) and NMR correlations. Although macrocyclic and oligomeric 3-alkylpyridines have been isolated,[1] the *cis*-cyclopent[*c*]-isoxazolidine structural motif is unique to the pyrinodemin family of alkaloids. Pyrinodemin A was isolated along with pyrinodemins B–D, cytotoxic bis-3-alkylpyridines containing the same bicyclic ring system showing minor structural variations in the right-hand side chain, and three monomeric 3-alkylpyridine alkaloids.[5]

As part of our ongoing studies into marine sponge alkaloids within the research group, we communicated the synthesis of three double bond positional (Δ-) isomers (**1**, **2**, **3**) of pyrinodemin A (Fig. 1).[6,7] The interesting structure of the natural product has attracted the attention of others and synthetic studies have also been reported by both the Snider group[8] and more recently Morimoto et al.[9] Herein we describe in full the syntheses and characterisation of these three molecules and give our rationalisation for the true identity of the natural product.

It was proposed that structure **1** could be biosynthetically formed via intramolecular cycloaddition of alkenyl-nitrone **4** (Scheme 1). This nitrone can be derived from the condensation of aldehyde **5** with hydroxylamine **6**, which in turn can be derived from aldehyde **7**, therefore the proposed structure of pyrinodemin A can be assembled from two 3-alkylpyridine aldehydes in a biomimetic synthesis. The retrosynthetic strategy towards aldehyde **5** (corresponding to the left-hand half common to all pyrinodemins) involved installation of the 3-alkylpyridine moiety using lithiated 3-picoline (Scheme 2). The alkyl chain derives from two further sections, a protected alkynol and an α,ω-dibromoalkane to act as electrophile. The modular nature of the convergent synthesis towards **1** allows the individual preparation of the left-hand and the right-hand sides, and thus potentially the synthesis of all the pyrinodemin alkaloids.

1.1. Synthesis of aldehyde 5

Commercially available 5-hexyn-1-ol **8** was protected as its *tert*-butyldiphenylsilyl ether **9** using *tert*-butyldiphenylchlorosilane and imidazole in 96% yield (Scheme 3). Deprotonation of **9** with *n*-butyllithium followed by

Keywords: Sponge; Pyrinodemin; Alkaloids; Nitrone; EIMS.
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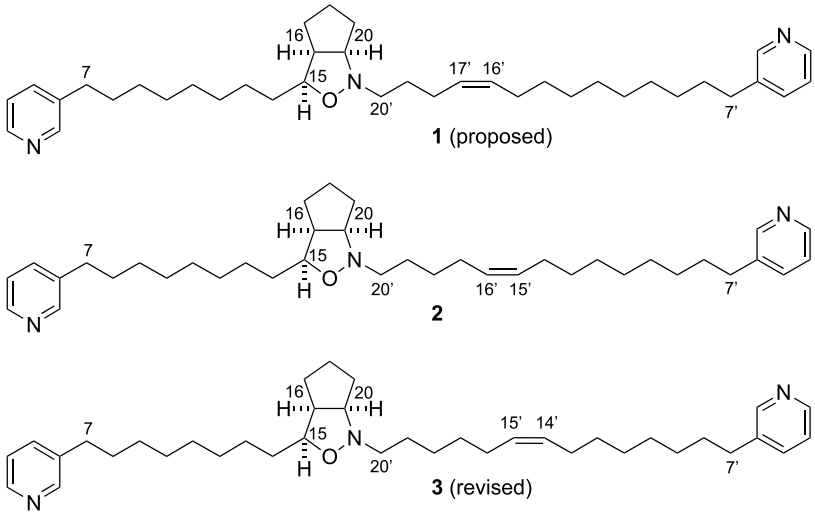
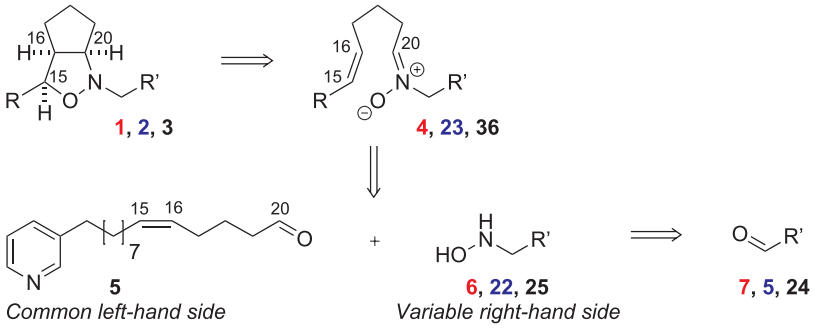
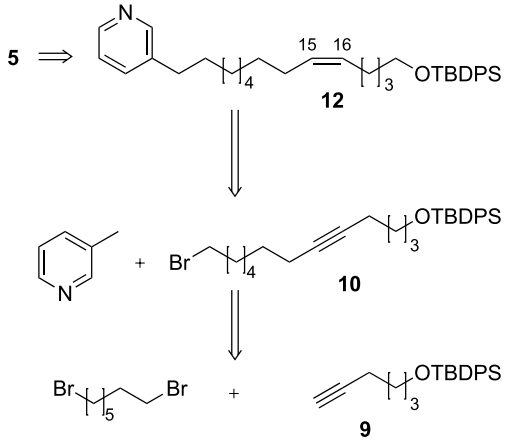


Figure 1. The three isomers of pyrinodemin A synthesised in this work.



Scheme 1. Retrosynthetic analysis of pyrinodemin A isomers **1**, **2** and **3**. For **1**, **4**, **6**, **7** R=Py$(CH_2)_8$ and R′=$(CH_2)_2$HC=CH$(CH_2)_9$Py; for **2**, **23**, **22**, **5** R′=$(CH_2)_3$HC=CH$(CH_2)_8$Py; for **3**, **36**, **25**, **24** R′=$(CH_2)_4$HC=CH$(CH_2)_7$Py.

addition of the acetylide anion to an excess of 1,7-dibromoheptane (prepared from 1,7-heptanediol and conc. HBr at reflux)[10] in 1,3-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone (DMPU)[11] gave **10** in 68% yield along with recovered starting material and dialkyation product (Section 1.5). Lindlar semi-hydrogenation revealed the *Z*-alkene **11** in 94% yield.[12] Displacement of the primary bromine using lithiated 3-picoline (generated using LDA in THF/DMPU)[13] gave **12** in 63% yield. Due to concerns over the work up and



Scheme 2. Retrosynthetic analysis of aldehyde **5**.

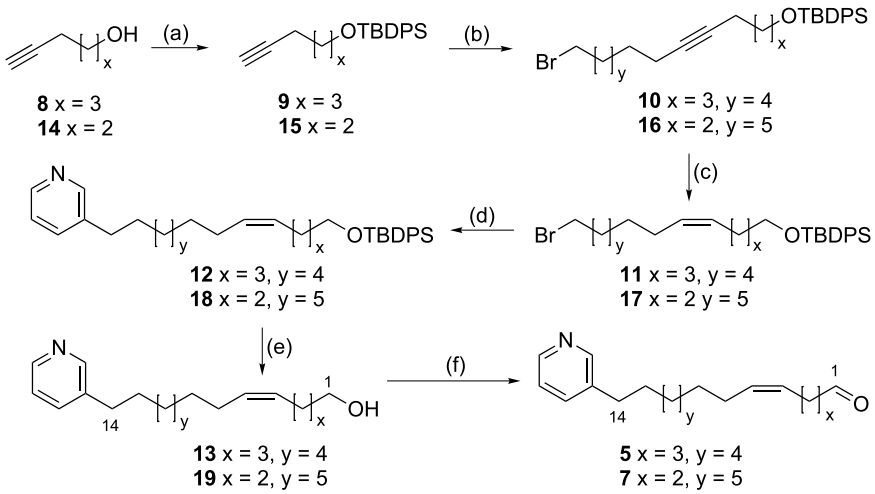
purification of the polar alcohol **13** in the presence of the tetra-*n*-butyl ammonium fluoride cation, ammonium fluoride in methanol[14] was used in preference to TBAF, and the desilylation proceeded in 97% yield. Oxidation using 2-iodoxybenzoic acid (IBX) in DMSO and THF delivered aldehyde **5** in 92% yield.[15]

1.2. Synthesis of aldehyde 7

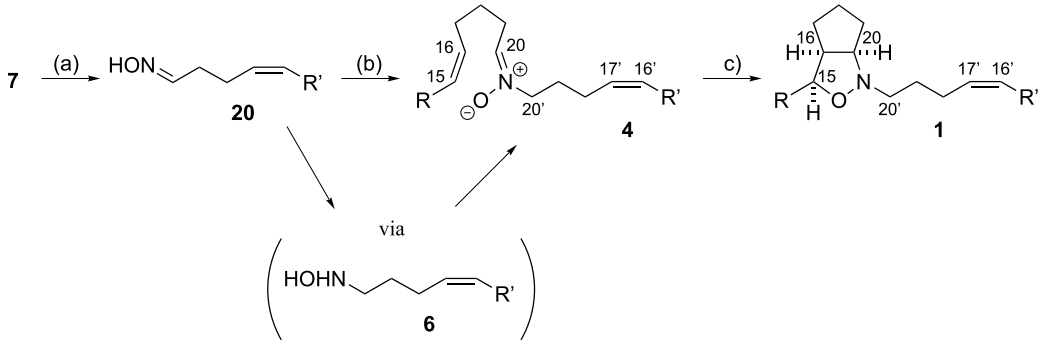
The synthesis commenced with the protection of the homologous 4-pentyn-1-ol **14** as its silyl ether **15** in 93% yield (Scheme 3). Deprotonation, followed by alkylation with excess 1,8-dibromooctane delivered **16** in 77% yield, which was subjected to Lindlar hydrogenation to give alkene **17** in 97% yield. Treatment with lithiated 3-picoline produced alkylpyridine **18** in 59% yield, deprotection with ammonium fluoride gave alcohol **19** in 97% yield, and subsequent IBX oxidation afforded the aldehyde **7** in 93% yield.

1.3. Synthesis of the C16′–C17′ isomer of pyrinodemin A (1)

With both aldehyde components in hand, the next step involved the biomimetic coupling of both aldehydes with a molecule of hydroxylamine. Aldehyde **7** was condensed



Scheme 3. Synthesis of aldehydes **5** and **7**. Reagents and conditions: (a) TBDPSCI, imidazole, THF, 96% for **9**, 93% for **15**; (b) *n*-BuLi, THF, then $Br(CH_2)_{y+3}Br$, DMPU, 68% for **10**, 77% for **16**; (c) Lindlar catalyst, quinoline, H_2, PhH, 94% for **11**, 97% for **17**; (d) 3-Picoline, LDA, THF, DMPU, 63% for **12**, 59% for **18**; (e) NH_4F, MeOH, 97% for **13**, 97% for **19**; (f) IBX, DMSO, THF, 92% for **5**, 93% for **7**.



Scheme 4. Synthesis of isomer **1**. $R=(CH_2)_8Py$, $R'=(CH_2)_9Py$. Reagents and conditions: (a) $NH_2OH\cdot HCl$, MeOH, NaOAc, 93%; (b) (i) $NaCNBH_3$, MeOH, pH 3; (ii) **5**, Na_2SO_4, DCM, 89% over two steps; (c) PhH, reflux, 41%.

with hydroxylamine hydrochloride using sodium acetate as base in methanol to give oxime **20** in 93% yield (Scheme 4). The product was identified as a ca. 1:1 mixture of *Z*:*E* oxime isomers from ^{1}H NMR, however this ratio was inconsequential as subsequent reduction with sodium cyanoborohydride delivered hydroxylamine **6**. 4-Ene-1-hydroxylamines have been shown to be thermally unstable,[16] decomposing via a reverse-Cope mechanism to give secondary hydroxylamines,[17] so the product was condensed immediately (without purification) with 1 equiv of aldehyde **5** in the presence of sodium sulphate to afford nitrone **4** in 89% yield over two steps. Heating nitrone **4** under reflux in benzene at high dilution (to promote intramolecular cyclisation) delivered a less-polar product in 41% yield. Mass-spectrometry indicated that the product was isomeric with nitrone **4** and ^{1}H NMR showed the disappearance of the distinctive triplet of the nitrone proton indicating that cyclisation had taken place.

The cyclised product of the reaction could be potentially any of four isomers of **1** (cycloaddition of the nitrone with either olefin and with either regioselectivity), therefore high-field (500 MHz) NMR experiments were required to confirm the structure (Fig. 2). HSQC-TOCSY[18] (τ_m=80 ms) indicated that C-20′ correlates with H-19′, H-18′ and H-17′ (in the olefinic region), thus locating the olefin between C-16′ and C-17′; HSQC-TOCSY and DQF-COSY confirmed the ring sizes in the bicyclic core; and 1D DPFGSE-NOESY[19] (τ_m= 400 ms) confirmed the *cis*-relationship of H-15 and the ring-junction protons H-16 and H-20. The product was thus assigned unambiguously as the C-16′, C-17′ isomer of pyrinodemin A (**1**).[20]

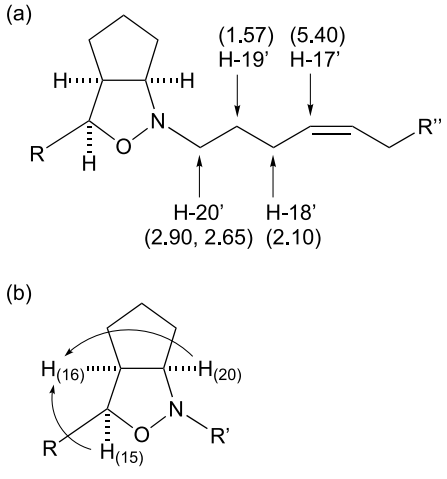
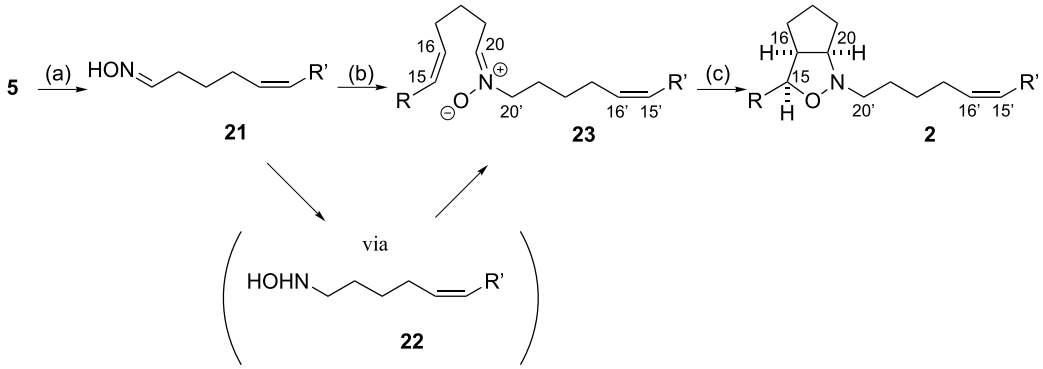


Figure 2. Structural determination of structure **1**.



Scheme 5. Synthesis of isomer **2**. R = $(CH_2)_8$Py, R′ = $(CH_2)_8$Py. Reagents and conditions: (a) $NH_2OH{\cdot}HCl$, MeOH, NaOAc, 84%; (b) (i) $NaCNBH_3$, MeOH, pH 3; (ii) **5**, Na_2SO_4, DCM, 71% over two steps; (c) PhH, heat, 63%.

The spectra of synthetic **1** and pyrinodemin A were similar and analysis of the ^1H and ^{13}C NMR spectra suggested that the gross structure (i.e., the central 5,5-bicyclic core and the 3-alkylpyridine chains) had been correctly assigned, however the olefinic and allylic regions showed some anomalies. Kobayashi reported that both the olefinic carbons and the allylic carbons appeared as coincidental peaks at 129.3 and 27.1 ppm, respectively. For synthetic **1** the olefinic carbons (C-16′ and C-17′) occur as distinct peaks at 129.2 and 130.3 ppm ($\Delta\delta = 1.1$), and the allylic carbons C-15′ and C-18′ at 27.1 and 24.8 ppm, respectively. The typical allylic carbon chemical shift for an *E*-olefin is ca. 31 ppm, and that for a *Z*-olefin is ca. 27 ppm.[21] Hence the observed spectral discrepancies did not originate from a mistakenly assigned C-16′-C17′ double bond geometry. The chemical shift deviation of C-18′ can be attributed to the proximity of the isoxazolidine nitrogen exerting a γ-shielding effect. Based on these data it was concluded that the proposed structure for the natural product was incorrect: structure **1** was not pyrinodemin A but rather a Δ-isomer. It was also concluded that the olefin must lie towards the centre of the chain, away from the isoxazolidine in a more magnetically symmetrical environment.

1.4. Synthesis of the C15′–C16′ isomer of pyrinodemin A (2)

The requirement for the olefin to reside further from the isoxazolidine would be satisfied by structure **2**, which derives from 2 equiv of aldehyde **5** (Scheme 1). This isomer is a more plausible candidate from a biosynthetic perspective, as it involves the coupling of two identical aldehyde units. This hypothesis was further encouraged by the isolation of oxime **21** from the same sponge extract as pyrinodemin A,[5] and we speculated that this oxime could be a biosynthetic precursor to pyrinodemin A. The proposed synthesis was put into practice and hydroxylamine hydrochloride was condensed with aldehyde **5** in the presence of sodium acetate to produce oxime **21** in 84% yield (Scheme 5). Reduction with sodium cyanoborohydride gave hydroxylamine **22** that was immediately condensed with a further equivalent of aldehyde **5** to form nitrone **23** in 71% yield over two steps. Thermal cyclisation of this nitrone gave a less-polar product in 63% yield: the structure of which was established as **2** by the same NMR experiments indicated above. The ^1H NMR and EIMS spectra were very similar to those of pyrinodemin A, however the ^{13}C NMR spectrum did not show coincidental olefinic or allylic carbon peaks: the olefinic carbons resonated at δ_C 130.0 and 130.4 ($\Delta\delta = 0.4$) and the allylic carbons at δ_C 27.0 and 27.1. In spite of the apparent similarities between pyrinodemin A and **2**, we observed two distinct and fully resolved peaks for both the allylic and olefinic carbons. Therefore, the critical regions of the spectra were inconsistent and we concluded that the C15′–C16′ isomer **2** was not the correct structure for pyrinodemin A.

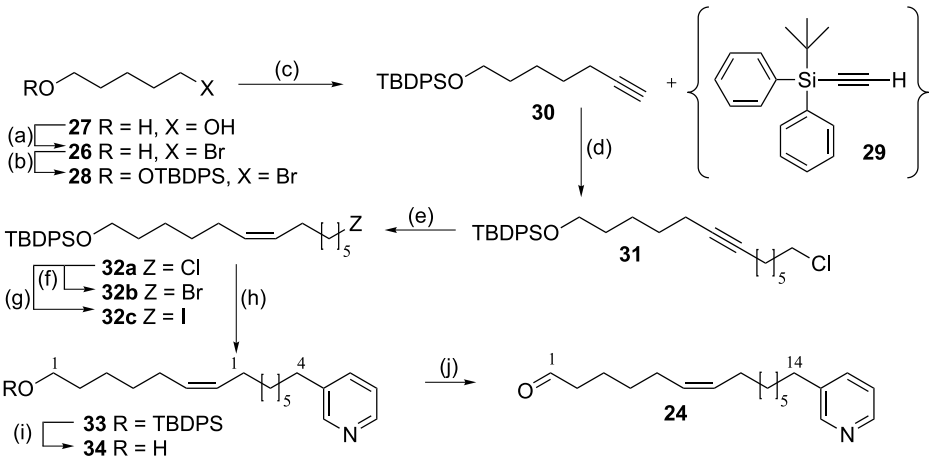
Independently and concurrently, Snider and Shi prepared structures **1** and **2**. Their results were identical (within a small experimental error) to those presented here (Table 1). They observed, but did not rationalise the non-coincident olefinic peaks and concluded that the double bond position in natural pyrinodemin A was at C15′–C16′. They described isomer **2** as ‘probably’ the structure of pyrinodemin A.[8]

1.5. Synthesis of aldehyde 24

We concluded that the magnitude of the difference in the chemical shifts of the olefinic carbons diminished as the olefin was moved further away from the central core, and therefore, set about the synthesis of the C14′–C15′ isomer of pyrinodemin A (**3**) This isomer can be derived from aldehyde **5** (as prepared above) and aldehyde **24** (via hydroxylamine **25**) according to our modular strategy (Scheme 1). It was envisaged that aldehyde **24** could be

Table 1. Comparison of the assignments of Snider and this work with pyrinodemin A

Isomer	δ_C Olefinic C (ppm)	$\Delta\delta$ (ppm)	δ_C Allylic C (ppm)
Pyrinodemin A[4]	129.3 (2C)	0	27.1 (2C)
C16′–C17′ **1** (Baldwin)[6]	129.2, 130.3	1.1	24.8, 27.1
C16′–C17′ **1** (Snider)[8]	129.3, 130.3	1.0	24.9, 27.0
C15′–C16′ **2** (Baldwin)[6]	129.5, 129.9	0.4	27.0, 27.1
C15′–C16′ **2** (Snider)[8]	129.6, 130.0	0.4	27.1, 27.2



Scheme 6. Synthesis of aldehyde **24**. Reagents and conditions: (a) $HBr_{(aq.)}$, toluene, reflux, 60%; (b)TBDPSCl, imidazole, THF, 96%; (c) LiC≡CH·eda, DMSO, THF, 84%; (d) *n*-BuLi, THF, DMPU, then $Cl(CH_2)_6I$, 85%; (e) Lindlar catalyst, H_2, quinoline, benzene, 83%; (f) NaI, acetone, reflux, 95%; (g) LiBr, butanone, reflux, 96%; (h) 3-picoline, LDA, DMPU, THF, 79% for **31a**, 63% for **31b**, 36% for **31c**; (i) NH_4F, MeOH, 95%; (j) IBX, DMSO, THF, 93%.

assembled using a similar synthetic route to the isomeric aldehydes **5** and **7**.

The corresponding alkynol (6-heptyn-1-ol) was not commercially available, so 5-bromopentan-1-ol **26** (obtained from 1,5-pentanediol **27** by selective monobromination)[22] was protected as its *tert*-butyldiphenylsilyl ether **28** in 96% yield, before conversion to the terminal alkyne (Scheme 6). The displacement of the bromide with lithium acetylide (stabilised as the ethylenediamine complex) at room temperature in DMSO was attempted,[23] however the yields were poor and inconsistent. Purification of the crude revealed the presence of *tert*-butyldiphenylsilyl ethyne **29**,[24] leading us to speculate that desilylation occurred due to the inefficient heat dissipation in the viscous liquid resulting in localised exotherms. In order to reduce the reaction temperature and decrease the viscosity, THF was added as a co-solvent. With precise temperature control at −5 °C and a slow addition of alkylbromide to the acetylide, the desilylation was avoided and the terminal alkyne **30** was delivered in 84% yield.

In the syntheses of the two previous fragments (aldehydes **5** and **7**), alkylation of a lithiated acetylene with a dibromide had been a key reaction. The starting material and the two products (mono and dialkylation of the dibromide) all had very similar R_f values and therefore the purification of the desired product was technically demanding. Although the reaction conditions were optimised, a small yet significant amount of dialkylation was observed (Table 2). It was decided to employ the commercially available 1-chloro-6-iodohexane instead, which gave a faster more efficient reaction. The alkylation was completely regioselective and no dialkylation product was detected. Deprotonation of acetylene **30** with *n*-butyllithium in THF/DMPU followed by addition of 2 equiv of 1-chloro-6-iodohexane afforded **31** in 85% yield, and subsequent Lindlar hydrogenation produced alkene **32a** in 83% yield.

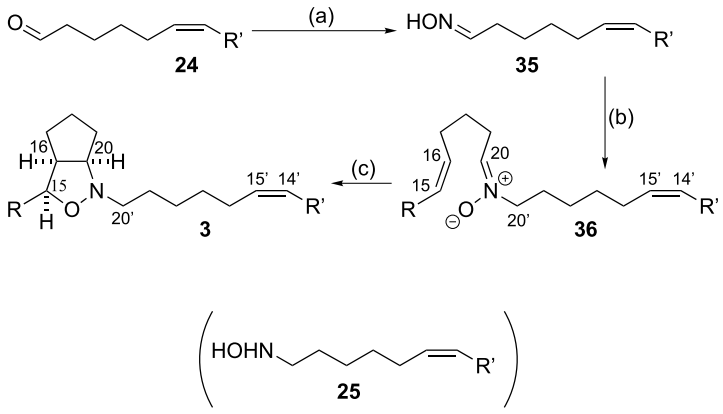
Table 2. Comparison of alkyne-anion alkylations

Alkynol	Electrophile	Alkynol (%)	Product (%)	Dialkylation (%)
TBDPSO (4, 5) **15**	$Br(CH_2)_8Br$ 4 equiv	4	77	4
TBDPSO (5, 6) **9**	$Br(CH_2)_7Br$ 4 equiv	9 (est.)[a]	68	4
TBDPSO (6, 7) **29**	$I(CH_2)_6Cl$ 2 equiv	5 (est.)[a]	85	—

[a] Yields of alkynol were estimated from the ^1H NMR of mixed fractions.

Table 3. Comparison of strategies towards 3-alkylpyridine **32**

Sequence X	Yield of Finkelstein reaction (%)	Yield of displacement reaction (%)	Overall yield (%)
Cl→I→CH_2Py	95	36	34
Cl→Br→CH_2Py	96	63	60
Cl→CH_2Py	—	79	79



Scheme 7. Synthesis of isomer **3**. R=$(CH_2)_8$Py, R′=$(CH_2)_7$Py. Reagents and conditions: (a) $NH_2OH\cdot HCl$, MeOH, NaOAc, 90%; (b) (i) $NaCNBH_3$, MeOH, pH 3; (ii) **5**, Na_2SO_4, DCM, 79% over two steps; (c) PhH, heat, 87%.

It had been proposed to transform the alkylchloride **32a** to the alkyliodide **32c** via a Finkelstein reaction[25] to improve the yield of the subsequent nucleophilic substitution with lithiated 3-picoline. Although halogen exchange was efficient, the yield of the subsequent S_N2 displacement reaction by lithiated 3-picoline was poor, proceeding at best in 36% yield, and typically in the range 10–20% yield. This was surprising given the efficient conversion observed by others for this reaction on similar substrates.[12,26] Conversion of **32a** to the alkylbromide **32b** and subsequent lithiated 3-picoline displacement gave moderate yields, consistent with an alkylation of this nature (vide supra), however using the original alkylchloride **32a** as a substrate the transformation proceeded cleanly in good yield, providing a superior route towards **33** (Table 3). Ammonium fluoride desilylation of **33** was achieved in 95% yield and subsequent oxidation with IBX in DMSO/THF delivered aldehyde **24** in 93% yield.

1.6. Synthesis of the C14′–C15′ isomer of pyrinodemin A (3)

Condensation of aldehyde **24** with hydroxylamine hydrochloride in the presence of sodium acetate in methanol gave oxime **35** in 90% yield (Scheme 7) Reduction with sodium cyanoborohydride in methanol at pH 3 gave hydroxylamine **25** and subsequent condensation with aldehyde **5** afforded nitrone **36** in 79% yield over two steps. Thermal cyclisation of nitrone **36** at high dilution delivered the C14′–C15′ isomer **3** in 87% yield. The compound was fully characterised:[27] the olefinic carbons were observed as two partially resolved peaks at 129.90 and 129.92 ppm ($\Delta\delta$ 0.02),[28] the allylic carbons exhibited a single resonance at 27.1 ppm and the signal distribution between 20 and 40 ppm appeared to be a better match with the published data than the two isomers previously prepared. As the available ^{13}C assignments for pyrinodemin A have been reported to only one decimal place, we conclude that this isomer is indistinguishable from the natural product. It is necessary to qualify that we cannot be absolutely certain that **3** is the true structure of pyrinodemin A until all other possible isomers have been discounted by synthesis or preferably by the re-isolation and characterisation of a pure authentic sample of the natural product using more reliable physical methods.

2. Morimoto's results

Morimoto et al. recently prepared isomers **2**, **3** and the C13′–C14′ isomer of pyrinodemin A, and based on the ^{13}C NMR $\Delta\delta$ values shown in Table 4, concluded that isomer **3** was the correct structure of pyrinodemin A.[9] Although the absolute ^{13}C NMR values do vary slightly, the $\Delta\delta$ values appear to be highly consistent between the synthetic groups. Morimoto's results rule-out the C13′–C14′ isomer as a candidate for the structure of pyrinodemin A, however it is curious that this isomer with the olefin in the exact centre of the chain should have such a high $\Delta\delta$ value. The result was not rationalised by the authors, however is presumably due to a conformational effect and it follows that other Δ-isomers (e.g., the C12′–C13′ isomer) could possess spectroscopic properties indistinguishable from the natural product.

Table 4. Morimoto's data in comparison to pyrinodemin A

Isomer	δ_C Olefinic C (ppm)	$\Delta\delta$	δ_C Allylic C (ppm)
Pyrinodemin A	129.3 (2C)	0	27.1 (2C)
C15′–C16′ (**2**)	129.6, 130.0	0.4	Unassigned
C14′–C15′ (**3**)	129.77, 129.79	0.02	Unassigned
C13′–C14′	129.6, 129.9	0.3	Unassigned

Data taken from Ref. 9.

3. EIMS analysis

Kobayashi assigned the location of the olefin in pyrinodemin A based on the EIMS fragmentation pattern shown in Figure 3.[4] The use of EIMS alone to ascertain the position of the olefin in an aliphatic chain is not a reliable technique (vide supra). It is known that alkene ions show a tendency to isomerise under EIMS conditions, and that the spectra of Δ-isomers are similar irrespective of double bond position.[29] The standard method to locate an olefin in an aliphatic chain is to functionalise the olefin, then examine the derivative using chemical ionisation.[30,31] More recently, collision activated decomposition in tandem mass spectrometry has been applied to natural products, without the

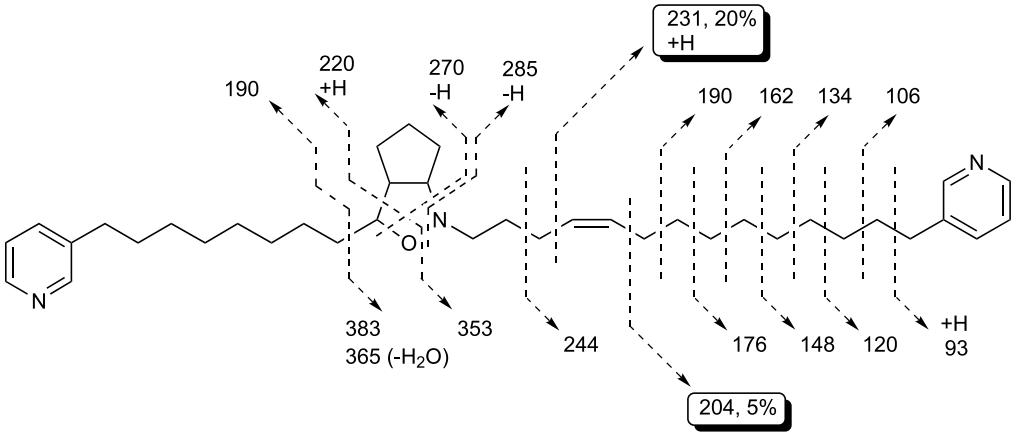


Figure 3. EIMS fragmentation pattern of the proposed structure of pyrinodemin A taken from Ref. 4. The fragments assigned as cleavage adjacent to the olefin are highlighted.

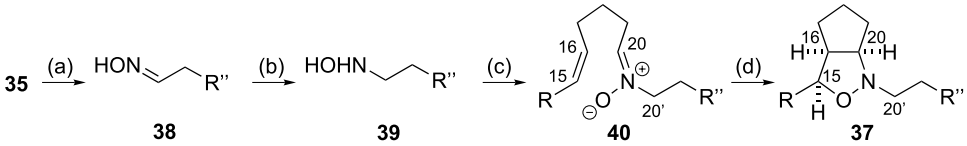
need for derivitisation.[32,33] In spite of this, the EIMS spectrum is the only other piece of indicative data available from the natural product, and it would be inadequate to neglect an analysis.

Kobayashi's EIMS spectrum of pyrinodemin A shows an $(M+2)^+$ peak at a higher intensity to the $(M+1)^+$ isotope peak.[34] This observation strongly suggested that the natural sample was contaminated with the dihydro analogue of pyrinodemin A **37**, possibly a natural product in its own right, inseparable from pyrinodemin A by the HPLC method used. In order to identify the contaminant peaks, and to provide a reference sample for the unsaturated isomers, analogue **37** was synthesised. It was hoped that the EIMS spectra of **37** and the three isomers already prepared would enable us to conduct a proper analysis of the EIMS data of the natural product.

The synthesis of **37** commenced from unsaturated oxime **35** which was selectively hydrogenated over palladium (5% on carbon) to give oxime **38** in 94% yield and subsequently reduced to the hydroxylamine **39** with sodium cyanoborohydride in 74% yield (Scheme 8). Condensation with aldehyde **5** gave nitrone **40** in 67% yield, and cyclisation produced the saturated analogue of pyrinodemin A (**37**) in 73% yield. High-resolution NMR experiments showed the presence of the 5,5-bicyclic isoxazolidine confirming the structure of the product as **37**.

The EIMS spectrum of any pyrinodemin A isomer is complicated by a contribution to intensity of peaks at $m/z \leq 190$ from fragmentation of the left-hand side of the molecule. Using the saturated analogue as a reference, it was possible to identify those peaks arising from the fragmentation of the right-hand side, and compare the intensities of these peaks for the different isomers (Table 5).

None of the EIMS spectra of the synthetic samples matched exactly that of the natural product but both the C15′–C16′ and the C14′–C15′ isomers (**2** and **3**) showed a reasonable fit. It should be noted that the natural product and synthetic samples were recorded on different instruments, which generates an experimental error. This is exemplified by the EIMS spectra of the C15′–C16′ isomer (**2**) recorded by Snider, Morimoto and ourselves where even significant peaks show a three-fold variation in intensity (e.g., *m/z* 231: Snider, 15%;[8] Morimoto, 48%;[9] this work, 29%). Given the experimental error inherent in this comparison, we conclude that anything more than this broad analysis is unjustified.



Scheme 8. Synthesis of saturated analogue **35**. R = $(CH_2)_8$Py, R″ = $(CH_2)_{12}$Py. Reagents and conditions: (a) Pd (5% on C), H_2, MeOH, 94%; (b) (i) $NaCNBH_3$, MeOH, pH 3, 74%; (ii) **5**, Na_2SO_4, DCM, 67% over two steps; (c) PhH, heat, 73%.

Table 5. EMIS data for pyrinodemin A and synthetically prepared Δ-isomers

m/z	Pyrinodemin A[a]	C16′–C17′ isomer (**1**)	C15′–C16′ isomer (**2**)	C14′–C15′ isomer (**3**)	C13′–C14′ isomer (Morimoto)[a]
231	20	2, (232) 6	29	30	0
244	25	16	43	18	12
259	10	15, (258) 40	6	27	37
270	17	11	18	23	17
285	42	43	49	82	75

[a] Data taken from Ref. 9.

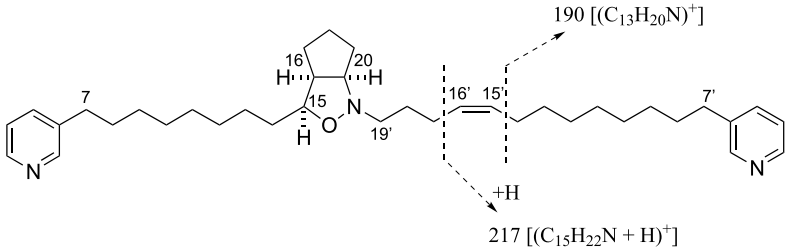


Figure 4. The EIMS fragmentation peaks used to assign the position of the olefin in pyrinodemin C (taken from Ref. 5).

4. A note on the structure of pyrinodemin C

Pyrinodemin C is a homologue of pyrinodemin A shorter by one-carbon in the right-hand alkyl chain. The position of the olefin was deduced by the application of the same EIMS analytical method (Fig. 4) as for pyrinodemin A (in this case from fragment ions *m*/*z* 190 and 217)[35] and assigned three methylenes from the isoxazolidine nitrogen. The only published ^{13}C NMR data for this compound are the allylic carbon chemical shifts (deduced from HMQC cross peaks), both of which are assigned as δ_C ca. 27 ppm. The results and rationalisation presented above suggest that the position of the olefin has been incorrectly assigned in pyrinodemin C and that a structural revision may be necessary for this natural product.

5. Conclusion

Prior to our communication on the synthesis of isomer **3**,[7] Snider proposed that the observed ^{13}C spectral discrepancy between natural pyrinodemin A and isomer **2** was unlikely to be due to the position of the olefin, but instead caused by concentration, pH or different parameters in the acquisition of the NMR spectra and maintained that isomer **2** was probably the correct structure of natural pyrinodemin A.[36] Experiments have shown that the olefinic ^{13}C NMR $\Delta\delta$ value of isomer **3** remains unchanged at low concentrations (1 mg), and furthermore our work on monomeric 3-alkylpyridine alkaloids has demonstrated that the chemical shifts of the pyridine aromatic protons are very sensitive to the presence of acid in the solution.[37] The spectra of pyrinodemin A and its synthetic isomers are not consistent with the presence of acid in the sample. If the olefinic ^{13}C chemical shifts of (natural) pyrinodemin A were sensitive to NMR acquisition parameters, then it would be difficult to explain the consistency of the olefinic $\Delta\delta^{13}$C as observed by the Baldwin, Morimoto and Snider groups for compounds **1** and **2**. In light of the smaller $\Delta\delta$ value observed with isomer **3** we believe that the ^{13}C spectral difference between natural pyrinodemin A and isomer **2** is due to the position of the olefin rather than the aforementioned factors or parameters.

In summary we have synthesised and characterised three Δ-isomers of pyrinodemin A. Based on comparisons of the ^{1}H and ^{13}C NMR data with those of the natural product, we believe that the C14′–C15′ isomer **3** is the best candidate for the structure of pyrinodemin A. There may however, be other isomers possessing spectroscopic properties indistinguishable from pyrinodemin A. In order to ascertain the true structure of the natural product all possible Δ-isomers would have to be synthesised or ideally, an authentic sample re-isolated and characterised using unambiguous techniques. Until these endeavours have been undertaken, we believe that the C14′–C15′ isomer (**3**) should be accepted as the structure of pyrinodemin A, and we have used this as a target for the asymmetric synthesis of the natural product.[38] In addition, analysis of the EIMS spectrum of pyrinodemin C also revealed that there may be a fundamental flaw in its structural assignment.

6. Experimental

6.1. General procedures

Proton magnetic resonance spectra were recorded on Brüker AC200 (200 MHz), Brüker DPX400 (400 MHz), Brüker DQX400 (400 MHz), Brüker AMX500 (500 MHz), and Brüker DRX500 (500 MHz), spectrometers at ambient temperature. Proton spectra assignments are supported by ^{1}H–^{1}H correlations (COSY) and by ^{1}H–^{13}C correlations (HMQC) where necessary. Chemical shifts (δ_H) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Coupling constants (*J*) are reported to the nearest 0.5 Hz. Carbon magnetic resonance spectra were recorded on Brüker AC200 (50.3 MHz), Brüker DPX400 (100.6 MHz), Brüker DQX400 (100.6 MHz), Brüker AMX500 (125.8 MHz), and Brüker DRX500 (125.8 MHz), spectrometers at ambient temperature. Chemical shifts (δ_C) are reported in parts per million (ppm) and are referenced to the residual solvent peak. Carbon spectra assignments are supported by DEPT or APT analysis and ^{13}C–^{1}H correlations (HSQC) where necessary. The ^{13}C spectra of the 5,5-bicyclic isoxazolidine structures synthesised showed some broad peaks particularly those proximate to the ring nitrogen. The chemical shift δ_C of those assigned from HSQC and HSQC-TOCSY analysis are indicated with the symbol (≈) and are quoted to the nearest ppm, those not observed using either technique are indicated as ‘not observed’. Superscript ‘a’ denotes one of a pair of diastereotopic protons.

Infrared spectra were recorded on a Perkin–Elmer Paragon 1000 Fourier Transform spectrometer between NaCl plates. Absorption maxima (ν_{max}) of the major peaks are reported in wavenumbers (cm^{-1}). Low-resolution mass spectra were recorded using a TRIO-1 GCMS spectrometer, a Micromass Platform (APCI) spectrometer, Micromass Autospec spectrometer (CI^+) and a micromass ZAB spectrometer (CI^+, EI). Only molecular ions (M^+), protonated molecular ions (MH^+), fragments from molecular ions and other major peaks are reported. High-resolution mass spectra were recorded on a Micromass Autospec spectrometer and are

accurate to ±10 ppm. Electrospray mass spectra were recorded on a Waters Micromass LCT spectrometer. Microanalyses were carried out by Elemental Microanalysis Limited, and are reported to three significant figures. Melting points were measured using a Cambridge Instruments Gallen™ III hot stage melting point apparatus and are uncorrected. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed plates precoated with silica gel 60 F_{254} (1.05554). Visualisation was by the quenching of UV fluorescence ($\lambda_{max}=254$ nm); staining with 10% w/v ammonium molybdate in 1 M sulphuric acid, 20% w/v phosphomolybdic acid in ethanol, 3% w/v ninhydrin in 97:3 *n*-BuOH/AcOH, followed by heating; or iodine on silica. Retention factors (R_f) are reported to 2 decimal places. Flash chromatography was performed using ICN silica 32–63, 60 Å. All reactions were carried out under a positive atmosphere of argon at room temperature unless otherwise specified.

Anhydrous diethyl ether, and THF were obtained by distillation from sodium/benzophenone ketyl under nitrogen, anhydrous DCM was distilled from calcium hydride under nitrogen. PE refers to the fraction of light petroleum ether boiling between 40 and 60 °C, and was distilled before use. Benzene, diisopropylamine, hexane, 3-methylpyridine, pyridine, triethylamine, and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) were distilled from calcium hydride under argon or reduced pressure and stored over 4 Å molecular sieves under argon until used. Methanol was distilled from 4 Å molecular sieves under reduced pressure and stored over 4 Å molecular sieves under argon until used. Dimethyl sulphoxide was dried over 4 Å molecular sieves. Imidazole was dried under vacuum before use.

6.1.1. Preparation of the C16′–C17′ isomer of pyrinodemin A 1. A solution of nitrone **4** (0.286 g, 0.50 mmol) in benzene (250 mL) was heated at reflux for 24 h. The solvent was removed in vacuo, and the crude product was purified by flash chromatography (100% EtOAc) to yield **1** (0.118 g, 0.21 mmol, 41%) as a colourless oil; $R_f=0.13$ (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2927 (s), 2854 (s), 1574 (m), 1478 (m), 1464 (m), 1422 (m), 1026 (m); *m/z* Probe APCI$^+$ (NH_3) 574 (MH^+, 100%); HRMS found 574.4735, $C_{38}H_{60}N_3O$ requires 574.4736; *m/z* Probe EIMS (+ve ion) 574 (1%), 556 (2%), 530 (9%), 515 (6%), 365 (28%), 355 (10%), 327 (9%), 315 (5%), 299 (15%), 285 (43%), 270 (11%), 259 (15%), 258 (40%), 244 (16%), 232 (6%), 231 (2%), 220 (20%), 218 (11%), 204 (6%), 190 (28%), 176 (44%), 162 (17%), 148 (20%), 136 (20%), 134 (14%), 120 (27%), 106 (100%), 93 (89%); δ_H (500 MHz, CD_3OD) 1.27–1.37 (24H, H-8 to H-12, H-8′ to H-14′), 1.33, 1.42 (2H, m, H-13), 1.46 (2H, m, H-18), 1.48 (1H, m, H-17), 1.50 (2H, m, H-14), 1.57 (2H, m, H-19′), 1.63 (1H, m, H-17), 1.65, 1.80 (2H, m, H-19), 2.03 (2H, m, H-15′), 2.10 (2H, m, H-18′), 2.65 (1H, m, H-20′), 2.65 (4H, t, $J=7.5$ Hz, H-7, H-7′), 2.85-2.95 (2H, m, H-16, H-20′^{a}), 3.50–3.60 (1H, m, H-20), 4.10–4.20 (1H, m, H-15), 5.40 (2H, m, H-17′, H-16′), 7.30–7.40 (2H, m, Py-*H*), 7.65–7.75 (2H, d, $J=8.0$ Hz, Py-*H*), 8.30–8.40 (4H, br, s, Py-*H*); δ_C (125.8 MHz, CD_3OD) 26.4, 27.8, 27.9, 28.7, 29.38, 30.8, 30.9, 31.0, 31.1, 31.2, 31.3, 31.4 (18CH_2), 32.8, 34.3 (4C, C-13, C-14, C13′, C14′), 51.5 (1C, C-16), 58.1 (1C, C-20′), 74.5 (1C, C-20), 79.6 (1C, C-15), 125.6 (2C, Py C-5*), 130.7, 131.9 (2CH, C-16′, C-17′), 138.4 (2C, Py C-4*), 140.6 (2C, Py C-3*), 148.0, 150.5 (4C, Py C-2*, C-6*).

δ_H (500 MHz, $CDCl_3$) 1.22–1.34 (20H, H-9 to H-12, H-9′ to H-14′), 1.34–1.49 (4H, m, H-13, H-18), 1.49–1.80 (12H, m, H-8, H-14, H-17, H-19, H-8′, H-19′), 1.91–2.16 (4H, m, H-15′, H-18′), 2.53–2.65 (1H, m, H-20′), 2.59 (4H, t, $J=7.7$ Hz, H-7, H-7′), 2.78–2.87 (2H, m, H-16, H-20′^{a}), 3.41–3.51 (1H, m, H-20), 4.01–4.08 (1H, m, H-15), 5.28–5.39 (2H, m, H-16′, H-17′), 7.16–7.22 (2H, m, Py-*H*), 7.43–7.50 (2H, m, Py-*H*), 8.38–8.50 (4H, br, s, Py-*H*); δ_C (125.8 MHz, $CDCl_3$) 24.8 (1C, C-18′), 26.2, 26.4 (2C, C-17, C-18), 26.9 (1C, C-13), 27.1 (1C, C-15′), 27.9, 28.7, 29.0, 29.2, 29.3, 29.4, 29.6 (13C, C-9 to C-14, C-9′ to C-14′, C-19′), 31.0 (2C, C-8, C-8′), 32.9 (2C, C-7, C-7′), 49.8 (1C, C-16), ≈57 (1C, C-20′), ≈73 (1C, C-20), ≈78 (1C, C-15), 123.1 (2C, Py C-5*), 129.2, 130.3 (2CH, C-16′, C-17′), 135.6 (2C, Py C-4*), 137.8 (2C, Py C-3*), 148.0, 149.8 (4C, Py C-2*, C-6*).

6.1.2. Preparation of the C15′–C16′ isomer of pyrinodemin A 2. A solution of nitrone **22** (0.142 g, 0.25 mmol) in benzene (100 mL) was heated at reflux for 18 h. The solvent was removed in vacuo to afford the crude product which was purified by flash chromatography (100% EtOAc) to yield **2** (0.089 g, 0.16 mmol, 63%) as a colourless oil; $R_f=0.30$ (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2928 (s), 2855 (s), 1575 (m), 1478 (m), 1465 (m), 1422 (m), 1337 (w), 1189 (w), 1026 (m), 793 (w), 714 (s); *m/z* Probe APCI$^+$ (NH_3) 574.6 (MH^+, 100%); *m/z* Probe EIMS (+ve ion) 572 (2%), 555 (3%), 365 (55%), 355 (10%), 327 (8%), 315 (4%), 301 (9%), 285 (49%), 270 (18%), 259 (6%), 244 (43%), 231 (29%), 220 (38%), 204 (5%), 190 (21%), 176 (37%), 162 (16%), 148 (18%), 134 (13%), 120 (26%), 106 (100%), 93 (97%); HRMS found $MH^+=574.4721$, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (500 MHz, $CDCl_3$) 1.28–1.42 (18H, m, H-9 to H-12, and H-9′ to H-13′), 1.34 (1H, m, H-13), 1.44 (2H, m, H-18′), 1.46 (1H, m, H-18), 1.47 (1H, m, H-13′^{a}), 1.49 (1H, m, H-17), 1.49 (1H, m, H-14), 1.59 (2H, m, H-19′), 1.59 (1H, m, H-14′^{a}), 1.64 (4H, m, H-8, H-8′), 1.69 (1H, m, H-17′^{a}), 1.70 (1H, m, H-18′^{a}), 1.72 (1H, m, H-19), 1.80 (1H, m, H-19′^{a}), 2.04 (2H, m, H-14′), 2.07 (2H, m, H-17′), 2.60–2.72 (1H, m, H-20′), 2.60 (4H, t, $J=7.7$ Hz, H-7, H-7′), 2.78–2.89 (2H, m, H-16, H-20′^{a}), 3.40–3.51 (1H, m, H-20), 4.00–4.08 (1H, m, H-15), 5.28–5.38 (2H, m, H-15′, H-16′), 7.14–7.21 (2H, m, Py-*H*), 7.43–7.50 (2H, m, Py-*H*), 8.36–8.49 (4H, br, s, Py-*H*); δ_C (125.8 MHz, $CDCl_3$) 26.2, 26.3 (2C, C-17, C-18), 26.9 (1C, C-13), 27.0 (1C, C-17′), 27.1 (1C, C-14′), 27.4 (1C, C-18′), 27.7 (1C, C-19′), 28.6 (1C, C-14), 29.0, 29.1, 29.2, 29.3, 29.5, 29.6, (9C, C-9 to C-12 and C-9′ to C-13′), 31.0 (2C, C-8, C-8′), 32.9 (2C, C-7, C-7′), 34.1, (1C, C-19), 49.8 (1C, C-16), 56.8 (1C, C-20′), 72.5 (1C, C-20), 77.6 (1C, C-15), 123.1 (2C, Py C-5*), 129.5, 129.9 (2CH, C-15′, C-16′), 135.7 (2C, Py C-4*), 137.9 (2C, Py C-3*), 147.0, 149.8 (4C, Py C-2*, C-6*).

6.1.3. Preparation of 1-(*tert*-butyldiphenylsilyloxy)-5-bromopentane 28. To a solution of 5-bromopentan-1-ol **26** (3.00 g, 18.0 mmol) and imidazole (3.06 g, 45.0 mmol) in THF (40 mL) at 0 °C was added *tert*-butyldiphenylchlorosilane (5.20 mL, 19.9 mmol) dropwise. The mixture was allowed to warm to room temperature over 3 h, then was quenched with $NH_4Cl_{(aq)}$ (sat., 90 mL) and extracted

with 1:1 Et_2O:PE (4×30 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 30 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (15% benzene, 85% PE) to yield **28** (6.96 g, 17.2 mmol, 96%) as a colourless oil; R_f=0.18 (15% benzene, 85% PE); ν_{max}/cm^{-1} (thin film) 3071 (m), 2932 (s), 2858 (s), 1590 (w), 1473 (m), 1428 (s), 1390 (w), 1362 (w), 1253 (w), 1189 (w), 1112 (s), 1008 (w), 823 (m), 740 (m), 702 (s); *m/z* Probe CI^+ (NH_3) 424.2 ($M[^{81}Br]NH_4^+$, 100%), 407.2 ($M[^{81}Br]H^+$, 84%); HRMS found MH^+=405.1249, $C_{21}H_{30}OSi^{79}Br$ requires 405.1249; microanalysis found C, 62.3; H, 7.44; $C_{21}H_{29}OSiBr$ requires C, 62.2; H, 7.21; δ_H (200 MHz, $CDCl_3$) 1.20 (9H, s, $C(CH_3)_3$), 1.55–1.80 (4H, m, H-2, H-3), 1.95 (2H, quin., J=7.0 Hz, H-4), 3.45 (2H, t, J=7.0 Hz, H-5), 3.80 (2H, t, J=5.5 Hz, H-1), 7.40–7.57 (6H, m, Ph-*H*) 7.75–7.85 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 19.3 (1C, $C(CH_3)_3$), 24.6 (1C, C-3), 27.0 (3C, $C(CH_3)_3$), 31.7 (1C, C-2), 32.6 (1C, C-5), 33.9 (1C, C-4), 63.6 (1C, C-1), 127.7 (4CH, Ph), 129.7 (2CH, Ph), 134.0 (2C, Ar*C*-Si), 135.7 (4CH, Ph).

6.1.4. Preparation of 1-(*tert*-butyldiphenylsilyloxy)-hept-6-yne 30. To a suspension of lithium acetylide-ethylene diamine complex (2.44 g, 90%, 23.9 mmol, 1.85 equiv) in DMSO (15 mL) and THF (5 mL) at −5 °C, was added a solution of 1-(*tert*-butyldiphenylsilyloxy)-5-bromopentane **28** (5.22 g, 12.9 mmol) in THF (5 mL) cooled to −40 °C via cannula dropwise over 30 min. The reaction was then stirred at room temperature for 1 h. The mixture was quenched with $NH_4Cl_{(aq)}$ (sat., 100 mL) and H_2O (20 mL), then extracted into 1:1 Et_2O:PE (3×100 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 2×50 mL), and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (20% benzene, 80% PE) to yield **30** (3.83 g, 10.9 mmol, 84%) as a colourless oil; R_f=0.34 (20% benzene, 80% PE); ν_{max}/cm^{-1} (thin film) 3309 (m), 3071 (w), 2933 (s), 2859 (s), 1459 (m), 1428 (s), 1371 (w), 1335 (w), 1112 (s), 823 (w), 740 (w), 702 (s); *m/z* Probe CI^+ (NH_3) 351.1 (MH^+, 100%); HRMS found MH^+= 351.2148, $C_{23}H_{31}OSi$ requires 351.2144; microanalysis found C, 78.9; H, 9.02; $C_{23}H_{30}OSi$ requires C, 78.8; H, 8.62; δ_H (200 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 1.45–1.70 (6H, m, H-2 to H-4), 1.95 (1H, t, J=2.5 Hz, H-7), 2.15–2.27 (2H, m, H-5), 3.70 (2H, t, J=6.0 Hz, H-1), 7.35–7.50 (6H, m, Ph-*H*), 7.65–7.75 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 18.4 (1C, C-5), 19.2 (1C, $C(CH_3)_3$), 25.0 (1C, C-3), 26.9 (3C, $C(CH_3)_3$), 28.2 (1C, C-4), 32.0 (1C, C-2), 63.7 (1C, C-1), 68.2 (1C, C-7), 84.6 (1C, C-6), 127.6 (4CH, Ph), 129.5 (2CH, Ph), 134.1 (2C, *C*-Si), 135.6 (4CH, Ph).

6.1.5. Preparation of 13-chloro-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-yne 31. To a solution of 1-(*tert*-butyldiphenylsilyloxy)-hept-6-yne **30** (1.09 g, 3.11 mmol) in THF (10 mL) cooled to −16 °C was added *n*-BuLi (2.03M in hexanes, 1.54 mL, 3.13 mmol). After stirring at −16 °C for 1 h, the solution was cooled to −78 °C, and DMPU (3.77 mL, 31.2 mmol, 10 equiv) was added. After a further 15 min stirring, the yellow solution was transferred via cannula to a solution of 1-chloro-6-iodohexane (1.55 g, 6.29 mmol, 2 equiv) in THF (4 mL) at −78 °C. The solution was stirred for 3 h from −78 °C to room temperature. The mixture was quenched with H_2O (25 mL) and $NH_4Cl_{(aq)}$ (sat., 25 mL), then extracted into EtOAc (4×60 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 50 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (15% toluene, 85% PE) to yield **31** (1.24 g, 2.64 mmol, 85%) as a colourless oil; R_f= 0.13 (15% toluene, 85% PE); ν_{max}/cm^{-1} (thin film) 3071 (m), 2933 (s), 2858 (s), 1590 (w), 1472 (m), 1462 (m), 1428 (s), 1389 (w), 1361 (w), 1112 (s), 1009 (w), 824 (m), 740 (w), 702 (s); *m/z* Probe CI^+ (NH_3) 469.4 ($M[^{35}Cl]H^+$, 100%), 411.3 (21%), 213.1 (72%), 178.9 (29%); HRMS found MH^+=469.2698, $C_{29}H_{42}OSi^{35}Cl$ requires 469.2693; δ_H (200 MHz, $CDCl_3$) 1.15 (9H, s, $C(CH_3)_3$), 1.40–1.75 (12H, m, H-2 to H-4 and H-9 to H-11), 1.75–1.90 (2H, m, H-12), 2.15–2.30 (4H, m, H-5, H-8), 3.58 (2H, t, J=7.0 Hz, H-13), 3.78 (2H, t, J=6.0 Hz, H-1), 7.40-7.55 (6H, m, Ph-*H*), 7.70–7.85 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 18.8 (2C, C-5, C-8), 19.3 (1C, $C(CH_3)_3$), 25.2, 26.5 ($2CH_2$), 27.0 (3C, $C(CH_3)_3$), 28.1, 29.0 ($3CH_2$), 32.2, 32.6 (2C, C-2, C-12), 45.0 (1C, C-13), 63.9 (1C, C-1), 80.0, 80.3 (2C, C-6, C-7), 127.7 (4CH, Ph), 129.6 (2CH, Ph), 134.1 (2C, *C*-Si), 135.6 0 (4CH, Ph).

6.1.6. Preparation of *Z*-13-chloro-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-ene 32a. To a solution of 13-chloro-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-yne **31** (2.13 g, 4.54 mmol) and benzene (30 mL) were added Lindlar catalyst (0.640 g) and quinoline (58 μL). The mixture was stirred under hydrogen gas (1 atm, balloon) for 1 h. The reaction had not reached completion, so additional Lindlar catalyst (0.410 g) was added, and the mixture stirred for a further 3 h. The mixture was filtered through cellulose and washed with benzene (150 mL). The organic phase was washed with $KHSO_{4(aq)}$ (1%, 30 mL), neutralised with $NaHCO_{3(aq)}$ (sat., 30 mL), then with $NaCl_{(aq)}$ (sat., 50 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (15% toluene, 85% PE) to yield **32a** (1.77 g, 3.76 mmol, 83%) as a colourless oil; R_f=0.20 (15% toluene, 85% PE); ν_{max}/cm^{-1} (thin film) 3071 (m), 3001 (m), 2931 (s), 2857 (s), 1656 (w), 1590 (w), 1472 (m), 1428 (m), 1390 (w), 1361 (w), 1188 (w), 1112 (s), 824 (m), 739 (w), 702 (s); *m/z* Probe CI^+ (NH_3) 471.4 ($M[^{35}Cl]H^+$, 100%), 256.2 (19%), 196.3 (33%), 179.9 (20%), 123.1 (21%), 95.1 (27%); HRMS found MH^+ 471.2848, $C_{29}H_{44}OSi^{35}Cl$ requires 471.2850; microanalysis found C, 73.8; H, 9.42; $C_{29}H_{43}OSiCl$ requires C, 73.9; H, 9.21; δ_H (200 MHz, $CDCl_3$) 1.10 (9H, s, $C(CH_3)_3$), 1.30–1.55 (10H, m, H-3, H-4, H-9 to H-11), 1.55-1.70 (2H, m, H-2), 1.80 (2H, quin., J= 7.0 Hz, H-12), 2.00–2.15 (4H, m, H-5, H-8), 3.55 (2H, t, J= 7.0 Hz, H-13), 3.72 (2H, t, J=6.5 Hz, H-1), 5.30–5.50 (2H, m, H-6, H-7), 7.35–7.55 (6H, m, Ph-*H*), 7.65–7.80 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 19.3 (1C, $C(CH_3)_3$), 25.5, 26.8 ($2CH_2$), 26.9 (3C, $C(CH_3)_3$), 27.1, 27.2, 28.5, 29.5, 29.6 ($5CH_2$), 32.5, 32.6 (2C, C-2, C-12), 45.1 (1C, C-13), 64.0 (1C, C-1), 127.6 (4CH, Ph), 129.5 (2CH, Ph), 129.7, 130.0 (2C, C-6, C-7), 134.2 (2C, *C*-Si), 135.6 (4CH, Ph).

6.1.7. Preparation of *Z*-13-bromo-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-ene 32b. A solution of *Z*-13-chloro-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-ene **32a** (0.099 g,

0.21 mmol), and LiBr (0.623 g, 7.18 mmol) in butanone (2 mL) was heated at reflux for 24 h. The butanone was removed in vacuo, and H_2O (25 mL) was added. The product was extracted into EtOAc (3×30 mL). The organic phases were washed with $Na_2S_2O_{3(aq)}$ (sat., 20 mL), then $NaCl_{(aq)}$ (sat., 30 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (15% benzene, 85% PE) to yield **32b** (0.104 g, 0.20 mmol, 96%) as a colourless oil; R_f=0.20 (15% benzene, 85% PE); ν_{max}/cm^{-1} (thin film) 3071 (m), 3000 (m), 2932 (s), 2857 (s), 1590 (w), 1462 (m), 1428 (m), 1389 (w), 1361 (w), 1260 (w), 1112 (s), 824 (m), 740 (m), 702 (s); 534.5 (10%, MNH_3^+), 517.5 (100%, MH^+), 471.5 (18%), 455.4 (33%), 437.6 (30%), 375.5 (64%), 256.3 (35%), 196.2 (60%); HRMS found MH+ 515.2337 $C_{29}H_{44}OSiBr_{79}$ requires 515.2345 δ_H (200 MHz, $CDCl_3$) 1.10 (9H, br, s, $C(CH_3)_3$), 1.30–1.53 (10H, m, H-3, H-4, H-9 to H-11), 1.53–1.70 (2H, m, H-2), 1.88 (2H, quin, J=7.5 Hz H-12), 1.98-2.16 (4H, m, H-5, H-8), 3.42 (2H, t, J=7.0 Hz, H-13), 3.70 (2H, t, J=6.5 Hz, H-1), 5.30–5.48 (2H, m, H-6, H-7), 7.35–7.52 (6H, m, Ph-*H*), 7.67–7.75 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 19.2 (1C, $C(CH_3)_3$), 25.5 ($1CH_2$), 26.9 (3C, $C(CH_3)_3$), 27.1, 27.2, 28.1, 28.4, 29.5, ($6CH_2$), 32.5, 32.8 (2C, C-2, C-12), 34.0 (1C, C-13), 64.0 (1C, C-1), 127.6 (4CH, Ph), 129.5 (2CH, Ph), 129.6, 130.0 (2C, C-6, C-7), 134.2 (2C, *C*-Si), 135.6 (4CH, Ph).

6.1.8. Preparation of *Z*-13-iodo-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-ene 32c. A solution of *Z*-13-chloro-1-(*tert*-butyldiphenylsilyloxy)-tridec-6-ene **32a** (0.835 g, 1.77 mmol), and NaI (2.69 g, 17.9 mmol, 10 equiv), in acetone (15 mL), was heated at reflux for 24 h. The acetone was removed in vacuo, and H_2O (50 mL) was added. The product was extracted into EtOAc (3×50 mL). The organic phases were washed with $Na_2S_2O_{3(aq)}$ (sat., 30 mL), then $NaCl_{(aq)}$ (sat., 50 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (15% benzene, 85% PE) to yield **32c** (0.948 g, 1.68 mmol, 95%) as a colourless oil; R_f=0.32 (15% benzene, 85% PE); ν_{max}/cm^{-1} (thin film) 3071 (m), 3001 (m), 2930 (s), 2856 (s), 2362 (w), 2344 (w), 1655 (w), 1590 (w), 1472 (m), 1428 (m), 1389 (w), 1361 (w), 1190 (w), 1112 (s), 824 (m), 740 (m), 701 (s); *m/z* Probe CI^+ (NH_3) 580.3 (MNH_4^+, 67%), 563.2 (MH^+, 100%), 437.3 (35%), 256.1 (27%), 196.0 (30%); HRMS found MH^+ 563.2209, $C_{29}H_{44}OSiI$ requires 563.2206; microanalysis found C, 61.8; H, 7.62; $C_{29}H_{43}OSiI$ requires C, 61.9; H, 7.71; δ_H (200 MHz, $CDCl_3$) 1.08 (9H, s, $C(CH_3)_3$), 1.25–1.50 (10H, m, H-3, H-4, H-9 to H-11), 1.50–1.67 (2H, m, H-2), 1.83 (2H, quin, J=7.5 Hz, H-12), 1.95–2.13 (4H, m, H-5, H-8), 3.20 (2H, t, J=7.0 Hz, H-13), 3.68 (2H, t, J=6.5 Hz, H-1), 5.27–5.47 (2H, m, H-6, H-7), 7.35–7.50 (6H, m, Ph-*H*), 7.65–7.75 (4H, m, Ph-*H*); δ_C (50.3 MHz, $CDCl_3$) 7.3 (1C, C-13), 19.2 (1C, $C(CH_3)_3$), 25.5 ($1CH_2$), 26.9 (3C, $C(CH_3)_3$), 27.1, 27.2, 28.2, 29.5, 30.4 ($6CH_2$), 32.5, 33.5 (2C, C-2, C-12), 63.9 (1C, C-1), 127.6 (4CH, Ph), 129.5 (2CH, Ph), 129.6, 130.0 (2C, C-6, C-7), 134.1 (2C, *C*-Si), 135.6 (4CH, Ph).

6.1.9. Preparation of *Z*-1-(*tert*-butyldiphenylsilyloxy)-14-(pyridin-3-yl)-tetradec-6-ene 33. To a solution of diisopropylamine (0.111 mL, 0.79 mmol, 3 equiv) in THF (2 mL) at −10 °C was added *n*-BuLi (2.03 M in hexanes, 0.390 mL, 0.79 mmol, 3 equiv). The solution was stirred at −10 °C for 30 min then DMPU (0.094 mL, 0.78 mmol, 3 equiv) was added. After 15 min stirring, 3-methylpyridine (0.077 mL, 0.79 mmol) was added dropwise. After a further 60 minutes stirring at −10 °C, the solution was cooled to −78 °C. This solution was added via cannula to a solution of halide **32a**, **32b**, or **32c** (0.26 mmol) in THF (2 mL) cooled to −78 °C. The reaction was stirred for 22 h from −78 °C to room temperature. The reaction was quenched with $NH_4Cl_{(aq)}$ (sat., 10 mL) and H_2O (10 mL) and extracted with EtOAc (3×30 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 20 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (25% EtOAc, 75% benzene) to yield **33** (79% from **32a**, 63% from **32b**, 36% from **32c**) as a pale yellow oil; R_f=0.33 (25% EtOAc, 75% benzene); ν_{max}/cm^{-1} (thin film) 3000 (w), 2930 (s), 2856 (s), 1575 (w), 1462 (w), 1428 (m), 1389 (w), 1111 (s), 1026 (w), 824 (m), 740 (m), 702 (s); *m/z* Probe CI^+ (NH_3) 528.4 (MH^+, 100%), 470.3 (23%); HRMS found MH^+ 528.3668, $C_{35}H_{50}NOSi$ requires 528.3662; δ_H (200 MHz, $CDCl_3$) 1.13 (9H, s, $C(CH_3)_3$), 1.30–1.55 (12H, m, H-3, H-4, H-9 to H-12), 1.55–1.70 (4H, m, H-2, H-13), 2.00–2.20 (4H, m, H-5, H-8), 2.68 (2H, t, J=7.5 Hz, H-14), 3.74 (2H, t, J=6.5 Hz, H-1), 5.32–5.52 (2H, m, H-6, H-7), 7.22–7.32 (1H, m, Py H-5*), 7.40–7.60 (7H, m, 6H Ph-*H*, 1H Py H-4*), 7.70–7.80 (4H, m, Ph-*H*), 8.50–8.55 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 19.7 (1C, $C(CH_3)_3$), 25.9 ($1CH_2$), 27.3 (3C, $C(CH_3)_3$), 27.7, 29.6, 29.7, 29.8, 30.0, 30.2, 31.6, 33.0, 33.5 ($10CH_2$), 64.4 (1C, C-1), 123.7 (1C, Py C-5*) 128.0 (4CH, Ph), 129.9 (2CH, Ph), 130.3 (2C, C-6, C-7), 134.6 (2C, Ar*C*-Si), 136.0 (4CH, Ph), 136.2 (1C, Py C-4*), 138.4 (1C, Py C-3*), 147.7, 150.4 (2C, Py C-2*, C-6*).

6.1.10. Preparation of *Z*-14-(pyridin-3-yl)-tetradec-6-en-1-ol 34. To a solution of **33** (1.44 g, 2.73 mmol) in MeOH (30 mL) was added NH_4F (1.43 g, 38.6 mmol, 14 equiv). The mixture was heated at 60 °C for 6.5 h. The reaction was quenched with $NaHCO_{3(aq)}$ (sat., 30 mL) and H_2O (30 mL) and extracted with EtOAc (3×100 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 50 mL) and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (30% Et_3N, 15% EtOAc, 55% PE) to yield **34** (0.754 g, 2.60 mmol, 95%) as a pale yellow oil; R_f=0.22 (30% Et_3N, 15% EtOAc, 55% PE); ν_{max}/cm^{-1} (thin film) 3339 (br, m), 3003 (m), 2928 (s), 2855 (s), 1578 (w), 1479 (w), 1461 (w), 1424 (m), 1065 (m), 713 (m); *m/z* Probe $APCI^+$ (NH_3) 290.4 (MH^+, 100%); HRMS found MH^+= 290.2496, $C_{19}H_{32}NO$ requires 290.2484; δ_H (200 MHz, $CDCl_3$) 1.15–1.45 (12H, m, H-3, H-4, and H-9 to H-12), 1.45–1.70 (4H, m, H-2, H-13), 1.85–2.10 (4H, m, H-5, H-8), 2.57 (2H, t, J=7.5 Hz, H-14), 2.90–3.30 (1H, br s, OH), 3.60 (2H, t, J=6.5 Hz, H-1), 5.20–5.42 (2H, m, H-6, H-7), 7.17 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz Py H-5*) 7.46 (1H, br, d, J=8.0 Hz Py H-4*), 8.34–8.45 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 25.5, 27.1, 29.0, 29.1, 29.2, 29.5, 29.6, 31.0, 32.5, 32.7, 32.9 ($11CH_2$), 62.5 (1C, C-1), 123.3 (1C, Py C-5*), 129.7, 129.9 (2C, C-6, C-7), 135.9 (1C, Py C-4*), 138.0 (1C, Py C-3*), 146.9, 149.7 (2C, Py C-2*, C-6*).

6.1.11. Preparation of *Z*-14-(pyridin-3-yl)-tetradec-6-en-1-al 24. To a solution of IBX (0.454 g, 1.62 mmol,

1.5 equiv) in DMSO (5 mL) was added a solution of **34** (0.310 g, 1.07 mmol) in THF (1 mL) via cannula. The reaction mixture was stirred for 5 h after which time it was diluted by H_2O (100 mL), filtered and extracted with EtOAc (3×30 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 30 mL) and dried over Na_2SO_4. Filtration and removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (50% EtOAc, 50% PE) to yield **24** (0.285 g, 0.99 mmol, 93%) as a pale yellow oil; R_f=0.27 (50% EtOAc, 50% PE); ν_{max}/cm^{-1} (thin film) 3004 (w), 2928 (s), 2855 (s), 2718 (w), 1725 (s), 1575 (m), 1478 (m), 1461 (m), 1422 (m), 1190 (w), 1027 (m), 794 (w), 714 (m); *m/z* APCI$^+$ (NH_3) 288.3 (MH^+, 100%); HRMS found MH^+=288.2328, $C_{19}H_{30}NO$ requires 288.2327; δ_H (200 MHz, $CDCl_3$) 1.15–1.45 (10H, m, H-4 and H-9 to H-12), 1.45–1.70 (4H, m, H-3, H-13), 1.85–2.10 (4H, m, H-5, H-8), 2.38 (2H, dt, J_1=7.5 Hz, J_2=2.0 Hz, H-2), 2.55 (2H, t, J=7.5 Hz, H-14), 5.20–5.40 (2H, m, H-6, H-7), 7.15 (1H, dd, J_1=8.0 Hz, J_2=5.0 Hz, Py H-5*) 7.44 (1H, dd, J=8.0 Hz, J_2=2.0 Hz, Py H-4*), 8.39 (2H, apparent broad s, Py, H-2*, H-6*), 9.71 (0.5H, t, J=2.0 Hz, H-1); δ_C (50.3 MHz, $CDCl_3$) 22.0 (1C, C-3), 26.4, 27.2, 29.1, 29.2, 29.3, 29.6, 31.1, 33.0, (10CH_2, C-3 to C-5 and C-7 to C-14), 43.2 (1C, C-2), 123.2 (1C, Py C-5*), 128.2, 131.3 (2CH, C-5, C-6) 135.8 (1C, Py C-4*), 137.9 (1C, Py C-3*), 147.1, 149.9 (2C, Py C-2*, C-6*), 202.6 (1C, C-1).

6.1.12. Preparation of *Z*-14-(pyridin-3-yl)-tetradec-6-en-1-oxime 35. To a solution of **24** (0.138 g, 0.48 mmol) in MeOH (6 mL) were added NaOAc (0.119 g, 1.45 mmol, 3 equiv), then hydroxylamine hydrochloride (0.100 g, 1.44 mmol, 3 equiv). The mixture was stirred for 4.5 h at room temperature. The solvent was removed in vacuo and DCM (4 mL) and H_2O (4 mL) with $NaHCO_{3(s)}$ (0.146 g, 1.74 mmol, 3.5 equiv) were added to neutralise the acetic acid produced. The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (3×30 mL). The organic phases were successively washed with $NaHCO_{3(aq)}$ (sat., 20 mL), H_2O (20 mL), and $NaCl_{(aq)}$ (sat., 20 mL), and dried over Na_2SO_4. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (50% EtOAc, 50% PE) to yield **35** (0.131 g, 0.43 mmol, 90%) as a colourless oil; R_f=0.20, 0.29 (*E*/*Z* isomers, 50% EtOAc, 50% PE); ν_{max}/cm^{-1} (thin film) 3214 (br, m), 3086 (br, m), 3005 (m), 2927 (s), 2855 (s), 1655 (w), 1580 (m), 1462 (m), 1426 (m), 1334 (br, w), 1191 (w), 1030 (w), 903 (w), 795 (w), 712 (m); *m/z* Probe APCI$^+$ (NH_3) 303.3 (MH^+, 30%), 285.3 ($[MH-H_2O]^+$, 100%); HRMS found MH^+=303.2444, $C_{19}H_{31}N_2O$ requires 303.2436. The subscripts *E* and *Z* differentiate between the *E* and *Z* isomers.[39] δ_H (200 MHz, $CDCl_3$) 1.20–1.70 (14H, m, H-3, H-4 and H-9 to H-13), 1.90–2.10 (4H, m, H-5, H-8), 2.20 (1H, apparent q, J=7.0 Hz, 2H ×0.5H-2_E), 2.40 (1H, apparent q, J=6.5 Hz, 2H ×0.5H-2_Z), 2.59 (2H, t, J=7.5 Hz, H-14), 5.23–5.45 (2H, m, H-6, H-7), 6.70 (0.5H, t, J=5.5 Hz, H-1_Z), 7.21 (1H, dd, J_1=5.0 Hz, J_2=7.5 Hz, Py H-5*) 7.40–7.55 (1.5H, m, 0.5H H-1_E, 1H Py H-4*), 8.35–8.50 (2H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 24.9, 25.7, 26.3, 26.8, 27.1, 29.0, 29.1, 29.2, 29.4, 29.6, 31.0, 32.9 (11CH_2), 123.4, (1C, Py C-5*), 129.3, 130.2 (2C, C-6, C-7), 136.2 (1C, Py C-4*), 138.1 (1C, Py C-3*), 146.7, 149.6 (2C, Py C-2*, C-6*), 151.5 (1C, C-1 *Z*-oxime), 152.3 (1C, C-1 *E*-oxime).

6.1.13. Preparation of 1-[*N*-*Z*-14-(pyridin-3-yl)-tetradec-6-enylideneamino]-Z-14-(pyridin-3-yl)-tetradec-5-ene *N*-oxide 36. To a solution of **35** (0.0552 g, 0.18 mmol) in MeOH (10 mL) at 0 °C was added of methyl orange (indicator, 2 mg) and conc. HCl (6 M) turning the indicator red (approx. pH 3). $NaBH_3CN$ (0.0473 g, 0.75 mmol, 4 equiv) in MeOH (3 mL) was added dropwise with concurrent addition of conc. HCl to keep the mixture at pH 3. The mixture was stirred for 2 h at 0 °C. The mixture was basified (dropwise, tested with pH paper) with $NaOH_{(aq)}$ (6 N), and worked up using solvents chilled to 0 °C. The mixture was diluted with $NaCl_{(aq)}$ (sat., 20 mL) and H_2O (20 mL) and extracted with DCM (3×30 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 30 mL) and dried over Na_2SO_4. Concentration in vacuo (without heating) gave a solution of hydroxylamine **25** in DCM (ca. 50 mL). To the hydroxylamine solution, was added Na_2SO_4 (0.512 g), and aldehyde **5** (0.0524 g, 0.18 mmol, 1 equiv) in DCM (5 mL) via cannula. The flask was stirred for 18 h at room temperature. The crude reaction mixture was filtered, the solvent removed in vacuo and was purified by flash chromatography (30% Et_3N, 50% EtOAc, 20% PE) to yield nitrone **36** (0.0829 g, 0.14 mmol, 79%) as a yellow oil; R_f=0.12 (30% Et_3N, 50% EtOAc, 20% PE); ν_{max}/cm^{-1} (thin film) 3292 (br, m), 3003 (m), 2927 (s), 2855 (s), 2361 (m), 2342 (w), 1670 (m), 1575 (m), 1478 (m), 1463 (m), 1422 (m), 1027 (w), 794 (w), 714 (m); *m/z* Probe APCI$^+$ (NH_3) 574.6 (MH^+, 100%); HRMS found MH^+=574.4730, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (200 MHz, $CDCl_3$) 1.35 (22H, br, s, H-8 to H-12, and H-3′, 4′, H-9′ to H-12′), 1.50-1.80 (6H, m, H-3, H-13, H-13′), 1.80–2.20 (10H, m, H-4, H-7, H-2′, H-5′, H-8′), 2.45 (2H, apparent q, J=7.5 Hz, H-2), 2.62 (4H, t, J=7.5 Hz, H-14, H-14′), 3.76 (2H, t, J=7.0 Hz, H-1′), 5.25–5.50 (4H, m, H-5, H-6, H-6′, H-7′), 6.70 (1H, t, J=6.0 Hz, H-1), 7.22 (2H, dd, J_1 7.5 Hz, J_2 5.0 Hz, Py H-5*), 7.51 (2H, d, J=8.0 Hz, Py H-4*), 8.40–8.50 (4H, m, Py H-2*, H-6*); δ_C (50.3 MHz, $CDCl_3$) 26.1, 26.5, 26.7, 27.4, 27.6, 27.8, 29.5, 29.7, 29.8, 30.1, 31.5 (18CH_2), 33.4 (4CH_2, C-13, C-14, C-13′, C-14′), 65.7 (1C, C-1′), 123.6 (2C, Py C-5*), 128.8, 129.7, 130.7, 131.4 (4C, C-5, C-6, C-6′, C-7′), 136.2 (2C, Py C-4*), 138.3 (2C, Py C-3*), 139.4 (1C, C-1), 147.6, 150.3 (4C, Py C-2*, C-6*).

6.1.14. Preparation of the C14′–C15′ isomer of pyrinodemin A 3. A solution of nitrone **36** (0.0682 g, 0.12 mmol) in benzene (80 mL) was heated at reflux for 24 h. The solvent was removed in vacuo, to afford the crude product which was purified by flash chromatography (100% EtOAc) to yield **3** (0.0598 g, 0.10 mmol, 87%) as a pale yellow oil; R_f=0.16 (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2928 (s), 2855 (s), 1575 (m), 1478 (m), 1465 (m), 1422 (m), 1339 (w), 1189 (w), 1026 (m), 794 (w), 714 (m); *m/z* Probe APCI$^+$ (NH_3) 574.4 (MH^+, 50%), 289.4 (67%), 286.4 (100%), 220.2 (67%); *m/z* Probe EIMS (+ve ion) 572 (3%), 555 (7%), 383 (14%), 365 (88%), 355 (15%), 327 (14%), 315 (9%), 299 (27%), 285 (82%), 270 (23%), 259 (27%), 244 (18%), 231 (30%), 220 (56%), 204 (6%), 190 (21%), 176 (34%), 162 (21%), 148 (19%), 134 (14%), 120 (28%), 106 (100%), 93 (84%); HRMS found 574.4729, $C_{38}H_{60}N_3O$ requires 574.4736; δ_H (500 MHz, $CDCl_3$) 1.22–1.38 (16H, m, H-9 to H-12, and H-9′ to H-12′), 1.41 (4H, m, H-17′, H-18′), 1.49 (2H, m, H-17, H-18), 1.51 (2H, m, H-13), 1.59 (2H, m, H-19′), 1.62 (2H, m, H-14), 1.68 (4H, m, H-8, H-8′),

1.72 (2H, m, H-17[a], H-18[a]), 1.73 (1H, m, H-19), 1.80 (1H, m, H-19[a]), 1.90–2.05 (4H, m, H-13′, H-16′), 2.53-2.61 (5H, m, H-7, H-7′, H-20′), 2.77–2.88 (2H, m, H-16, H-20′[a]), 3.40–3.50 (1H, m, H-20), 4.00–4.08 (1H, m, H-15), 5.30–5.38 (2H, m, H-14′, H-15′), 7.15–7.20 (2H, m, Py-*H*), 7.45–7.50 (2H, m, Py-*H*), 8.38–8.45 (4H, br, s, Py-*H*); δ_C (125.8 MHz, $CDCl_3$) 26.2 (1C, C-17), 26.4 (1C, C-18), 26.9 (2C, C-13, and C-17′ or C-18′), 27.1 (2C, C-13′, C-16′), 28.0 (1C, C-19′), 28.7 (1C, C-14), 29.0, 29.1, 29.2[†], 29.3, 29.5, 29.6[‡], (9C, C-9 to C-12 and C-9′ to C-12′ and C-18′ or C-17′), 31.0 (2C, C-8, C-8′), 32.9 (2C, C-7, C-7′), 34.5, (1C, C-19), 49.8 (1C, C-16), 57.4 (1C, C20′), 72.8 (1C, C-20), 77.5 (1C, C-15), 123.1 (2C, Py C-5[*]), 129.70, 129.72 (2CH, C-15′, C-16′), 135.6 (2C, Py C-4[*]), 137.8 (2C, Py C-3[*]), 147.1, 149.9 (4C, Py C-2[*], C-6[*]).

6.1.15. Preparation of 14-(pyridin-3-yl)-tetradecan-1-oxime 38. A solution of **35** (0.0492 g, 0.16 mmol) and catalyst (5% Pd on C, 5.9 mg) in MeOH (2 mL) was stirred under hydrogen (1 atm, balloon) for 5 h. Removal of solvent in vacuo afforded the crude which was purified by flash chromatography (60% EtOAc, 40% PE) to yield 14-(pyridin-3-yl)-tetradecan-1-oxime **38** (0.0465 g, 0.15 mmol, 94%) as a white waxy solid; R_f=0.23, 0.35 (*E*/*Z* isomers, 60% EtOAc, 40% PE); mp=81–85 °C; ν_{max}/cm^{-1} ($CHCl_3$) 3020 (br, w), 2929 (s), 2856 (s), 2361 (w), 2343 (w), 1578 (w), 1466 (w), 1425 (w), 1029 (w); *m*/*z* Probe APCI$^+$ (NH_3) 305.3 (MH^+, 44%), 287.3 ($[MH-H_2O]^+$, 100%); HRMS found MH^+=305.2607, $C_{19}H_{33}N_2O$ requires 305.2593; *m*/*z* Probe EIMS (+ve ion) 304.2 (5%), 287.2 (14%), 246.2 (62%), 232.2 (13%), 218.2 (16%), 204.1 (18%), 190.1 (14%), 176.1 (10%), 162.1 (13%), 148 (14%), 134.1 (8%), 120.1 (16%), 106.1 (100%), 93.0 (70%). The subscripts $_E$ and $_Z$ differentiate between the *E* and *Z* isomers.[39] δ_H (200 MHz, $CDCl_3$) 1.25 (18H, br, s, H-4 to H-12), 1.40–1.70 (4H, m, H-3, H-13), 2.11–2.27 (1H, m, 2H × 0.5H-2_E), 2.31–2.45 (1H, m, 2H ×0.5H-2_Z), 2.59 (2H, t, *J*=7.5 Hz, H-14), 6.67–6.76 (0.5H, m, H-1_Z), 7.16–7.29 (1H, m, Py H-5[*]) 7.39–7.55 (1.5H, m, 0.5H H-1_E, 1H Py H-4[*]), 8.38–8.51 (2H, m, Py H-2[*], H-6[*]); δ_C (50.3 MHz, $CDCl_3$) 25.0, 26.1, 26.7, 29.1, 29.3, 29.5 (11C, C-2 to C-12), 31.0, 33.0 (2C, C-13, C-14), 123.3, (1C, Py C-5[*]), 136.1 (1C, Py C-4[*]), 138.2 (1C, Py C-3[*]), 146.8, 149.6 (2C, Py C-2[*], C-6[*]), 151.8 (1C, C-1 *Z*-oxime), 152.5 (1C, C-1 *E*-oxime).

6.1.16. Preparation of 14-(pyridin-3-yl)-tetradecane-1-hydroxylamine 39. To a stirred solution of **38** (0.0453 g, 0.15 mmol) in MeOH (10 mL) at 0 °C was added of methyl orange (indicator, 2 mg) and conc. HCl (6 M) turning the indicator red (ca. pH 3). $NaBH_3CN$ (0.0354 g, 0.56 mmol, 4 equiv) in MeOH (1 mL) was added dropwise with concurrent addition of conc. HCl to keep the mixture at pH 3. The mixture was stirred for 3.5 h at room temperature. The mixture was basified (dropwise and tested with pH paper) with $NaOH_{(aq)}$ (6 N), diluted with $NaCl_{(aq)}$ (sat. 20 mL) and extracted with DCM (3×30 mL). The organic phases were washed with $NaCl_{(aq)}$ (sat., 20 mL) and dried over Na_2SO_4. Removal of solvent in vacuo to afford the crude product which was purified by flash chromatography (33.3% Et_3N, 33.3% EtOAc, 33.3% PE) to yield **39** (0.0341 g, 0.11 mmol, 74%) as a white waxy solid; R_f=0.13 (33.3% Et_3N, 33.3% EtOAc, 33.3% PE); mp=70–71 °C; *m*/*z* Probe CI$^+$ (NH_3) 307.2 (MH^+, 36%), 291.2 (100%, MH^+–H_2O); HRMS found MH^+=307.2754, $C_{19}H_{35}N_2O$ requires 307.2749; δ_H (200 MHz, $CDCl_3$) 1.24 (20H, br, s, H-3 to H-12), 1.43–1.70 (4H, m, H-2, H-13), 2.59 (2H, t, *J*=7.5 Hz, H-14), 2.93 (2H, t, *J*=7.0 Hz, H-1), 7.19 (1H, dd, J_1=5.0 Hz, J_2=7.5 Hz, Py H-5[*]) 7.42–7.52 (1H, m, Py H-4[*]), 8.40–8.45 (2H, m, Py H-2[*], H-6[*]); δ_C (50.3 MHz, $CDCl_3$) 27.0, 27.1, 29.1, 29.4, 29.6 (11C, C-2 to C-12), 31.1, 33.0 (2C, C-13, C-14), 54.0 (1C, C-1) 123.2, (1C, Py C-5[*]), 135.8 (1C, Py C-4[*]), 138.0 (1C, Py C-3[*]), 147.1, 149.9 (2C, Py C-2[*], C-6[*]).

6.1.17. Preparation of 1-[*N*-14-(pyridin-3-yl)-tetradecyl-ideneamino]-*Z*-14-(pyridin-3-yl)-tetradec-5-ene *N*-oxide 40. To a solution of **39** (0.0328 g, 0.11 mmol) in DCM (5 mL) was added Na_2SO_4 (1.16 g), and aldehyde **5** (0.0360 g, 0.13 mmol) in DCM (2 mL) via cannula. The reaction was stirred for 20 h at room temperature. The crude reaction mixture was filtered, the solvent removed in vacuo to afford the crude product which was purified by flash chromatography (40% Et_3N, 40% EtOAc, 20% PE) to yield nitrone **40** (0.0415 g, 0.072 mmol, 67%) as a pale yellow oil; R_f=0.28 (40% Et_3N, 40% EtOAc, 20% PE); ν_{max}/cm^{-1} ($CHCl_3$) 3306 (br, m), 2929 (s), 2856 (s), 1657 (m), 1578 (w), 1480 (w), 1464 (m), 1424 (m), 1028 (w), 713 (m); *m*/*z* Probe CI$^+$ (NH_3) 576.5 (MH^+, 100%), 367.2 (13%), 287.1 (5%); HRMS found MH^+=576.4897, $C_{38}H_{62}N_3O$ requires 576.4893; δ_H (200 MHz, $CDCl_3$) 1.10–1.40 (30H, m, H-8 to H-12 and H-3′ to H-12′), 1.40–1.70 (6H, m, H-3, H-13, H-13′), 1.80–2.12 (6H, m, H-4, H-7, H-2′), 2.48 (2H, apparent q, *J*=6.5 Hz, H-2), 2.58 (4H, t, *J*=7.5 Hz, H-14, H-14′), 3.71 (2H, t, *J*=7.0 Hz, H-1′), 5.22–5.46 (2H, m, H-5, H-6), 6.66 (1H, t, *J*=5.0 Hz, H-1), 7.18 (2H, dd, J_1=8.0 Hz, J_2=5.0 Hz, Py H-5[*]), 7.47 (2H, d, *J*=8.0 Hz, Py H-4[*]), 8.35–8.45 (4H, m, Py H-2[*], H-6[*]); δ_C (50.3 MHz, $CDCl_3$) 25.6, 26.3, 26.4, 27.0, 27.2, 27.4, 29.1, 29.4, 29.6, 31.1, 33.0, 34.4 (24CH_2), 65.4 (1C, C-1′), 123.2 (2C, Py C-5[*]), 128.4, 131.0 (2C, C-5, C-6), 135.8 (2C, Py C-4[*]), 138.0 (2C, Py C-3[*]), 139.1 (1C, C-1), 147.0, 149.8 (4C, Py C-2[*], C-6[*]).

6.1.18. Preparation of a saturated analogue of pyrinodemin A 37. A solution of nitrone **40** (0.0415 g, 0.072 mmol) in benzene (100 mL) was heated at reflux for 24 h. Removal of solvent in vacuo afforded the crude product which was purified by flash chromatography (100% EtOAc) to yield **37** (0.0304 g, 0.053 mmol, 73%) as a colourless oil; R_f=0.23 (100% EtOAc); ν_{max}/cm^{-1} (thin film) 2927 (s), 2854 (s), 1676 (w), 1575 (m), 1465 (m), 1422 (m), 1026 (m), 714 (s); *m*/*z* Probe APCI$^+$ (NH_3) 576.5 (MH^+, 100%), 291.4 (42%); EIMS (+ve ion) 575 (12%), 557 (10%), 483 (5%), 385 (24%), 367 (100%), 357 (24%), 329 (13%), 315 (16%), 301 (23%), 287 (80%), 274 (23%), 270 (20%), 246 (35%), 232 (13%), 231 (1%), 220 (59%), 218 (25%), 204 (12%), 190 (26%), 176 (30%), 162 (16%), 148 (18%), 134 (10%), 120 (21%), 106 (77%), 93 (73%); HRMS found 576.4897, $C_{38}H_{62}N_3O$ requires 576.4893; δ_H (400 MHz, $CDCl_3$) 1.18–1.84 (44H, m, H-8 to H-14, H-17, H-18, H-19, H-8′ to H-19′), 2.60–2.75 (1H, m, H-20′), 2.60 (4H, t, *J*=8.0 Hz, H-7, H-7′), 2.80–2.90 (2H, m, H-16, H-20′[a]), 3.42–3.51 (1H, m, H-20), 4.02–4.10 (1H, m, H-15),

[†] This data point can be resolved into two signals at 29.18 and 29.21 ppm.
[‡] This data point can be resolved into two signals at 29.58 and 29.63 ppm.

7.20 (2H, dd, $J_1=5.0$ Hz, $J_2=7.5$ Hz, Py H-5*), 7.48 (2H, d, $J=8.0$ Hz, Py H-4*), 8.40–8.48 (4H, m, Py H-2*, H-6*); δ_C (100.6 MHz, $CDCl_3$) 26.3, 26.5, 27.0, 27.4, 28.1, 28.8, 29.1[§], 29.3, 29.4, 29.5, 29.6[¶], 29.7, 31.1, 33.0 (CH_2), 49.9 (1C, C-16), 123.2 (2C, Py C-5*), 135.8 (2C, Py C-4*), 137.9 (2C, Py C-3*), 147.1, 149.9 (4C, Py C-2*, C-6*); C-15, C-20 and C-20′ were not observed.

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[§] This data point can be resolved into two signals at 29.09 and 29.13 ppm.
[¶] This data point can be resolved into two signals at 29.57 and 29.60 ppm.

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Total synthesis of two 12-nordrimanes and the pharmacological active sesquiterpene hydroquinone yahazunol

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Abstract—The synthesis of two 12-nordrimanes and yahazunol was achieved via 8-oxo-12-nordrimanic acid methyl ester. The cytotoxic activity of yahazunol and seven other sesquiterpene hydroquinones and sesquiterpene quinones has been determined.

1. Introduction

The both nordrimanes (+)-(8*S*)-12-nordrimane-8,11-diacetate ((+)-**4**) and (+)-11-hydroxy-12-nordrim-9-en-8-one ((+)-**6**) have been isolated from the marine sponge *Dysidea* sp.[1] (Fig. 1). Compound (+)-**4** exhibited a weak inhibition of the bioluminescence reaction of *Photobacterium leiognathi*, a symbiotic luminous bacterium of tropical fish.[1]

The sesquiterpene hydroquinone yahazunol (**11**),[2] zonarol (**12**), zonarone (**13**), isozonarol (**14**), isozonarone (**15**),[3] cyclozonarone (**16**),[4] zonaroic acid and chromazonarol have been obtained from the brown algae *Dictyopteris undulata* Okamura.[2] The compounds **12**–**16** and chromazonarol show feeding-deterrent activity against the young abalone *Heliotis discus* hannai.[4] The sesquiterpene hydroquinones and quinones **12**–**15**, chromazonarol, zonaroic acid and dictyochromenol possess toxicity against killifish.[5]

Recently, we published the total syntheses of **11**,[6] **12**–**16**,[6,7] spongiaquinone (**17**) and hyatellaquinone (**18**)[8] starting from (−)- and (+)-albicanal (Fig. 1).

In this paper, we describe the syntheses of the 12-nordrimanes (+)-**4**, (+)-**6** and yahazunol ((−)-**11**) starting from (±)-8-oxo-12-nordrimanic acid methyl ester ((±)-**1**). Our synthesis of the building block (±)-**1** was reported earlier.[6] The marine sesquiterpene hydroquinones and sesquiterpene quinones **11**–**18** were tested for their cytotoxic activity.

Keywords: Terpenes; Phenols; Quinones.
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2. Results and discussion

According to the procedure of Furuichi et al.[9] the racemate of (±)-8-oxo-12-nordrimanic acid methyl ester ((±)-**1**) was transformed with (2*S*,3*S*)-1,4-di-*O*-benzylthreitol to the diastereomeric mixture of dioxolanes. Hydrogenolytic splitting of the benzyl groups led to the diols, which could be separated by silica gel MPLC. Hydrolysis of the both dioxolanes with 2 N sulfuric acid in MeOH yielded (+)-**1** and (−)-**1**. The keto group in position 8 of (−)-**1** was selectively reduced with $NaBH_4/CeCl_3$ to the hydroxy function in (+)-**2** (Scheme 1). In the second step the methyl ester (+)-**2** was reduced with DIBAH to the diol (+)-**3**. The one pot reduction of (−)-**1** to (+)-**3** with $NaBH_4/CeCl_3$ and DIBAH showed a better yield. Acetylation of (+)-**3** with acetyl chloride/pyridine gave (+)-(8*S*)-12-nordrimane-8,11-diacetate ((+)-**4**).

(+)-11-Hydroxy-12-nordriman-8-one ((+)-**5**) was obtained as follows.[9] The racemate of (±)-**1** reacted with (2*R*,3*R*)-2,3-butanediol to the both diastereomers which were reduced with DIBAH to the diastereomeric alcohols. These could be separated by silica gel MPLC. Hydrolysis of both dioxolanes with Nafion NR 50 led to (+)-**5** and (−)-**5**. Pyridinium chlorochromate (PCC) oxidation of (+)-**5** gave in quantitative yield (+)-11-hydroxy-12-nordrim-9-en-8-one ((+)-**6**) (Scheme 2).

The comparison of the optical rotations of (+)-(8*S*)-12-nordrimane-8,11-diacetate ((+)-**4**) ($[\alpha]_D=+72$, MeOH) and (+)-11-hydroxy-12-nordrim-9-en-8-one ((+)-**6**) ($[\alpha]_D=+9.5$, MeOH) with natural (+)-**4**[1] ($[\alpha]_D=+36$, MeOH) and (+)-**6**[1] ($[\alpha]_D=+9.6$, MeOH) led to the absolute configurations of the both nordrimanes. We assume

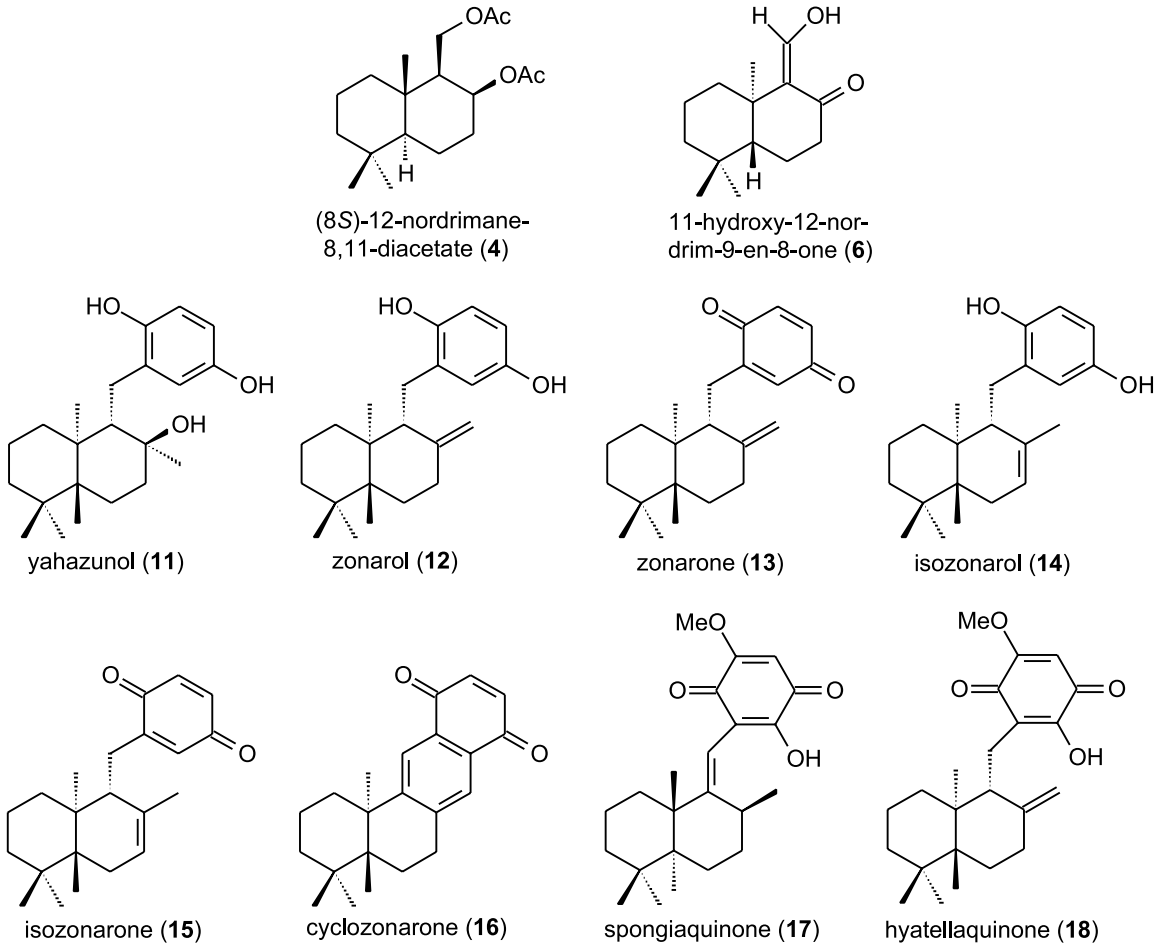
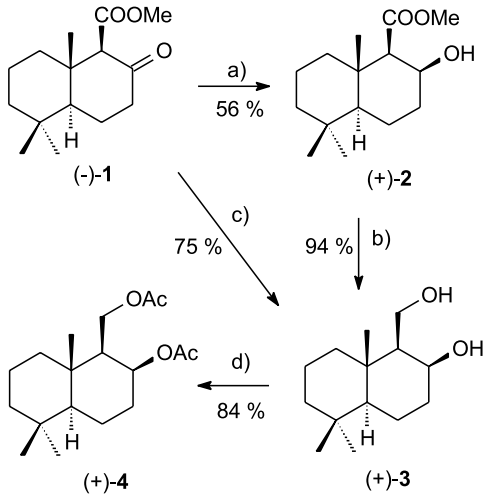


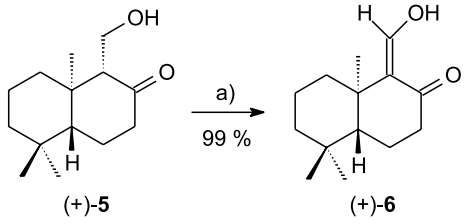
Figure 1. 12-Nordrimanes and pharmacologically tested sesquiterpene hydroquinones and sesquiterpene quinones.

that the determination of the optical rotation of natural **4** was not correct. It is interesting that the two 12-nordrimanes have been isolated from the same sponge *Dysidea* sp. but their absolute configurations are different: (+)-**4** (5*S*,10*S*), (+)-**6** (5*R*,10*R*).

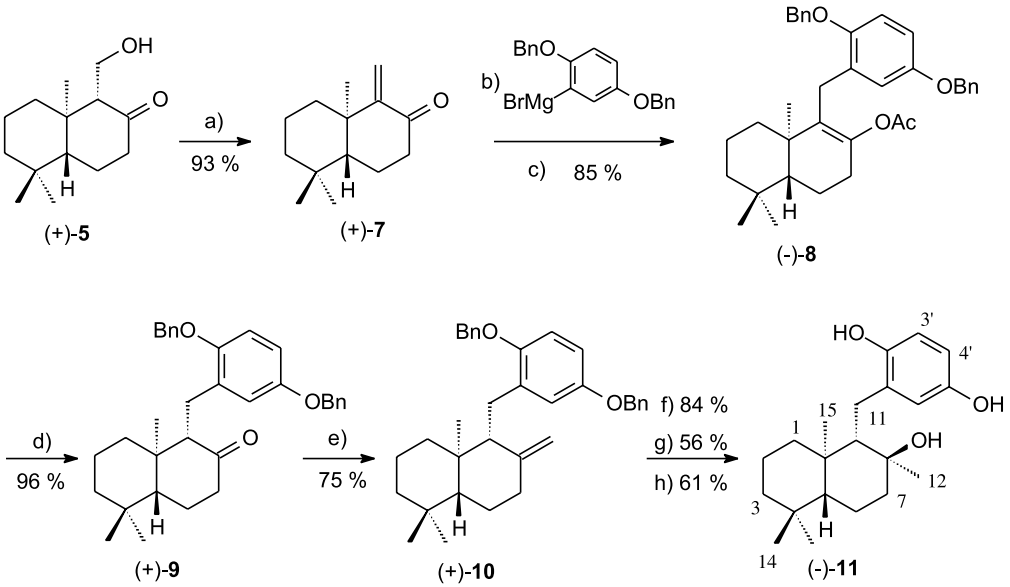


Scheme 1. Synthesis of (+)-(8*S*)-12-nordrimane-8,11-diacetat ((+)-**4**). (a) $NaBH_4$, $CeCl_3$, THF/MeOH (2:1), room temperature, 30 min; (b) DIBAH, CH_2Cl_2, room temperature, 30 min; (c) $NaBH_4$, $CeCl_3$, THF, 30 min; DIBAH, room temperature, 30 min; (d) AcCl, DMAP, Pyridin, CH_2Cl_2, room temperature, 16 h.

Our first seven step synthesis of yahazunol ((−)-**11**) started from (+)-albicanal. The change of the protecting group tetrahydopyranyl (THP) to benzyl (Bn) in (+)-**10** (Scheme 3) was a disadvantage of this route.[6] For that reason we used (+)-11-hydroxy-12-nordriman-8-one ((+)-**5**) which was transformed with *p*-toluene sulfonic acid by elimination of water to the enone (+)-**7** (Scheme 3) synthesized before starting from 12-nordrimane-8,11-diol[10,11] and (−)-**7** from 11-hydroxy-12-nordriman-8-one.[12] The cuprate catalyzed conjugated 1,4-addition[10] of 2,4-dibenzyloxyphenylmagnesium bromide to (+)-12-nordrim-9-en-8-one ((+)-**7**) yielded the enolate anion trapping with acetic anhydride. Treatment of the resulting enolacetate (−)-**8** with potassium hydroxide in methanol afforded the ketone (+)-**9**. Wittig reaction of (+)-**9** with Ph_3PCH_2 gave (+)-zonarol dibenzyl ether (+)-**10**.



Scheme 2. Synthesis of (+)-11-hydroxy-12-nordrim-9-en-8-one ((+)-**6**). (a) PCC, $CaCO_3$, CH_2Cl_2, room temperature, 20 min.



Scheme 3. Synthesis of yahazunol ((−)-**11**). (a) PTS, benzene, 50 °C, 30 min; (b) CuI, 0 °C, 10 min, room temperature, 1 h; (c) Ac_2O, 0 °C, room temperature, 20 min; (d) KOH, MeOH, room temperature, 6 h; (e) Ph_3PCH_2, THF, 80 °C, 48 h; (f) MCPBA, CH_2Cl_2, room temperature, 50 min; (g) $LiAlH_4$, Et_2O, reflux; 2 h; (h) H_2, Pd/C, EtOH, 40 °C, 30 min.

Table 1. Cytoxic activity against the tumour cell lines L-929 (murine fibroblasts), K-562 (human leukaemia) and HeLa (human cervix carcinoma) of (+)-zonarol ((+)-**12**), (+)-zonarone ((+)-**13**), (+)-isozonarol ((+)-**14**) and (+)-isozonarone ((+)-**15**)

Compound	L-929	K-562	HeLa
Zonarol ((+)-**12**)	2	2	2
Zonarone ((+)-**13**)	2	2	1
Isozonarol ((+)-**14**)	2	2	2
Isozonarone ((+)-**15**)	1	2	1

3, high activity; 2, middle activity; 1, low activity

The overall yield leading to (+)-**10** starting from (±)-8-oxo-12-nordrimanic acid methyl ester ((±)-**1**) is 24% over seven steps according to Scheme 3. The overall yield starting from (±)-**1** to (+)-**10** of our first yahazunol synthesis is 18% over 11 steps.[6] The yields of the racemate separations of (±)-**1** and (±)-albicanic acid were considered as 50%. (+)-Zonarol dibenzyl ether ((+)-**10**) was epoxidized in position 8, 12 with MCPBA. The oxirane ring was opened with $LiAlH_4$ to (+)-yahazunol dibenzyl ether as described before.[6] The yield of debenzylation of (+)-yahazunol dibenzyl ether with H_2 and Pd/C in EtOH to yahazunol ((−)-**11**) could be improved from 54 to 61% by heating the reaction mixture at 40 °C for 30 min.

The sesquiterpene hydroquinones and sesquiterpene quinones **11**–**18** (Fig. 1) were tested for their cytotoxic/cytostatic activity.

Zonarol ((+)-**12**), zonarone ((+)-**13**) and isozonarol ((+)-**14**) show a good cytotoxic activity against tumour cell lines L-929 (murine fibroblasts) and K-562 (human leukemia) and (+)-**12**, (+)-**14** a good activity against the HeLa cell line (human cervix carcinoma) (Table 1). The cytotoxic activity was determined at the Hans-Knöll-Institute in Jena according to Ref. 13.

(±)-Yahazunol ((±)-**11**), (±)-cyclozonarone ((±)-**16**), (±)-spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**) were investigated for their cytostatic/cytotoxic activity against the human tumour cell lines HM02 (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma) and MCF 7 (breast carcinoma). (±)-Spongiaquinone ((±)-**17**) possesses the highest cytostatic/cytotoxic activity (the lowest GI50-value) against the cell lines HMO2 and

Table 2. Cytostatic/cytotoxic activity of (±)-yahazunol ((±)-**11**), (±)-cyclozonarone ((±)-**16**), (±)-spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**) against the tumour cell lines HM02 (gastric adenocarcinoma), HepG2 (hepatocellular carcinoma) and MCF 7 (breast carcinoma)

Compound	GI_{50}[a] (μg/ml)			TGI[b] (μg/ml)		
	HM02	HepG2	MCF 7	HM02	HepG2	MCF 7
(±)-Yahazunol (±)-**11**	4.2	7.1	6.0	10.0	>10[c]	95
(±)-Cyclozonarone (±)-**16**	5.7	9.6	>10	7.8	>10	>10
(±)-Spongiaquinone (±)-**17**	3.1	3.6	2.6	>10[d]	>10[e]	7.1
(±)-Hyatellaquinone (±)-**18**	5.3	6.0	2.4	>10[f]	>10[g]	6.9

[a] Drug concentration causing 50% growth inhibition.
[b] Drug concentration causing 100% growth inhibition.
[c] 70% inhibition at 10 μg/ml.
[d] 66% inhibition at 10 μg/ml.
[e] 52% inhibition at 10 μg/ml.
[f] 77% inhibition at 10 μg/ml.
[g] 64% inhibition at 10 μg/ml.

Table 3. Cell cycle analysis of MCF 7 cells exposed to (±)-yahazunol ((±)-**11**), (±)-spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**)

Compound	SubG1-phase	G1-phase	S-phase	G2/M-phase
(±)-Yahazunol ((±)-**11**) (20 μg/ml)	16.8±2.7*	44.0±3.9*	13.4±3.6	29.0±3.0*
(±)-Spongiaquinone ((±)-**17**) (40 μg/ml)	17.3±4.9*	44.0±2.4*	21.7±1.0*	16.3±1.5
(±)-Hyatellaquinone ((±)-**18**) (40 μg/ml)	23.5±3.6*	43.7±0.6*	22.2±0.4*	6.8±1.3*
Control	6.8±0.28	61.0±0.8	16.0±1.6	15.6±0.7

Data represent percentage of cells in each stage of the cell cycle. Values are mean±SE of four experiments. *$p<0.05$ versus control (*t* test).

HepG2 and hyatellaquinone ((±)-**18**) against the cell line MCF 7 (Table 2).

The cell cycle analysis of MCF 7 cells exposed to (±)-yahazunol ((±)-**11**), (±)-cyclozonarone ((±)-**16**), (±)-spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**) led to the following results (Table 3): (±)-yahazunol ((±)-**11**) locks the cells initially (as vincristine) in the mitose phase (G2/M-phase) and induces apoptose. (±)-Spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**) lock the cells initially (as 5-fluorouracil) in the synthesis phase with replication of the DNA (S-phase). This is connected with a decrease in the cell number in the G1-phase. The apoptose of the cells is based on the blockade of the DNA replication (increase in the cell number of the SubG1-phase). (±)-Cyclozonarone ((±)-**16**) was investigated in a broad concentration range. In each case, an increase in apoptotic/necrotic cells was found. A lock of the cell cycle in a specific cell phase could not be observed (data are not given). In this way (±)-yahazunol ((±)-**11**), (±)-spongiaquinone ((±)-**17**) and (±)-hyatellaquinone ((±)-**18**) block the growth of tumour cells phase specific in the G2/M- and S-phase.

3. Experimental

3.1. General

All solvents were dried and purified prior to use. THF and diethyl ether were dried by distillation from Na/K under Ar. Flash chromatography: Merck silica gel 60, 0.040–0.063 mm (230–400 mesh). MPLC: Büchi B688 pump and Büchi B687 gradient former. IR: Perkin-Elmer 1420 Ratio Recording Spectrometer; solvent $CHCl_3$. Optical rotation values: JASCO Polarimeter P-1020 (589 nm). MS: Finnigan MAT 8500 and Finnigan MAT SS 300; 70 eV.

NMR: Bruker Avance 300 and Bruker DRX 500, $CDCl_3$/$CHCl_3$, acetone-D_6/acetone and DMSO-D_6/DMSO as internal standards.

For TLC runs, precoated silica-gel foils 60 F_{254} (5×10 cm^2) from Merck were used. Spots were visualised by irradiation under UV lamp or by treatment with phosphomolybdic acid test spray.

3.2. Preparation, physical and spectroscopic data of the compounds

3.2.1. (+)-(8*S*)-8-Hydroxy-12-nordrimanic acid methyl ester ((+)-2). To a solution of $CeCl_3$ (0.4 M, 40 mmol) in THF/MeOH (100 ml, 2:1) (−)-**1** (1.00 g, 3.96 mmol) was added and stirred for 15 min. $NaBH_4$ (650 mg, 17.2 mmol) was added and stirring continued for 30 min. HCl (60 ml, 10%) and saturated NaCl-solution (20 ml) were added and the mixture was extracted three times with ethyl acetate. The combined organic layers were washed with saturated $KHCO_3$-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 7:1, 20 bar, 30 ml/min) to obtain (+)-**2** (564 mg, 2.22 mmol, 56%) as colourless crystals. Mp 164–165 °C (hexane/ethyl acetate). $[\alpha]_D^{25}=+54$ (*c* 1.00, $CHCl_3$). Ref. 10: $[\alpha]_D^{24}=+53.8$ (*c* 1.13, $CHCl_3$). IR (cm^{-1}): 3522 (w), 3010 (m), 2954 (s), 2927 (s), 2871 (m), 2850 (m), 1743 (s), 1706 (s), 1459 (m), 1438 (m), 1348 (m), 1272 (w), 1258 (w), 1232 (w), 1196 (s). MS *m*/*z* (%): 254 (17, $M^{+\cdot}$), 236 (39), 221 (94), 205 (13), 189 (10), 177 (19), 161 (61), 137 (100), 123 (95), 109 (80), 95 (85), 81 (89), 69 (87), 55 (73), 41 (89). HRMS: Calcd for $C_{15}H_{26}O_3$ 254.1882. Found 254.1882. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.2. (+)-(8*S*)-12-Nordrimane-8,11-diol ((+)-3). To a solution of (+)-**2** (470 mg, 1.85 mmol) in 10 ml of abs. CH_2Cl_2 DIBAH (Aldrich, 1.0 M in abs. CH_2Cl_2, 7.4 ml, 7.4 mmol) was added dropwise. After 30 min the solution was slowly poured into a mixture of 10 ml of concd HCl and 25 g of ice. The organic layer was separated and the aqueous layer extracted two times with ethyl acetate. The combined organic layers were washed with saturated $KHCO_3$-solution, saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 2:1, 20 bar, 30 ml/min) to yield (+)-**3** (394 mg, 1.74 mmol, 94%) as colourless crystals. Mp 146–147 °C (hexane/ethyl acetate). $[\alpha]_D^{25}=+26$ (*c* 1.00, $CHCl_3$). Ref. 14: $[\alpha]_D^{23}=+26.1$ (*c* 0.93, $CHCl_3$). IR (cm^{-1}): 3500 (b), 2957 (s), 2925 (s), 2875 (m), 2847 (m), 2363 (w), 2330 (w), 1729 (m), 1457 (w), 1416 (m), 1389 (w), 1368 (w), 1334 (m), 1286 (w), 1160 (w). MS *m*/*z* (%): 226 (2, $M^{+\cdot}$), 208 (100), 193 (74), 175 (28), 165 (7), 152 (8), 149 (15), 137 (63), 123 (81), 109 (74), 95 (61), 81 (63), 69 (46), 55 (20), 41 (16). HRMS: Calcd for $C_{14}H_{26}O_2$ 226.1933. Found 226.1933. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.3. (+)-(8*S*)-12-Nordrimane-8,11-diol ((+)-3) directly from (−)-1. To a solution of $CeCl_3$ (0.4 M, 40 mmol) in THF (100 ml) (−)-**1** (1.00 g, 3.96 mmol) was added and stirred for 15 min. $NaBH_4$ (650 mg, 17.2 mmol) was added and stirring continued for 30 min. DIBAH (Aldrich, 1.0 M in abs. CH_2Cl_2, 16 ml, 16 mmol) was added dropwise. After 30 min the solution was slowly poured into a mixture of 30 ml of concd HCl and 75 g of ice. Further procedure is the same as described under Section 3.2.2 and yielded (+)-**3** (672 mg, 2.97 mmol, 75%).

Table 4. ^{1}H NMR data of compounds (+)-**2**, (+)-**3**, (+)-**4**, (+)-**6**, (+)-**7**, (−)-**8**, (+)-**9**, (+)-**10** and (−)-**11**

Position	(+)-**2**[a] ($CDCl_3$)	(+)-**3**[a] (D.-D_6)	(+)-**4**[a] ($CDCl_3$)	(+)-**6**[a] ($CDCl_3$)	(+)-**7**[a] ($CDCl_3$)	(−)-**8**[b] ($CDCl_3$)	(+)-**9**[b] ($CDCl_3$)	(+)-**10**[a] ($CDCl_3$)	(−)-**11**[a] (A.-D_6)
1	1.06	0.93	1.01 dd (13.1/3.5)	1.27	1.42	0.90	1.01	1.01	0.72 dd (17.9/4.4)
	1.31	1.67	1.69	2.01	1.75	1.61	1.61	1.73	1.84
2	1.27	1.36	1.37	1.53	1.52	1.28	1.21	1.41	1.34
	1.47	1.48	1.56	1.58	1.57	1.61	1.42	1.55	1.62
3	1.05	1.12	1.13	1.17	1.19	1.07 dd (13.2/4.4)	1.01	1.10	1.11
	1.28	1.35	1.37	1.41	1.46	1.28	1.35	1.32	1.33
5	0.82 dd (12.3/2.0)	0.82	0.88	1.14	1.38	1.19	1.34	1.10	0.94
6	1.36	1.37	1.39	1.55	1.60	1.68	1.61	1.30	1.34
	1.56	1.56	1.47	1.77	1.74	1.79	1.98	1.73	1.66
7	1.30	1.38	1.45	2.41	2.23	2.17 dd (17.0/6.2)	2.15	1.95	1.57
	1.88	1.79	1.95	2.45	2.65	2.45	2.31	2.32	1.92 dd (16.9/4.0)
8	3.99	3.53	5.10 ddd (3.4)	—	—	—	—	—	—
9	2.07 d (2.2)	0.98	1.51	—	—	—	2.49 d (9.4)	2.23	1.57
11	—	4.04	3.99 d (10.7)	8.59 d (4.4)	4.97 d (1.2)	3.31	2.69 dd (13.1/1.7)	2.73	2.40 dd (20.7/8.5)
			4.11 dd (10.7/3.8)		5.50 d (1.2)	3.33	2.85 dd (13.1/9.4)	2.81	2.85 dd (20.7/2.7)
12	—	—	—	—	—	—	—	4.63	1.30 s
								4.72	
13	0.77 s	0.83 s	0.83 s	0.89 s	0.93 s	0.91 s	0.91 s	0.86 s	0.86 s
14	0.74 s	0.79 s	0.81 s	0.83 s	0.98 s	0.82 s	0.81 s	0.80 s	0.83 s
15	1.08 s	0.91 s	0.97	1.13 s	0.89 s	1.00 s	0.73 s	0.76 s	0.97 s
1′	—	—	—	—	—	—	—	—	—
2′	—	—	—	—	—	—	—	—	—
3′	—	—	—	—	—	6.79 d (8.8)	6.78 d (8.8)	6.78 d (8.7)	6.53 d (8.5)
4′	—	—	—	—	—	6.71 dd (8.8/3.0)	6.71 dd (8.8/3.0)	6.68 dd (8.7/2.8)	6.49 dd (8.5/2.7)
5′	—	—	—	—	—	—	—	—	—
6′	—	—	—	—	—	6.81 d (3.0)	7.04 d (3.0)	6.81 d (2.8)	6.64 d (2.7)
C2′OCH_2	—	—	—	—	—	5.04	4.96	4.97	—
C5′OCH_2	—	—	—	—	—	5.02	4.99	5.01	—
Ac (8)	—	—	1.98 s	—	—	1.91 s	—		—
Ac (11)	—	—	2.00 s	—	—	—	—		—
OH	3.80 br s	3.50	—	15.37 d (4.4)	—	—	—		—
OH	—	3.97	—	—	—	—	—		—
Me	3.57 s	—	—	—	—	—	—		—
Benzyl	—	—	—	—	—	7.43—7.24	7.46—7.25	7.44—7.30	—

Coupling constants J in Hz. A.-D_6, acetone-D_6; D.-D_6, DMSO-D_6.
[a] Bruker DRX 500 spectrometer.
[b] Bruker AC 300 spectrometer.

Table 5. ^{13}C NMR data of compounds (+)-**2**, (+)-**3**, (+)-**4**, (+)-**6**, (+)-**7**, (−)-**8**, (+)-**9**, (+)-**10** and (−)-**11**

Position	(+)-**2**[a] ($CDCl_3$)	(+)-**3**[a] (D.-D_6)	(+)-**4**[a] ($CDCl_3$)	(+)-**6**[a] ($CDCl_3$)	(+)-**7**[a] ($CDCl_3$)	(−)-**8**[b] ($CDCl_3$)	(+)-**9**[b] ($CDCl_3$)	(+)-**10**[a] ($CDCl_3$)	(−)-**11**[a] (A.-D_6)
1	40.1	39.3	39.3	38.0	37.7	35.8	38.6	38.9	41.4
2	17.9	18.0	18.2	18.7	18.7	18.7	18.9	19.4	19.1
3	41.7	41.7	41.7	41.2	41.8	41.4	41.8	42.1	42.6
4	33.1	32.9	33.1	32.8	33.7	33.2	33.6	33.6	33.8
5	55.1	55.4	55.1	50.0	50.5	51.1	54.1	55.6	57.0
6	16.6	16.9	17.2	17.5	20.6	18.7	24.1	24.4	21.2
7	33.0	35.2	31.4	32.6	40.8	28.0	42.6	38.3	44.6
8	67.4	64.5	69.1	188.6	204.2	144.9	211.6	148.4	75.1
9	58.6	56.2	51.4	122.5	159.0	132.1	63.9	55.7	62.4
10	37.7	36.7	36.9	35.0	40.5	38.6	43.1	39.9	40.6
11	175.7	57.4	60.9	183.0	113.5	24.3	23.2	24.0	28.0
12	—	—	—	—	—	—	—	107.6	24.6
13	33.3	33.6	33.6	33.0	33.5	33.2	33.5	33.7	33.9
14	21.3	21.7	21.6	21.1	21.5	21.7	21.6	21.7	21.9
15	16.5	16.5	15.9	24.8	21.0	20.4	14.5	14.5	15.9
1′	—	—	—	—	—	130.7	131.8	132.5	131.2
2′	—	—	—	—	—	150.1	151.0	152.7	149.7
3′	—	—	—	—	—	112.5	112.5	112.5	117.4
4′	—	—	—	—	—	112.9	112.0	111.2	114.3
5′	—	—	—	—	—	152.8	152.5	151.1	150.4
6′	—	—	—	—	—	115.9	118.9	117.6	118.9
C2′OCH_2	—	—	—	—	—	70.8	70.9	70.9	—
C5′OCH_2	—	—	—	—	—	70.2	70.4	70.5	—
C2′Bn 1	—	—	—	—	—	137.6[c]	137.2	137.5	—
C5′Bn 1	—	—	—	—	—	137.7[c]	137.5	137.4	—
Ac (8)	—	—	21.3	—	—	20.9	—	—	—
Ac (11)	—	—	21.0	—	—	—	—	—	—
CO (8)	—	—	170.5	—	—	169.2	—	—	—
CO (11)	—	—	171.3	—	—	—	—	—	—
Me	51.0	—	—	—	—	—	—	—	—
Benzyl	—	—	—	—	—		128.4	128.5	
						127.7	128.3	128.4	
						127.6	128.2	127.8	
						127.3	128.0	127.7	
						127.2	127.7	127.6	
							127.5	127.5	—

A.-D_6, acetone-D_6; D.-D_6, DMSO-D_6.
[a] Bruker DRX 500 spectrometer.
[b] Bruker AC 300 spectrometer.
[c] Signals are exchangeable.

3.2.4. (+)-(8*S*)-12-Nordrimane-8,11-diacetate ((+)-4). To a solution of (+)-**3** (149 mg, 0.66 mmol) in abs. CH_2Cl_2 (10 ml) DMAP (20 mg), abs. pyridine (1 ml, 12 mmol) and AcCl (0.85 ml, 10 mmol) were added. After 16 h MeOH (1 ml) was added and stirring continued for 30 min. The solution was filtered through silica gel and purified using MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 6:1, 20 bar, 30 ml/min) to get (+)-**4** (172 mg, 0.55 mmol, 84%) as colourless crystals. Mp 84–85 °C (hexane/ethyl acetate). $[\alpha]_D^{24}=+72$ (*c* 1.00, MeOH). Ref. 1: $[\alpha]_D^{25}=+36.0$ (*c* 0.20, MeOH). IR (cm^{-1}): 2954 (s), 2934 (s), 2871 (m), 2850 (m), 1729 (s), 1459 (m), 1438 (w), 1390 (m), 1369 (m), 1265 (s), 1155 (w), 1125 (w), 1025 (m). MS *m*/*z* (%): 310 (2, $M^{+\cdot}$), 267 (15), 250 (8), 235 (6), 207 (61), 190 (100), 175 (76), 147 (38), 137 (49), 136 (71), 109 (54), 95 (48), 69 (36), 55 (14), 43 (56). HRMS: Calcd for $C_{18}H_{30}O_4$ 310.2144. Found 310.2144. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.5. (+)-11-Hydroxy-12-nordrim-9-en-8-one ((+)-6). Pyridinium chlorochromate (1.44 g, 6.7 mmol) and $CaCO_3$ (0.65 g, 6 mmol) were stirred for 15 min in 30 ml of abs. CH_2Cl_2. A solution of (+)-**5** (100 mg, 0.45 mmol) was added. The reaction was monitored until the educt has completely disappeared (20 min). The mixture was filtered through a short silica gel column (10 cm) to separate the chromium salts. Removing the solvent in vacuo at room temperature gave (+)-**6** (99 mg, 0.45 mmol, 99%) as colourless crystals. Mp 79–80 °C (CH_2Cl_2), $[\alpha]_D^{23}=+9.5$ (*c* 0.95, MeOH). Ref. 1: $[\alpha]_D^{25}=+9.6$ (*c* 0.10, MeOH). IR (cm^{-1}): 3500 (s), 2930 (s), 2870 (m), 1620 (s), 1590 (s), 1460 (m), 1380 (m), 1290 (w), 1200 (m), 940 (w). MS *m*/*z* (%): 222 (13, $M^{+\cdot}$), 207 (100), 189 (18), 179 (60), 137 (11), 69 (17), 41 (19). HRMS: Calcd for $C_{14}H_{22}O_2$ 222.1619. Found 222.1621. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.6. (+)-12-Nordrim-9-en-8-one ((+)-7). To a solution of (+)-**5** (400 mg, 1.78 mmol) in benzene (50 ml) *p*-toluene sulfonic acid (50 mg, 0.26 mmol) was added and the mixture was stirred for 30 min at 50 °C. Saturated Na_2CO_3-solution was added, the organic layer was separated and the aqueous layer extracted two times with ethyl acetate. The combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 20:1, 20 bar, 30 ml/min) to obtain (+)-**7** (341 mg, 1.65 mmol, 93%) as a colourless oil. $[\alpha]_D^{24}=+70$ (*c* 1.00, $CHCl_3$). Ref. 10: $[\alpha]_D^{23}=+71.9$ (*c* 0.69, $CHCl_3$). IR (cm^{-1}): 3095 (s), 2950 (m), 2930 (m), 2870 (m), 2845 (s), 1700 (s), 1610 (m), 1460 (m), 1415 (m), 1380 (w), 1300 (w), 1280 (m), 1240 (w), 1200 (m), 1175 (m), 1100 (w), 1060 (w), 1040 (w). MS *m*/*z* (%): 206 (100, $M^{+\cdot}$), 191 (72), 69 (9), 55 (10). HRMS: Calcd for $C_{14}H_{22}O$ 206.1670. Found 206.1678. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.7. (−)-11-(2′,5′-Dibenzyloxyphenyl)-12-nordrim-8,9-en-8-yl acetate ((−)-8). A mixture of Mg (320 mg, 13 mmol) and 2-bromo-1,4-hydroquinone dibenzyl ether (4.42 g, 12 mmol) in THF (75 ml) was refluxed for 2.5 h under argon. The generated Grignard reagent was added dropwise to CuI (30 mg, 3.83 mmol) at 0 °C under argon and the whole mixture was stirred at 0 °C for 10 min. A solution of (+)-**7** (620 mg, 3.0 mmol) in THF (10 ml) was added to the above cuprate reagent, stirred for 15 min at 0 °C and then 1 h at room temperature. After cooling to 0 °C Ac_2O (2 ml, 21.8 mmol) was added to the mixture and stirring was continued for 20 min at room temperature. The reaction mixture was diluted with saturated NH_4Cl-solution and saturated $NaHCO_3$-solution, extracted with *t*-butyl methyl ether and the organic layer was separated. The aqueous layer was extracted two times with ethyl acetate, the combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 12:1, 20 bar, 30 ml/min) to get (−)-**8** (1374 mg, 2.55 mmol, 85%) as a colourless oil. $[\alpha]_D^{23}=-4$ (*c* 0.80, $CHCl_3$). IR (cm^{-1}): 3030 (s), 2915 (m), 1747 (s), 1505 (m), 1235 (w), 1200 (m), 1020 (w). MS *m*/*z* (%): 538 (2, $M^{+\cdot}$), 495 (14), 91 (100), 43 (36). HRMS: Calcd for $C_{36}H_{42}O_4$ 538.3083. Found 538.3087. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.8. (+)-11-(2′,5′-Dibenzyloxyphenyl)-8-oxo-12-nordrimane ((+)-9). A mixture of (−)-**8** (1.8 g, 3.34 mmol) and KOH (4.0 g) in MeOH (40 ml) was stirred at room temperature for 6 h. The reaction mixture was diluted with saturated NaCl-solution, extracted with *t*-butyl methyl ether and the organic layer was separated. The aqueous layer was extracted two times with ethyl acetate, the combined organic layers were washed with saturated NaCl-solution and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); hexane/ethyl acetate 12:1, 20 bar, 30 ml/min) to yield (+)-**9** (1593 mg, 3.21 mmol, 96%) as a colourless oil. $[\alpha]_D^{24}=+7$ (*c* 0.90, $CHCl_3$). IR (cm^{-1}): 3035 (s), 2925 (m), 1709 (s), 1485 (m), 1255 (w), 1190 (m), 1020 (w). MS *m*/*z* (%): 496 (1, $M^{+\cdot}$), 332 (10), 91 (100), 65 (13). HRMS: Calcd for $C_{34}H_{40}O_3$ 496.2977. Found 496.2979. ^1H and ^{13}C NMR: Tables 4 and 5.

3.2.9. (+)-Zonarol dibenzyl ether ((+)-10). *n*-BuLi (1.8 ml, 2.88 mmol) was added to a suspension of $Ph_3P^+MeBr^-$ (1.37 g; 5.76 mmol) in THF (40 ml) at −78 °C under argon and the mixture was stirred for 30 min. A solution of (+)-**9** (790 mg; 2.28 mmol) in THF (5 ml) was added. After stirring at 80 °C for 48 h the reaction mixture was diluted with saturated NaCl-solution (20 ml) and extracted with *t*-butyl methyl ether. The organic layer was washed with H_2O and dried with Na_2SO_4. After filtration through silica gel and removing the solvent further purification was carried out by MPLC (LiChrospher® Si-60 (15 μm); pentane/Et_2O 25:1, 20 bar, 30 ml/min) to get (+)-**10** (846 mg, 1.71 mmol, 75%) as colourless crystals. Mp 110–111 °C (pentane/Et_2O). $[\alpha]_D^{23}=+18$ (*c* 1.00, $CHCl_3$). IR (cm^{-1}): 3020 (s), 2930 (m), 1495 (m), 1227 (m), 1205 (w), 1024 (w). MS *m*/*z* (%): 494 (72, $M^{+\cdot}$), 403 (6), 213 (8), 137 (7), 123 (8), 91 (100). HRMS: Calcd for $C_{35}H_{42}O_2$ 494.3185. Found 494.3184. ^1H and ^{13}C NMR: Tables 4 and 5.

The synthesis of 8,12-epoxyzonarol dibenzyl ether, (+)-yahazunol dibenzyl ether and yahazunol ((−)-**11**) was

described before.[6] The ^{1}H and ^{13}C NMR data of (−)-**11** were given in Tables 4 and 5.

3.3. Determination of the pharmacological activity

3.3.1. Test for cytostatic/cytotoxic activity. The investigations were carried out according to the NCI guidelines with the tumour cell lines HMO2, HepG2 and MCF 7. The cells were cultivated in RPMI 1640 medium with 10% fetal bovine serum on 96-well microtiter plates. After sowing the test samples (24 h) (concentrations: 0.1, 0.5, 1.0, 5.0, 10.0 μg/ml) were added and the cells were cultivated for further 48 h. The cell number was obtained by protein determination with sulforhodanine. The test samples were dissolved in MeOH. The MeOH concentration in the test was 0.1%. The concentration activity curves led to the following values: GI50=concentration which produces a half maximum inhibition of the cell growth; TGI= concentration which produces a complete inhibition of the cell growth.

3.3.2. Cell cycle analysis. Cell cycle distribution was determined by staining DNA with propidium iodide. Cells were treated for 24 h with indicated concentrations of each drug, harvested by trypsination, washed with RPMI 1640 containing 1% fetal bovine serum and resuspended in 125 μl of a solution containing 150 μg/ml propidium iodide, 1% Triton X-100, 1% bovine serum albumin and 4 mM sodium citrate buffer, pH 7.4. After 15 min incubation at room temperature under light exclusion, the same volume of RNase A (10 μg/ml in 10 mM Tris and 15 mM NaCl, pH 7.4) was added and cells were incubated for additional 30 min at room temperature. At the end of incubation period cells were analyzed using a Becton Dickinson FACSscan and Lysis II software.

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Synthesis of upper rim calix[4]arene divalent glycoclusters via amide bond conjugation

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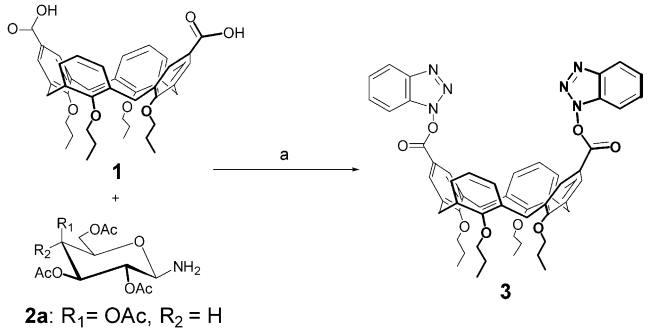
Abstract—Synthetic routes for linking two sugar units at the upper rim of cone calix[4]arenes, through the formation of amide bonds, have been explored. Steric effects prevent the coupling of calix[4]arene dicarboxylic acid with simple aminoglycosides, whereas the corresponding reaction with carbohydrates bearing a two or three carbon atoms spacer, terminating with a primary amino group, allows the synthesis of several difunctionalized calix[4]arene neoglycoconjugates, attractive in chemical glycobiology and supramolecular chemistry.

1. Introduction

Carbohydrate clusters are becoming interesting targets as model systems for studying protein–sugar[1] and sugar–sugar[2] interactions, which play a central role in glycobiology.[3] Neoglycoconjugates based on cyclodextrin and calixarene cores[4] have been used for this purpose and they are also attractive as potential molecular delivery systems.[5] For this purpose, the presence of binding groups in addition to the sugar units is useful in order to complex substrates to be delivered to a specific target. In the case of calix[4]arenes, the sugar moieties were almost exclusively attached at the lower or upper rim through the formation of ether bonds or carbon–carbon bonds[6] exploiting trimethylsilyl triflate[7a] and copper(II) triflate[7b] mediated glycosylation reactions on bis- and tetrahydroxymethylcalix[4]arenes, a Suzuki type reaction using calix[4]arene di- and monoboronic acid derivatives[7d] and Wittig reactions[7c,e] on formylated calix[4]arenes. Only a couple of examples of thiourea containing glycocalixarenes are known where the hydrogen bonding spacer is able to complex anionic species.[8] The dicarboxylic acid **1** is a well known cone calix[4]arene intermediate[9] and has been used for the synthesis of cleft-like[10] and macrobicyclic[11] N-linked peptidocalix[4]arenes and other molecular receptors.[12] We therefore explored the possibility of using compound **1** as a starting material for the synthesis of novel upper rim calix[4]arene glycoconjugates through amide bond formation, where the amide group could be exploited for the binding of acidic and/or basic substrates, and report in this paper the synthetic results obtained. An amide bond has been used to synthesize lower rim calix[4]arene–monosaccharide conjugates,[13] but to the best of our knowledge the synthesis of upper rim derivatives has never been reported.

2. Results and discussion

Reaction of the calix[4]arene diacid **1**[9] with 2,3,4,6-tetra-*O*-acetyl-β-D-galactosamine **2a**[14] and 2,3,4,6-tetra-*O*-acetyl-β-D-glucosamine **2b**[14] in the presence of *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU) and triethylamine (TEA) at rt (Scheme 1) did not give a glycosylated calixarene, but the benzotriazole ester **3**, which was isolated in yields higher than 70% and characterized since it is quite stable. Heating compound **3** with these monosaccharides overnight in presence of an excess of base in acetonitrile led to the complete



Scheme 1. (a) HBTU, TEA, CH_2Cl_2, rt, 5 h.

Keywords: Calix[4]arene; Neoglycoconjugates; Glycoside; Amide bond.
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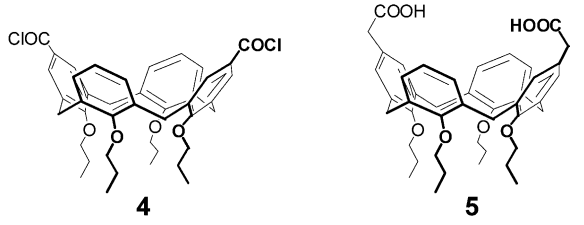
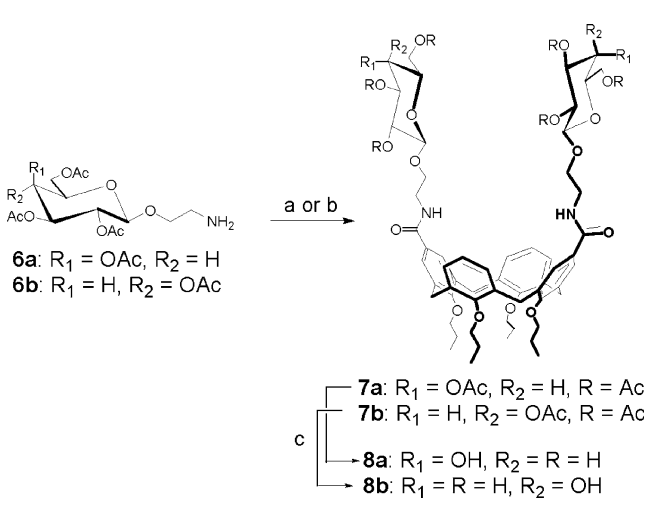
decomposition of **3** without forming any coupling product with glycosamines **2a**,**b**. Similarly, when the acid chloride **4**[11] was reacted with glycosylamines **2a**,**b** using TEA as base, the calix[4]arene acid **1** and the sugar were found after aqueous work-up and no coupling product could be detected.



Suspecting that failure in the coupling reaction between **2a**,**b** and **3** or **4** could be mainly ascribed to repulsive steric interactions between the reacting partners, we decided to introduce a spacer either on the calixarene or on the sugar moiety. Nevertheless, the condensation reaction of calix[4]-arene–acetic acid derivative **5**[15] with galactosamine **2a** was unsuccessful in a variety of conditions. On the other hand, the reaction of the calix[4]arene dicarboxylic acid **1** with the galactosamine derivative **6a**,[16] having a two methylene unit spacer between the sugar moiety and the amine group, in the presence of HBTU and an excess of base (pH > 12) at 80 °C in acetonitrile, led to the synthesis of the coupling product **7a** (Scheme 2). Comparable results were obtained using glucosamine **6b** as glycosyl donor to obtain **7b**, and also reacting at rt the two glycosylamines **6a** and **6b** with the calixarene diacylchloride **4**. Deprotection of **7a**,**b** with triethylamine in aqueous methanol gave the amide-linked glycoconjugates **8a**,**b** in 30–33% overall yield. The ^{1}H NMR spectra of derivatives **7a**,**b** in $CDCl_3$ show sharp signals, which allow the exclusion of intermolecular aggregation phenomena. It is well known[17] that calix[4]arenes difunctionalized at the upper rim with hydrogen bonding donor and acceptor groups can experience intramolecular H-bonding in apolar solvents, which stabilize a closed flattened cone conformation (Fig. 1) with respect to the open flattened cone conformation, which is more stable in strong donor solvents. Usually, these conformational preferences can be recognized very clearly by inspecting the aromatic region of the ^{1}H NMR spectra of these compounds. In the case of glycocalixarenes **7a**,**b**, the aromatic protons of the unsubstituted aromatic rings resonate at $\delta \sim 6.30$ and those of the substituted ones at $\delta \sim 7.35$, thus confirming that these compounds exist mainly in the open flattened cone conformation, in $CDCl_3$.



Scheme 2. (a) **1**, HBTU, TEA, CH_3CN, 80 °C, 12 h, 35–37%; (b) **4**, TEA, CH_2Cl_2, rt; (c) TEA, MeOH, H_2O, rt, 16 h, 96–98%.

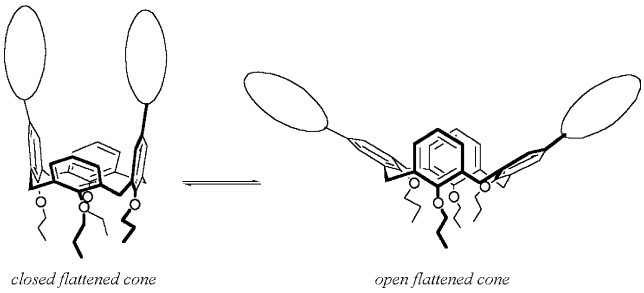
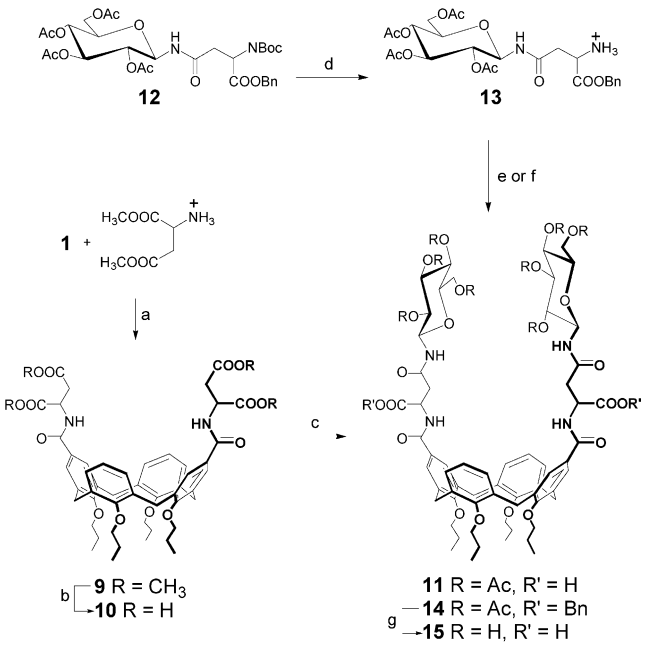


Figure 1. The two possible flattened cone conformers of a upper rim difunctionalised tetrapropoxycalix[4]arene.

Therefore, no intramolecular hydrogen bonding is taking place between the two amide groups in compounds **7a**,**b** which could be ascribed to the intrinsic weakness of the noncovalent interaction or to steric repulsion between the two protected sugar units. The ^{1}H NMR spectra of the deprotected glycocalixarenes **8a**,**b** in the same solvent give very broad signals, which tend to sharpen upon dilution, thus indicating extensive intermolecular aggregation due to the large number of free OH groups. In CD_3OD, the spectra show sharp signals instead. The relative position of the signals of the aromatic protons in this solvent indicates again a preference for the open flattened cone conformation also for compounds **8a**,**b**. Both for the protected and the deprotected compounds **7a**,**b** and **8a**,**b** no splitting could be observed for the signals of the *ortho* aromatic and of the axial and equatorial protons of the calixarene Ar–CH_2–Ar methylene bridge, which is indeed typical for other calix[4]arene derivatives bearing chiral units at the upper rim.[7b,10,11] Evidently, because of the spacer, the carbohydrate chiral units are too far away from the calixarene skeleton to influence its NMR signals.

The second approach we investigated was the formation of an amide bond with an amino acid spacer. This constitutes an attractive route to build up a novel type of hybrid sugar–peptidocalix[4]arene receptors to be used in the recognition of biologically relevant substrates. We focused our attention on aspartic acid as spacer, because of its wide use in natural and synthetic peptides for the linkage of sugar units, and on glucose as saccharide unit, because of its higher solubility in water in comparison with other neutral monosaccharides, which could lead to water soluble glycocalixarenes. L-Aspartic acid dimethyl ester hydrochloride was then reacted with the calix[4]arene diacid **1** giving **9** and, after hydrolysis, **10** in moderate overall yields. The reaction of compound **10** with glucosamine **2b** in the presence of HBTU (Scheme 3) gave a complex mixture of products in which the sugar–peptide conjugate **11** was detected by ESI-MS but could not be isolated. Significantly better results were obtained through the alternative synthetic route consisting in the condensation of the sugar–amino acid derivative **13** with calix[4]arene dicarboxylic acid **1** or diacylchloride **4** (Scheme 3). In these cases, the protected

sugar–peptidocalix[4]arene conjugate **14** was obtained in 68–72% yield and the full deprotection both from benzyl and acetyl groups with TEA in a 8/1 methanol/water mixture easily occurred, leading to the isolation of the glycopeptidocalix[4]arene **15** as bis triethylammonium salt.



Scheme 3. (a) HBTU, TEA, CH_2Cl_2, rt, 4 h, 64%; (b) LiOH, THF, H_2O, from 0 °C to rt, 6 h, 92%; (c) **2b**, HBTU, TEA, CH_2Cl_2, rt, 12 h; (d) CF_3COOH, CH_2Cl_2, from 0 °C to rt, 2 h, quantitative; (e) **1**, HBTU, TEA, CH_2Cl_2, rt, 4 h, 72%; (f) **4**, TEA, CH_2Cl_2, rt, 4 h, 68%; (g) TEA, MeOH, H_2O, rt, 16 h, Amberlite IR-120 resin, 95%.

The protected derivative **14** in $CDCl_3$ exists in the open flattened cone conformation and the corresponding deprotected glycocalix[4]arene **15** shows similar properties to those described above for compounds **8a**,**b** in $CDCl_3$ and CD_3OD. Titration of **15** with an aqueous solution of NaOH gave the corresponding sodium salt which shows good solubility in water up to 1.4×10^{-2} M. The ^{1}H NMR spectrum in D_2O of this compound is rather broad indicating extensive aggregation phenomena which are currently under investigation.

3. Conclusion

Several synthetic routes for linking two sugar units at the upper rim of cone calix[4]arenes, through the formation of amide bonds, have been investigated. Steric effects prevent the coupling of calix[4]arene dicarboxylic acid with simple aminoglycosides, whereas the corresponding reaction with carbohydrates bearing a two or three carbon atoms spacer terminating with a primary amino group was more successful. This strategy allowed the synthesis of several difunctionalized calix[4]arene neoglycoconjugates, attractive in chemical glycobiology and supramolecular chemistry. The conformational properties of the compounds synthesized have been established by ^{1}H NMR experiments in different solvents.

4. Experimental

All moisture sensitive reactions were carried out under nitrogen atmosphere. All dry solvents were prepared according to standard procedures and stored over molecular sieves. Melting points were determined on an Electrothermal apparatus with samples in tubes sealed under nitrogen atmosphere or on a Kofler apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker AC300 and Bruker AMX400 spectrometers. Spectra are reported in ppm downfield from TMS as internal standard. Mass spectra by electrospray ionization (ESI) and chemical ionization (CI) methods were recorded on a Micromass ZMD and on a Finnigan Mat SSQ710 spectrometer, respectively. Elemental analyses were performed using a CHN 1106 Carlo Erba instrument and are reported as percentage. Analytical TLC was performed using Merck prepared plates (silica gel 60 F-254 on aluminum). Merck silica gel (40–63 μm) was used for flash-chromatography. *N*-Boc-L-Asp-OBn was purchased from Novabiochem. The calix[4]arene dicarboxylic acid **1**,[9] the corresponding diacyl chloride **4**,[11] the 2,3,4,6-tetra-*O*-acetyl-β-D-galacto- and β-D-glucosamine **2a**,**b**[14] and the 2,3,4,6-tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galacto- and β-D-glucoside **6a**,**b**[16] were synthesized according to literature procedures.

4.1. General procedures for the coupling of amines with carboxylic calix[4]arene derivatives

(A) The amine and triethylamine (TEA) were added to a suspension in dry methylene chloride of the calix[4]arene dicarboxylic acid derivative. Then HBTU was added. The reaction was stirred for 4 h at rt unless otherwise specified. During the first 30 min, the pH-value was frequently checked and TEA was added if necessary to keep pH at ca. 8.5. The reaction was quenched with a 5% NH_4Cl water solution. The organic layer was separated, washed with 5% $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash-chromatography on silica gel.

(B) A solution of calixarene diacylchloride **4**, amine and TEA in dry methylene chloride was stirred at rt for 4 h, then the reaction was quenched by addition of a 5% NH_4Cl water solution. The organic layer was separated, washed with 5% $NaHCO_3$ aqueous solution and water, dried over Na_2SO_4 and evaporated to dryness in vacuo. The crude was purified by flash-chromatography on silica gel.

4.2. General procedure for the deprotection of the glycocalixarenes from the acetyl groups

(C) The protected glycocalixarene was treated with the mixture methanol/water/TEA 8/1/1 at rt overnight. The reaction was quenched by evaporation to dryness in vacuo, then the residue was dissolved in methanol and treated with Amberlite IR-120 resin until neutral pH. The resin was filtered off and the solution was evaporated to dryness in vacuo.

4.2.1. 5,17-Bis(benzotriazolyloxycarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (3). This compound was isolated as main product from the reaction of 5,17-

bis(hydroxycarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]-arene[9] (**1**) with 2,3,4,6-tetra-*O*-acetylgalactosamine[14] (**2a**) and with 2,3,4,6-tetra-*O*-acetylglucosamine[14] (**2b**) according to the reported general procedure A. White crystals; yield 75–78%; mp 237–238 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 (dd, J=8.0, 1.0 Hz, 2H, Ar), 7.89 (s, 4H, Ar), 7.39 (m_c, 6H, Ar), 6.52 (t, J=6.0 Hz, 2H, Ar), 6.44 (d, J=6.0 Hz, 4H, Ar), 4.55 (d, J=13.5 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.14 (t, J=7.7 Hz, 4H, $OCH_2CH_2CH_3$), 3.81 (t, J=7.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.34 (d, J=13.6 Hz, 4H, H_{eq} of $ArCH_2Ar$), 1.96 (m_c, 8H, $OCH_2CH_2CH_3$), 1.09 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 1.01 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.0, 162.7 (C=O, C_{ar}), 155.5, 143.4, 137.3, 132.9, 131.4, 128.4, 128.2, 124.6, 122.7, 120.1, 117.9, 108.4 (C_{ar}), 77.14, 77.09 ($OCH_2CH_2CH_3$), 30.9 ($ArCH_2Ar$), 23.3 ($OCH_2CH_2CH_3$), 10.5, 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{54}H_{54}N_6O_8$ (914.40): m/z 937.5 $[M^+ + Na]^+$. Anal. Calcd for $C_{54}H_{54}N_6O_8$: C, 70.88; H, 5.95; N, 9.18. Found C, 70.85; H, 5.96; N, 9.21.

4.2.2. 5,17-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (7a). 2,3,4,6-Tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galactoside (**6a**)[16] (0.61 g, 1.55 mmol) and compound **1** (0.26 g, 0.39 mmol) were reacted in presence of HBTU (0.43 g, 0.94 mmol) and TEA (1.00 mL, 7.64 mmol) following the general procedure A but using dry acetonitrile (20 mL) as solvent. In this case, the reaction was also heated to reflux overnight. Alternatively, 2,3,4,6-tetra-*O*-acetyl-(2-aminoethyloxy)-β-D-galactoside (**6a**)[16] (0.60 g, 1.53 mmol) and compound **4** (0.28 g, 0.39 mmol) were reacted in presence of TEA (0.2 mL, 1.53 mmol) following procedure B. The crude product was chromatographed with ethyl acetate. Light yellow oil; yield 0.19 g (37%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 4H, Ar), 6.51–6.39 (m, 4H, Ar, NH), 6.38–6.27 (m, 4H, Ar), 5.38 (d, J=3.4 Hz, 2H, H-4), 5.20 (dd, J=10.5, 7.9 Hz, 2H, H-2), 5.02 (dd, J=10.5, 3.4 Hz, 2H, H-3), 4.50 (d, J=7.8 Hz, 2H, H-1), 4.45 (d, J=13.4 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.15–4.04 (m, 4H, H-6,6′), 4.03–3.85 (m, 6H, H-5, $OCH_2CH_2CH_3$), 3.80–3.63 (m, 8H, $C(O)NHCH_2CH_2$, $OCH_2CH_2CH_3$), 3.63–3.45 (m, 4H, $C(O)NHCH_2CH_2$), 3.21 (d, J=13.4 Hz, 4H, H_{eq} of $ArCH_2Ar$), 2.13, 2.02, 1.97, 1.89 (4s, 6H each, $C(O)CH_3$), 2.01–1.82 (2m, 4H each, $OCH_2CH_2CH_3$), 1.04 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.92 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=170.3, 170.2, 170.1, 170.0, 169.6 ($C(O)NH$, $C(O)CH_3$), 160.5, 155.8, 135.9, 133.5, 128.1, 128.0, 127.7, 122.3 (C_{ar}), 101.4 (C-1), 76.8, 76.6 ($OCH_2CH_2CH_3$), 70.8, 70.7, 68.9, 68.0, 66.9, 61.2 (C-2, C-3, C-4, C-5, C-6, $NHCH_2CH_2O$), 39.5 ($NHCH_2CH_2O$), 30.9 ($ArCH_2Ar$), 23.3, 23.25, 23.20, 23.1 ($OCH_2CH_2CH_3$), 20.5, 20.4 ($C(O)CH_3$), 10.4, 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{74}H_{94}N_2O_{26}$ (1426.61): m/z 1449.6 $[M+Na]^+$. Anal. Calcd for $C_{74}H_{94}N_2O_{26}$: C, 62.26; H, 6.64; N, 1.96. Found C, 62.30; H, 6.63; N, 1.99.

4.2.3. 5,17-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (7b). The compound was obtained following the general procedure B starting from calixarene **4**[11] (0.15 g, 0.21 mmol) and glucoside **6b**[16] (0.33 g, 0.84 mmol) in presence of TEA (0.12 mL, 0.84 mmol). The crude product was chromatographed using as eluent the mixture hexane/acetone from 1.5/1 to 1.2/1, v/v. Yield 0.10 g (35%); mp 136–138 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.36 (s, 4H, Ar), 6.48 (t, J=7.2 Hz, 2H, NH), 6.40–6.34 (m, 6H, Ar), 5.23 (t, J=9.6 Hz, 2H, H-3), 5.09 (t, J=9.9 Hz, 2H, H-4) 5.02 (dd, J=9.9, 8.4 Hz, 2H, H-2), 4.55 (d, J=8.4 Hz, 2H, H-1), 4.46 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.27 (dd, J=12.6, 5.1 Hz, H2, H-6), 4.14 (dd, J=12.6, 2.1 Hz, H2, H-6′), 4.02–3.95 (m, 6H, $OCHHCH_2$-NH and $OCH_2CH_2CH_3$), 3.80–3.67 (m, 10H, $OCHHCH_2$-NH, $OCH_2CH_2CH_3$, H-5 and OCH_2CHHNH), 3.62–3.50 (m, 2H, OCH_2CHHNH), 3.23 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 2.07 (s, 3H, CH_3CO), 2.04 (s, 3H, CH_3CO), 2.01 (s, 3H, CH_3CO), 1.98–1.88 (m, 8H, $OCH_2CH_2CH_3$), 1.92 (s, 3H, CH_3CO), 1.06 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ =170.6, 170.1, 169.4 and 167.7 (C=O), 160.4, 155.6, 136.3, 133.3, 128.0, 127.8, 127.4 and 122.3 (C_{ar}), 100.9 (C-1), 77.0 and 76.6 ($OCH_2CH_2CH_3$), 72.6, 71.9, 71.3 and 68.3 (C-2, C-3, C-4, C-5), 69.1 (C-6), 61.8 ($NHCH_2CH_2O$), 39.5 ($NHCH_2CH_2O$), 30.9 ($ArCH_2Ar$), 23.3 and 23.1 ($OCH_2CH_2CH_3$), 20.7 and 20.6 (CH_3CO), 10.5 and 10.0 ($OCH_2CH_2CH_3$); ESI-MS for $C_{74}H_{94}N_2O_{26}$ (1426.61): m/z 1449.6 $[M+Na]^+$. Anal. Calcd for $C_{74}H_{94}N_2O_{26}$: C, 62.26; H, 6.64; N, 1.96. Found C, 62.30; H, 6.63; N, 1.99.

4.2.4. 5,17-Bis[(β-D-galactopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (8a). The compound was obtained following the general procedure C. Colorless crystals; yield 96%; mp 148–149 °C; ^{1}H NMR (300 MHz, CD_3OD): δ=7.57 (s, 4H, Ar), 6.30 (bs, 6H, Ar), 4.52 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.33 (d, J=7.4 Hz, 2H, H-1), 4.09 (t, J=7.2 Hz, 4H, $OCH_2CH_2CH_3$), 3.87 (d, J=2.4 Hz, 2H, H-4), 3.88–3.66 (m, 18H, H-2, H-3, H-5, H-6, $OCH_2CH_2CH_3$), 3.66–3.50 (m, 8H, $C(O)NHCH_2CH_2$), 3.27 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 1.97 (m_c, 8H, $OCH_2CH_2CH_3$), 1.14 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.97 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=170.8 (C=O), 162.3, 157.0, 138.2, 134.5, 129.5, 129.4, 129.2, 123.7 (C_{ar}), 105.5 (C-1), 78.4, 75.2, 72.9, 70.6, 70.0, 62.8 (C-2, C-3, C-4, C-5, C-6, $NHCH_2CH_2O$), 78.3, 77.0 ($OCH_2CH_2CH_3$), 41.5 ($C(O)NHCH_2CH_2$), 32.0 ($ArCH_2Ar$), 24.9, 24.7 ($OCH_2CH_2CH_3$), 11.6, 10.7 ($OCH_2CH_2CH_3$); ESI-MS for $C_{58}H_{78}N_2O_{18}$ (1090.52): m/z 1112.8 $[M+Na]^+$. Anal. Calcd for $C_{58}H_{78}N_2O_{18}$: C, 63.84; H, 7.20; N, 2.57. Found C, 63.88; H, 7.22; N, 2.54.

4.2.5. 5,17-Bis[(β-D-glucopyranosyloxyethylamino)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (8b). General procedure C. Yield 97%; mp 185–187 °C; ^{1}H NMR (300 MHz, CD_3OD): δ=7.52 (s, 4H, Ar), 6.32–6.26 (m, 6H, Ar), 4.49 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.34 (d, J=7.8 Hz, 2H, H-1), 4.08 (t, J=7.6 Hz, 4H, $OCH_2CH_2CH_3$), 4.09–4.00 (m, 2H, $NHCH_2CHHO$), 3.86 (d, J=10.8 Hz, 4H, H-6 and H-6′), 3.81–3.60 (m, 10H, $NHCH_2CHHO$, $OCH_2CH_2CH_3$, $NHCHHCH_2O$ and H-5), 3.59–3.49 (m, 2H, $NHCHHCH_2O$), 3.43–3.20 (m, 10H, H-3, H-4, H-2 and H_{eq} of $ArCH_2Ar$), 2.02–1.85 (m, 8H, $OCH_2CH_2CH_3$), 1.11 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, J=7.2 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=170.5 (C=O), 161.9, 156.7, 137.8, 134.3, 129.1 and 123.4 (C_{ar}), 104.6 (C-1), 78.1

($OCH_2CH_2CH_3$), 77.9, 75.1 and 71.6 (C-2, C-3, C-4, C-5), 69.6 (C-6), 62.7 ($NHCH_2CH_2O$), 41.1 ($NHCH_2CH_2O$), 31.9 ($ArCH_2Ar$), 24.6 and 24.4 ($OCH_2CH_2CH_3$), 11.2, 10.5 ($OCH_2CH_2CH_3$); ESI-MS for $C_{58}H_{78}N_2O_{18}$ (1090.52): *m/z* 1112.8 $[M+Na]^+$. Anal. Calcd for $C_{58}H_{78}N_2O_{18}$: C, 63.84; H, 7.20; N, 2.57. Found C, 63.88; H, 7.22; N, 2.54.

4.2.6. 5,17-Bis(*N*-L-aspartylcarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (10). The general coupling procedure A was used with aspartic acid dimethyl ester hydrochloride (0.31 g, 1.55 mmol) and dicarboxylic acid **1**[9] (0.26 g, 0.39 mmol) in presence of HBTU (0.43 g, 0.94 mmol) and TEA (0.44 mL, 3.12 mmol). The crude product was chromatographed using as eluent the mixture hexane/ethyl acetate 1/1 (v/v). Selected data for 5,17-bis(dimethoxy-L-aspartylcarbonyl)-25,26,27,28-tetra-*n*-propoxycalix[4]arene (**9**): colorless solid; yield 0.24 g (64%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.50 (d, J=2.0 Hz, 2H, Ar), 7.46 (d, J=2.1 Hz, 2H, Ar), 7.20 (d, J=7.8 Hz, 2H, NH), 6.30–6.22 (m, 2H, Ar), 6.21–6.15 (m, 4H, Ar), 5.09–4.98 (m, 2H, $NHCHCH_2$), 4.42 (d, J=13.4 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.04 (t, J=7.9 Hz, 4H, $OCH_2CH_2CH_3$), 3.76 (s, 6H, OCH_3), 3.68 (s, 6H, OCH_3) 3.66 (t, J=8.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.5 Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.12 (dd, J=17.2, 4.4 Hz, 2H, $NHCHCH_2$), 2.99 (dd, J=17.2, 4.8 Hz, 2H, $NHCHCH_2$), 1.95–1.80 (m, 8H, $OCH_2CH_2CH_3$), 1.05 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.88 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$); ESI-MS for $C_{54}H_{66}N_2O_{14}$ (966.45): *m/z* 989.6 $[M+Na]^+$. A solution of compound **9** (0.088 g, 0.09 mmol) in THF (10 mL) was cooled to 0 °C. After addition of lithium hydroxide (0.008 g, 0.36 mmol) dissolved in water (3 mL), the mixture was stirred at rt for 6 h. The reaction was quenched by evaporation of the organic solvent and subsequent addition of 1 N HCl until acidic pH. Product **10** precipitated as white solid and was filtered and dried. Colorless solid; yield 0.075 g (92%); mp 142–143 °C; ^{1}H NMR (300 MHz, $CDCl_3/CD_3OD$ 1/10, v/v): δ=7.60 (bs, 4H, Ar), 6.28–6.12 (m, 6H, Ar), 4.97 (bs, 2H, $NHCHCH_2$), 4.47 (d, J=13.2 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.10 (t, J=7.1 Hz, 4H, $OCH_2CH_2CH_3$), 3.69 (t, J=6.7 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.2 Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.00 (d, J=5.3 Hz, 4H, $NHCHCH_2$), 2.01–1.84 (m, 8H, $OCH_2CH_2CH_3$), 1.10 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$), 0.91 (t, J=7.4 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, CD_3OD): δ=174.8, 162.7 (CO), 156.6, 138.5, 134.2, 129.7, 129.6, 129.3, 123.7 (C_{ar}), 78.5, 78.2 ($OCH_2CH_2CH_3$), 51.3 ($NHCHCH_2$), 37.4 ($NHCHCH_2$), 32.2 ($ArCH_2Ar$), 24.9, 24.7 ($OCH_2CH_2CH_3$), 11.6, 10.6 ($OCH_2CH_2CH_3$); ES-MS for $C_{50}H_{58}N_2O_{14}$ (910.39): *m/z* 967.9 $[M-H+Na+Cl]^-$. Anal. Calcd for $C_{50}H_{58}N_2O_{14}$: C, 65.92; H, 6.42; N, 3.07. Found C, 65.89; H, 6.46; N, 3.10.

4.2.7. *N*-Boc-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester (12). Glucosamine **2b**[14] (1.5 g, 4.32 mmol) and *N*-Boc-L-Asp-OBn (1.16 g, 3.60 mmol) were reacted in presence of HBTU (3.0 g, 7.91 mmol) and TEA (1.10 mL, 7.91 mmol) in dry CH_2Cl_2 (30 mL) at rt for 1 h then the reaction was quenched by addition of a 5% $NaHCO_3$ aqueous solution (20 mL). The organic phase was separated, washed with water and evaporated to dryness in vacuo. The compound was obtained pure as colorless solid by flash-chromatography on silica gel (eluent: ethyl acetate/hexane 1/1, v/v). Yield 1.76 g (75%). The compound was identified by ^{1}H and ^{13}C NMR[18] and by ESI mass spectrometry: for $C_{30}H_{40}N_2O_{14}$ (652.68): *m/z* 675.2 $[M+Na]^+$, 1327.7 $[2M+Na]^+$.

4.2.8. 4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester·CF_3COOH (13). A solution of *N*-Boc-4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-L-aspartic acid 1-benzyl ester[18] (1.50 g, 2.24 mmol) in CH_2Cl_2 (25 mL) was cooled with ice-bath and TFA (2.5 mL) was added. The reaction proceeded without bath for 1 h, then was quenched by evaporation of the organic solvent and by removing the excess of TFA under high vacuum. The compound was then used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.15 (bs, 3H, NH_3^+) 7.53 (d, J=9.3 Hz, 1H, N*H*CO), 7.45–7.27 (m, 2H, Ar), 7.33 (t, J=7.5 Hz, 1H, Ar), 7.22 (d, J=7.5 Hz, 2H, Ar), 5.38 (t, J=9.3 Hz, 1H, H-3), 5.30–5.20 (m, 3H, CH_2Ph and H-1), 5.16 (t, J=9.3 Hz, 1H, H-4), 5.01 (t, J=9.3 Hz, 1H, H-2), 4.48 (bs, 1H, $CHCH_2$), 4.29 (dd, J=12.4, 4.3 Hz, 1H, H-6), 4.22 (dd, J=12.4, 6.4 Hz, 1H, H-6′), 3.85 (bd, 1H, H-5), 3.18 (bs, 2H, $CHCH_2$), 2.09, 2.08 and 1.99 (3s, 12H, $OCCH_3$); ^{13}C NMR (75 MHz, $CDCl_3$): δ=172.3, 171.5, 171.0, 170.8, 170.5, 167.6 (CO), 160.3 (q, J=40 Hz, CF_3CO), 137.8, 129.1, 129.0, 128.7, 128.3, 128.2 (C_{ar}), 115.1 (q, J=285 Hz, CF_3CO), 78.0, 73.5, 70.5, 69.1, 68.3, 62.0 (C-1, C-2, C-3, C-4, C-5, C-6), 72.9 (OCH_2Ph), 50.2 ($CHCH_2$), 33.6 ($CHCH_2$), 20.3 and 19.9 (CH_3CO); ESI-MS for $C_{25}H_{32}N_2O_{12}$ (552.2): *m/z* 553.2 $[M+H]^+$, 575.2 $[M+Na]^+$, 1105.6 $[2M+H]^+$, 1127.5 $[2M+Na]^+$.

4.2.9. 5,17-Bis[(4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosylamino)-1-benzyloxyaspartyl)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (14). The glycopeptidocalixarene **14** was obtained from **1** (0.1 g, 0.15 mmol) and **13** (0.4 g, 0.6 mmol) in presence of TEA (0.17 mL, 1.2 mmol) following the general procedure A (yield 0.19 g, 72%) or from **4** (0.11 g, 0.15 mmol) following the general procedure B (yield 0.18 g, 68%). Eluent for flash-chromatography: CH_2Cl_2/MeOH 30/1, v/v). ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.52 (d, J=1.8 Hz, 2H, *Ar*CO), 7.50 (d, J=1.8 Hz, 2H, *Ar*CO), 7.47 (d, J=7.2 Hz, 2H, ArCONH), 7.38–7.30 (m, 10H, Bn), 6.77 (d, J=9.3 Hz, 2H, N*H*COCH), 6.25–6.23 (m, 2H, Ar), 6.16–6.09 (m, 4H, Ar), 5.32 (t, J=9.3 Hz, 2H, H-3), 5.25–5.21 (m, 6H, H-1 and $PhCH_2$), 5.15–5.05 (m, 2H, NHC*H*CO), 5.08 (t, J=9.3 Hz, 2H, H-4), 4.96 (t, J=9.3 Hz, 2H, H-2), 4.43 (d, J=13.5 Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.27 (dd, J=12.3, 4.2 Hz, 2H, H-6), 4.10–4.00 (m, 6H, H-6′ and $OCH_2CH_2CH_3$), 3.84–3.78 (m, 2H, H-5), 3.68 (t, J=6.9 Hz, 4H, $OCH_2CH_2CH_3$), 3.22 (d, J=13.5 Hz, 2H, H_{eq} of $ArCH_2Ar$), 3.20 (d, J=13.5 Hz, 2H, H_{eq} of $ArCH_2Ar$), 3.04 (dd, J=15.6, 3.9 Hz, 2H, $CHCHH$), 2.89 (dd, J=15.6, 4.2 Hz, 2H, $CHCHH$) 2.03–1.82 (m, 32H, CH_3CO and $OCH_2CH_2CH_3$), 1.10 (t, J=7.5 Hz, 6H, $OCH_2CH_2CH_3$), 0.90 (t, J=7.8 Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=171.2, 171.1, 170.6, 169.9, 169.5 and 167.2 (C=O), 161.4, 155.2, 137.1, 137.1, 135.4, 132.6, 128.6, 128.4, 128.0, 127.9, 127.8, 126.9 and 122.3 (C_{ar}), 78.2 and 77.1 ($OCH_2CH_2CH_3$), 76.7, 73.7, 72.7, 70.5, 68.0 (C-1, C-2, C-3, C-4, C-5), 67.4 ($PhCH_2$), 61.6 (C-6), 49.2 ($CHCH_2$), 37.3 ($CHCH_2$), 30.9 ($ArCH_2Ar$), 23.5 and 23.1 ($OCH_2CH_2CH_3$), 20.7, 20.6 and 20.5 (CH_3CO), 10.8 and 9.9 ($OCH_2CH_2CH_3$); ESI-MS for $C_{92}H_{108}N_4O_{30}$ (1748.7): *m/z* 897.8 $[M+2Na]^{2+}$, 1771.9

$[M+Na]^+$. Anal. Calcd for $C_{92}H_{108}N_4O_{30}$: C, 63.15; H, 6.22; N, 3.20. Found C, 63.21; H, 6.15; N, 3.06.

4.2.10. 5,17-Bis[(4-(β-D-glucopyranosylamino)-1-aspartyl)carbonyl]-25,26,27,28-tetra-*n*-propoxycalix[4]arene (15). Calixarene **14** was reacted following the general procedure C. In this case, the yellowish oil obtained was triturated with Et_2O to obtain a white solid corresponding to the bis triethylammonium salt of **15** [^{1}H NMR (300 MHz, MeOD) $\delta=7.70$ (s, 4H, Ar), 6.25–6.12 (bs, 6H, Ar), 5.00–4.85 (m, 4H, H-1 and C*H*CH_2), 4.53 (d, $J=13.5$ Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.16 (t, $J=8.1$ Hz, 4H, $OCH_2CH_2CH_3$), 3.87–3.60 (m, 10H, H-6,6′, H-5, $OCH_2CH_2CH_3$), 3.45–3.28 (m, 8H, H-4, H-2, H_{eq} of $ArCH_2Ar$), 3.15 (q, $J=7.5$ Hz, 12H, $HNCH_2CH_3$), 2.95–2.77 (m, 4H, $CHCH_2$), 2.08–1.88 (m, 8H, $OCH_2CH_2CH_3$),1.32 (t, $J=7.5$ Hz, 18H, $HNCH_2CH_3$), 1.17 (t, $J=8.1$ Hz, 6H, $OCH_2CH_2CH_3$), 0.95 (t, $J=8.1$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, MeOD) $\delta=177.4$, 174.5 and 169.5 (C=O), 162.3, 156.5, 138.3, 133.9, 129.3, 129.0 and 123.4 (Ar), 81.3, 79.7, 78.9, 74.3, 71.6 (C-1, C-2, C-3, C-4, C-5), 78.2 and 77.9 ($OCH_2CH_2CH_3$), 62.9 (C-6), 53.5 ($CHCH_2$), 47.8 ($HNCH_2CH_3$), 40.5 ($CHCH_2$), 32.0 ($ArCH_2Ar$), 24.7 and 24.4 ($OCH_2CH_2CH_3$), 11.4 and 10.4 ($OCH_2CH_2CH_3$), 9.3 ($HNCH_2CH_3$)]. This was subsequently dissolved in methanol and treated with Amberlite IR-120 resin, to give the neutral product **15**. Yield 0.10 g (96%); mp 177 (dec.); ν_{max}/cm^{-1} (KBr) 1727, 1645 (CO); ^{1}H NMR (300 MHz, MeOD) $\delta=7.61$ (bs, 4H, Ar), 6.32–6.17 (m, 6H, Ar), 5.00–4.85 (m, 4H, C*H*CH_2 and H-1), 4.49 (d, $J=13.2$ Hz, 4H, H_{ax} of $ArCH_2Ar$), 4.12 (t, $J=7.8$ Hz, 4H, $OCH_2CH_2CH_3$), 3.78 (d, $J=12.3$ Hz, 2H, H-6), 3.70 (t, $J=6.4$ Hz, 4H, $OCH_2CH_2CH_3$), 3.60 (dd, $J=12.3$, 4.8 Hz, 2H, H-6′), 3.42–3.23 (m, 8H, H-4, H-5, H-3 and H-2), 3.24 (d, $J=13.2$ Hz, 4H, H_{eq} of $ArCH_2Ar$), 3.03–2.96 (m, 4H, $CHCH_2$), 2.05–1.85 (m, 8H, $OCH_2CH_2CH_3$), 1.13 (t, $J=7.2$ Hz, 6H, $OCH_2CH_2CH_3$), 0.93 ($J=7.5$ Hz, 6H, $OCH_2CH_2CH_3$); ^{13}C NMR (75 MHz, MeOD) $\delta=173.7$, 173.4 and 170.0 (CO), 162.4, 156.6, 138.2, 134.0, 129.3, 129.1, 128.4 and 123.4 (C_{ar}), 81.1, 79.7, 79.0, 73.9, 71.4 and 62.7 (C-1, C-2, C-3, C-4, C-5, C-6), 78.2 and 78.0 ($OCH_2CH_2CH_3$), 51.1 ($CHCH_2$), 38.3 ($CHCH_2$) 31.9 ($ArCH_2Ar$), 24.5 and 24.4 ($OCH_2CH_2CH_3$), 11.3 and 10.4 ($OCH_2CH_2CH_3$); ESI-MS for $C_{62}H_{80}N_4O_{22}$ 1232.5): *m/z* 661.53 $[M-2H+4Na]^{2+}$, 1299.7 $[M-2H+3Na]^+$. Anal. Calcd for $C_{62}H_{80}N_4O_{22}$: C, 60.38; H, 6.54; N, 4.54. Found C, 60.23; H, 6.39; N, 4.50.

Acknowledgements

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Synthesis of the necine bases (±)-macronecine and (±)-supinidine via an aza-ene reaction and allylsilane induced ring closure

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Abstract—An aza-ene reaction has been used for the first time for the synthesis of two 5-membered lactam-hydrazides, each with a built-in allylsilane terminator for further elaboration. One of the lactam-hydrazides was transformed via an allylsilane-hydrazonium ion ring closure to a fused tetrahydropyrazole which may be considered as a mono-nitrogen analog of the biologically significant necine bases. A density functional theoretical study (B3LYP/6-21G*) was undertaken to provide insight into the factors that favor a synclinal transition structure of the hydrazonium ion intermediate leading to the tetrahydropyrazole. This stereocontrolled synthesis served as a model for the multi-step conversion of the other lactam-hydrazide, the substituted 2-pyrrolidinone, to necine bases (±)-supinidine and (±)-macronecine. An allylsilane-aldehyde ring closure formed the key step in the synthesis of these natural products.

1. Introduction

Over the past several decades the pyrrolizidine alkaloids have continued to attract significant interest from synthetic and medicinal chemists alike partly because of their diverse biological activities which allow their utility as research tools in pharmacology, but also because they provide challenging targets for testing new synthetic methodologies.[1] Necine bases, having a 1-hydroxymethyl group in the pyrrolizidine ring system, comprise the majority of the pyrrolizidine alkaloids. Many approaches to these pyrrolizidine alcohols converge on building a second five-membered ring on to a preformed, functionalized 2-pyrrolidinone, though the final bond formed in the synthesis can be N–C_5, C_6–C_7 or C_7–C_{7a} (Fig. 1).[1a]

Although allylsilanes have been widely recognized as intermediates for many applications, especially in the area of natural products synthesis, it is surprising that they have found only limited use in the synthesis of necine bases.[2] Indeed, to our knowledge there is only one example of a pyrrolizidine-3-one synthesis reported in the literature involving intramolecular cyclization (C_7–C_{7a} bond formation) of an acyl iminium ion with an allylsilane (Scheme 1).[3]

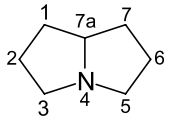
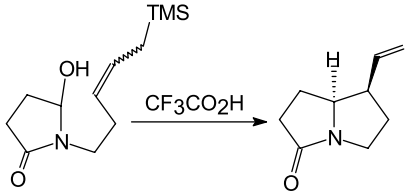


Figure 1.



Scheme 1.

We have previously described the use of 3-cyclopentyl allylsilanes to form a range of bicyclo-[3.3.0]octanes including a demonstration in the stereoselective construction of various natural products.[4] The 3-cyclopentyl

Keywords: Aza-ene reaction; Heterocyclic allylsilanes; Fused tetrahydropyrazole; Necine bases; Supinidine; Macronecine.
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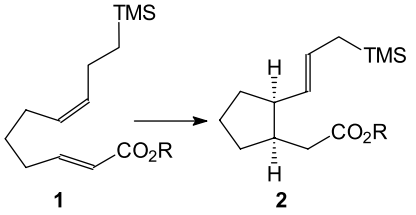
allylsilane intermediates are available in near quantitative yields by 5-(3,4) ene cyclization[5] of activated 1,6-dienes containing a homoallylsilane unit as ene donor (**1**→**2**, Scheme 2).



Scheme 2.

The foregoing work prompted us to examine a related aza-ene reaction[6] and subsequent allylsilane chemistry to gain entry into necine bases. Our retrosynthetic analysis towards this end is outlined in Scheme 3. Thus, 7-substituted pyrrolizidinones, e.g. **7**, precursor to various necine bases, could be accessed from compound **6** by an allylsilane–aldehyde ring closure. Compound **6**, in turn, could be obtained from the cyclic hydrazide **5** via reductive cleavage of the N–N bond and alkylation of the resulting pyrrolidinone with a two-carbon electrophile. Compound **5** was imagined to be accessed via an aza-ene reaction of the reactive azodicarbonyl intermediate **4** which may be generated by mild oxidation of the readily available acyl hydrazide **3**. It should be mentioned here that several 7-substituted pyrrolizidinones, reducible to necine bases at a late stage of the synthesis, were synthesized earlier either by nucleophilic substitution or radical cyclization of 5-substituted 1-halogenoethyl pyrrolidin-2-ones.[7]

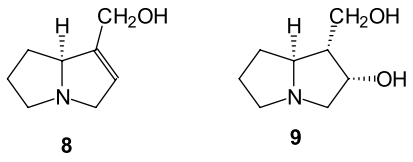


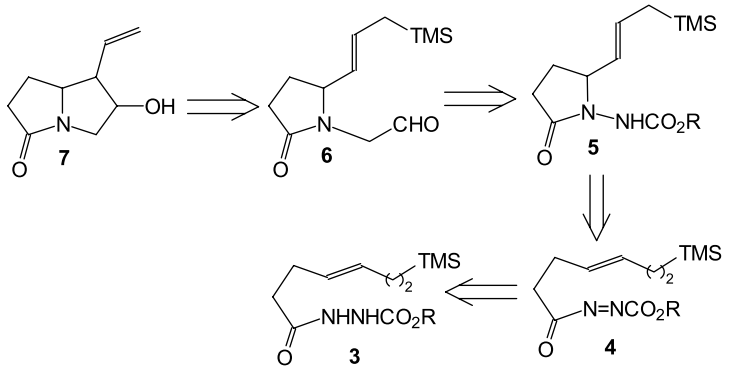
Figure 2.

In this paper we report the full details[8] of our efforts in this area which culminated in the synthesis of necine bases, e.g. (±)-supinidine (**8**)[9] and (±)-macronecine (**9**)[10] (Fig. 2).

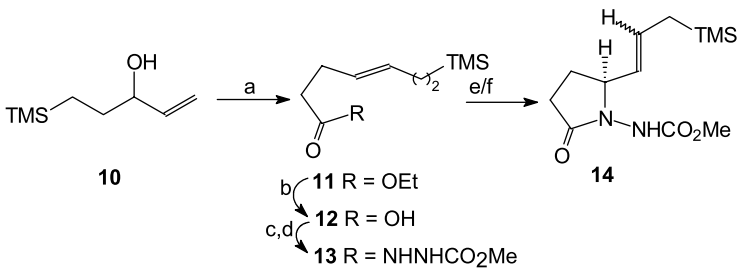
2. Results and discussion

2.1. Synthesis of cyclic hydrazide 14

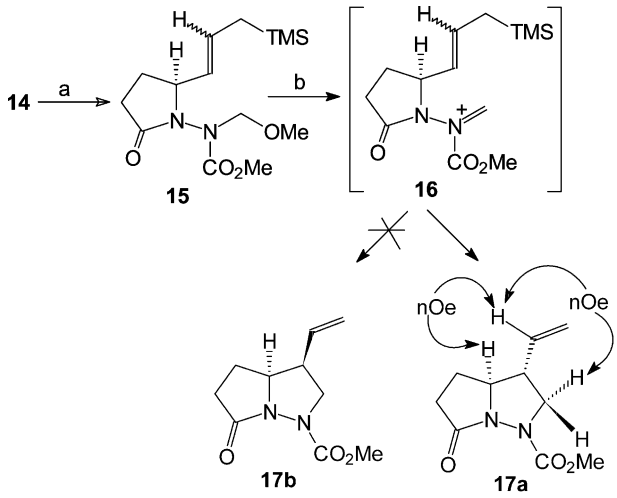
The synthesis of the substrate for the aza-ene reaction began with the silylated carbinol **10**, obtainable by addition of vinylmagnesium bromide to 3-(trimethylsilyl)propanal,[11] which on orthoester Claisen rearrangement gave the γ, δ-unsaturated ester **11** (Scheme 4); the configuration of the double bond in this case was tentatively assigned *E* on the basis of literature precedent. Saponification of **11** gave **12** which was next converted into the crystalline acyl hydrazide **13** in high yield via the acid chloride. Based on the original work of Vedejs and Meier,[6a] it was envisaged that oxidants capable of converting hydrazides into azo compounds (cf. **4**) would convert **13** into the cyclic hydrazide **14**. It was also deemed necessary to make use of neutral or slightly basic oxidants to ensure that the acid labile allylsilane functionality of **14** survived. Two different oxidizing agents, silver carbonate impregnated celite[12] and activated manganese dioxide,[6a,13] were initially selected for optimum results.



Scheme 3.



Scheme 4. (a) $CH_3C(OEt)_3$, H^+, toluene, 81%; (b) KOH, MeOH, 91%; (c) NaH, $(COCl)_2$, benzene; (d) NH_2NHCO_2Me, Et_3N, CH_2Cl_2, 88% from **12**; (e) MnO_2, $ClCH_2CH_2Cl$, 15 °C, 89%; (f) Ag_2CO_3-celite, benzene, 38%.



Scheme 5. (a) NaH, THF, and then MOMCl; (b) $BF_3 \cdot OEt_2$, CH_2Cl_2, 51% from **14**.

After considerable experimentation it was found that the aza-ene reaction could be run with only 12 equiv of MnO_2 (instead of 25–30 equiv as reported by Vedejs and Meier[6]) and sonication somewhat accelerated the reaction compared to mechanical stirring to give **14** containing 5–10% of the *Z*-isomer in high yield. However, the percentage of *Z*-isomer varied from batch to batch and the maximum amount of *Z*-isomer contaminated with the *E*-isomer in one run was found to be as high as 30%. The structural and stereochemical assignment of **14** followed from analysis of its ^1H and ^{13}C NMR spectroscopic data. Sonicating **13** with 10 equiv of Ag_2CO_3/celite reagent[12] followed by chromatography of the crude product also gave a semisolid material (38%) as a mixture (the isomers do not resolve on TLC) of *E*-**14** and *Z*-**15** in a ratio of 4.5:1, respectively. It is our experience that MnO_2 oxidation generally gives a purer ene product **14** in consistently good yields.

2.2. Synthesis of fused pyrazole 17a

With compound **14** in hand we were in a position to effect reductive cleavage of the N–N bond and elaborate the resulting 2-pyrrolidone for the synthesis of necine bases. However, before embarking on this work, we felt it important to study the efficacy of the allylsilane functionality to take part in some Lewis acid catalyzed ring closure reactions, such as the formation of the fused pyrazole 1**7a** (Scheme 5). The diastereoselectivity of this reaction which creates two adjacent stereogenic centers is important in light of possible application to the synthesis of necine bases. Additionally, the cyclic hydrazide derivative **17a** belongs to a class of compounds which are attractive objects of study in their own right and as analogs of bioactive mono-nitrogen compounds.[14] In the event, exposure of **14** to 1 equiv of

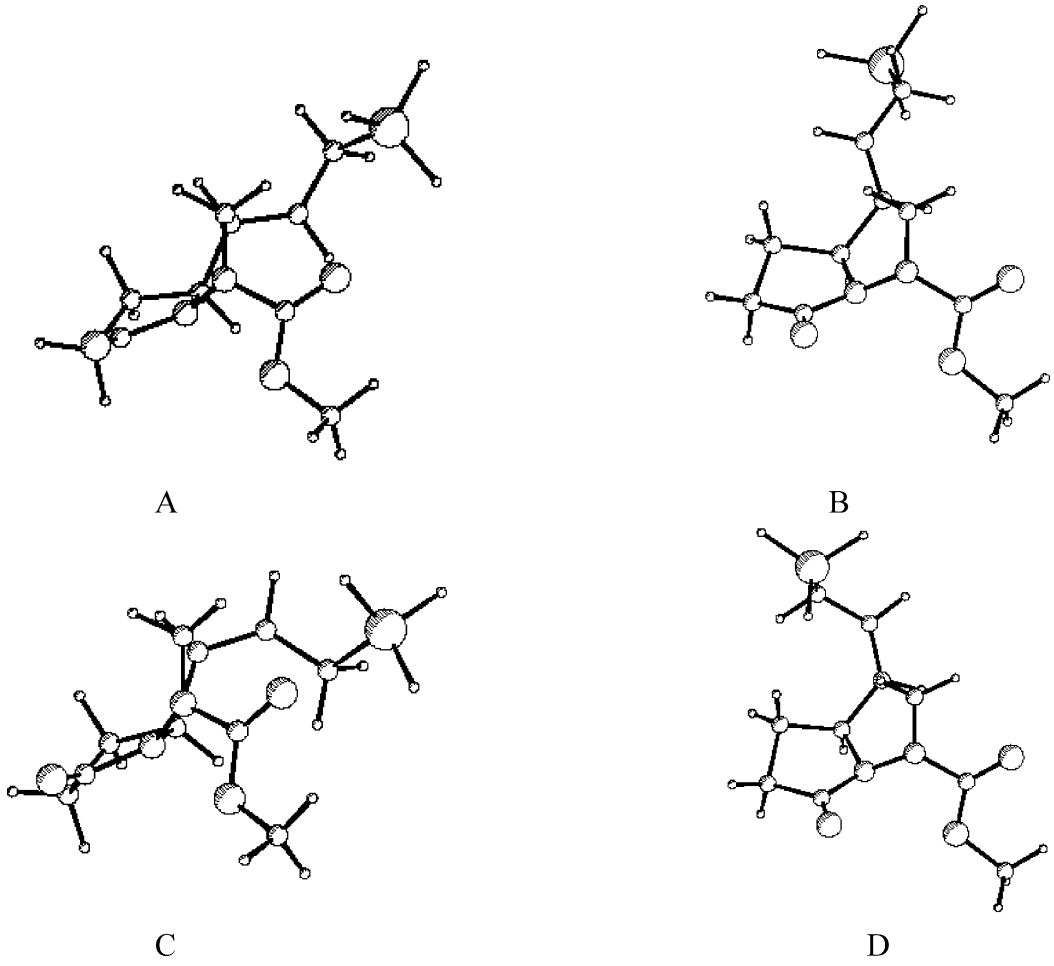


Figure 3.

Table 1. Relative energies in kcal/mol

Activated complex	B3LYP/3-21G*	MP2/6-31G*	MP2/6-311++G*	MP2/6-311++G(2df,p)
A	0.0	0.0	0.0	0.0
B	3.49	3.12	3.27	2.57
C	0.0	0.0	0.0	0.0
D	7.24	5.49	5.55	5.12

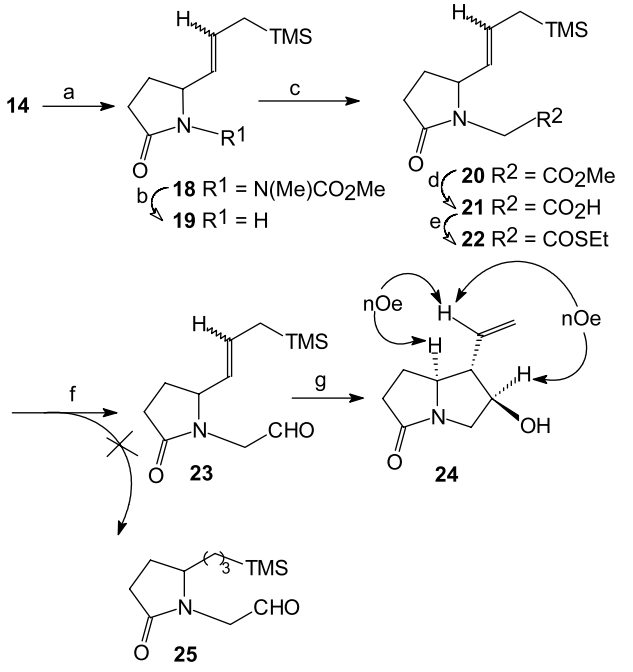
All computations were carried out in the B3LYP/3-21G* optimized geometries; MP2 done as MP2=FC.

sodium hydride in THF followed by treatment with methoxymethyl chloride (MOMCl) gave **15** (Scheme 5) which without further purification was treated with $BF_3 \cdot OEt_2$ (2.5 equiv) in CH_2Cl_2 to give the fused tetrahydropyrazole **17a** in good yield. Careful GC–MS analysis of the crude product showed total absence of the other diastereomer **17b**. Incidentally, **17a** had some nagging impurity which could not be removed by preparative layer chromatography. For analytical purposes, however, it could be readily purified by preparative HPLC. The structure and stereochemistry of **17a** were confirmed from its ^1H and ^{13}C NMR, COSY, HMQC and NOE-difference spectra.

In order to understand the high stereoselectivity in the reactions of *E* and *Z*-**15** to **17a** where the reactions obviously involve intramolecular trapping of the *N*-acyl hydrazonium ion intermediate **16** by the allylsilane terminator, ab initio calculations[15] were carried out to arrive at the four optimized activated complexes A–D (Fig. 3). The torsion angles (B3LYP/3-21G*) between the C,C and N,C double bonds in the synclinal transition structures A and C are 98.3 and 106.5°, respectively, whereas in the antiperiplanar transition structures B and D, they are 163.6 and 171.9°, respectively. The relative energies are shown in Table 1. Clearly, A (from *E*-**16**) and C (from *Z*-**16**) which give rise to **17a** are favored over B (from *E*-**16**) and D (from *Z*-**16**) which might have led to **17b**. These findings are in line with previous work on allylsilane-iminium ion ring closure reactions where useful selectivity compatible with synclinal transition structures has been found for the formation of five-membered rings, when either both double bonds are exocyclic to the ring being formed or when one of them is endocyclic.[16]

2.3. Synthesis of 7-vinyl substituted pyrrolizidinone 24

The synthesis began with the ene adduct **14** which gave 2-pyrrolidinone **19** via a two-step alkylation reduction sequence (Scheme 6). Thus, N-methylation gave a rotameric mixture of **18** whose N–N bond could be cleaved to give **19** in high yield using Li/NH_3 in the presence of excess ethanol for 1 min. If the alcohol was omitted, or if longer reaction were used, the yield and purity of the product decreased dramatically. Incidentally, in a selective mono-N-debenzylation of a substituted allylsilane using Li/NH_3 a similar observation including total loss of the silyl group was made by Weinreb et al.[17] Our plan at this stage was to attach a 2-carbon electrophile at the nitrogen atom in **19** and effect an allylsilane induced ring closure leading to a 7-substituted pyrrolizidinone (cf. **7**). Based on our model study on the synthesis of fused tetrahydropyrazole **17a**, we expected that the vinyl side chain at C_1 in this case would be cis with respect to C_{7a}–H, although the stereochemical disposition of the group at C_2 could not be clearly predicted. In the event, N-alkylation with methyl bromoacetate gave **20** in good yield. However, attempts to selectively reduce the ester group with DIBAL-H yielded only traces of **23** and a lot of polar compounds which were not further investigated. In view of these difficulties, a somewhat roundabout route was followed which involved transformation of **19** to thioester **22** via the acid **21** and reduction of the thioester to the aldehyde **23** following the procedure reported by Fukuyama et al.[18] The thioester reduction was initially plagued by the formation of a substantial amount of the overreduced aldehyde **25**. Hence, optimum conditions had to be worked out which delivered **23** uncontaminated with any of **25**. With sufficient quantities of **23** in hand, the stage was set to build up the second 5-membered ring. Thus, when **23** was exposed to $BF_3 \cdot OEt_2$ in methylene chloride, **24** was formed as the major product along with three minor diastereomers in a moderate yield. LCMS of the crude product showed that the four diastereomers were present in a relative ratio of 86.4: 5.8: 3.4: 4.4. Since the diastereomers do not resolve on TLC (silica gel), the major product **24** was purified by preparative HPLC. The structure and stereochemistry of **24** rest on a full complement of NMR spectroscopic data including those from NOE experiments,



Scheme 6. (a) NaH, THF; then CH_3I, 86%; (b) Li/NH_3/EtOH, 96%; (c) BuLi/THF; then $BrCH_2CO_2Me$, HMPA, 74%; (d) NaOH/MeOH, 85%; (e) EtSH, DCC, cat. DMAP, CH_2Cl_2, 76%; (f) Et_3SiH, Pd–C (10%), CH_2Cl_2, 94%; (g) $BF_3 \cdot OEt_2$, CH_2Cl_2, 44% (contains 3 other minor diastereomers).

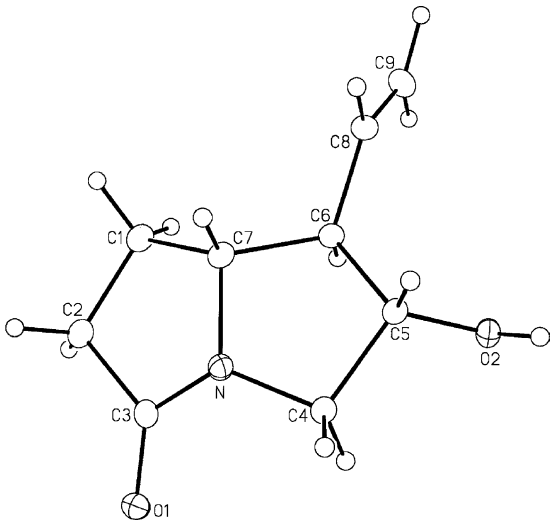


Figure 4. ORTEP perspective view of **24** with the numbering structure.

and finally confirmed by X-ray crystal structure determination (CCDC 251447, Fig. 4).

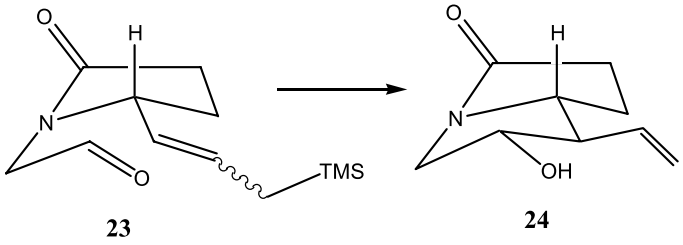
Based on the work of Tokoroyama et al.[19] on the stereoselective cyclization of (*E*)- and (*Z*)-5,6-dimethyl-8-trimethylsilyl-6-octenals and also based on our own theoretical analysis in the case of **15→17a**, a chair like transition state is proposed to account for the formation of the major diastereomer **24** (Scheme 7).

2.4. Correction of configuration at C_2

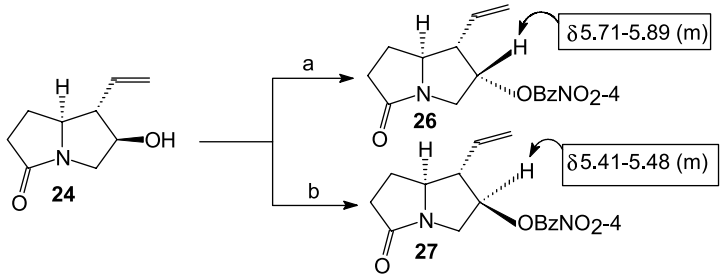
The pyrrolizidinone **24** possessed all the correct features of (±)-macronecine (**9**). However, to convert it to the natural molecule, inversion of configuration at C_2 was required. The configuration at C_2 was now corrected under standard Mitsunobu reaction conditions[20] on the crude product **24** (contaminated with three other minor diastereomers) using 4-nitrobenzoic acid as the nucleophile (Scheme 8). The only complication in this reaction was the similar polarity of the substitution product and triphenylphosphine oxide, requiring multiple purification[21] by silica gel chromatography to obtain **26** in a pure form. For confirmation that **24** had, indeed, undergone invertive substitution and was not simply acylated in the Mitsunobu reaction, the pyrrolidinone **24** was treated with 4-nitrobenzoyl chloride to obtain the epimeric 4-nitrobenzoate **27**. Comparison of ^{1}H NMR spectra of the two esters confirmed that the Mitsunobu reaction had occurred with inversion.

2.5. Synthesis of (±)-supinidine (8) and (±)-macronecine (9)

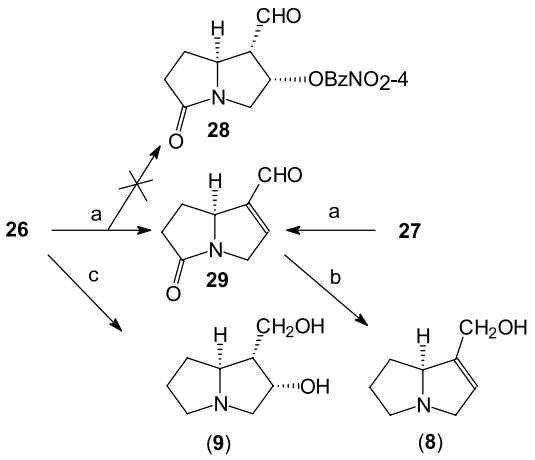
With ready access to substantial quantities of **26**, studies were next directed to the synthesis of the target natural product (±)-macronecine (**9**). Ozonolysis of **26** followed by reduction of the resulting ozonide gave none of the desired aldehyde **28**; instead the α, β-unsaturated aldehyde **29** was obtained as a crystalline solid (Scheme 9). The ^{1}H NMR data of **29** completely match with those reported for the same compound by Chamberlin et al.[9g] as well as Tsai and Ke.[7d] As one would expect, the diastereomeric pyrrolizidinone **27** under similar conditions yielded the identical aldehyde, e.g. **29**. The structure of **29** was best confirmed by its ready conversion to (±)-supinidine (**8**) by reduction with excess Red-Al in THF. The ^{1}H NMR of our synthetic product is superimposable with those of the racemic product reported by Hart et al.[9e] Since the aldehyde **28**, an intermediate for the synthesis of (±)-macronecine (**9**) was not available via the usual ozonolysis route, the experimental conditions were modified so as to reach the targeted natural product directly in one pot. Thus, ozonolysis of **26** was carried out as before in methylene chloride at −78 °C, then the bulk of the solvent was removed in vacuo at −30 °C and replaced by THF followed by the addition of excess Red-Al. This protocol effected reduction of the ozonide, the lactam carbonyl group and the ester in one pot to yield (±)-macronecine (**9**) whose ^{1}H and ^{13}C NMR data



Scheme 7.



Scheme 8. (a) Ph_3P/DEAD/4-$NO_2C_6H_4CO_2H$/THF, 53%; (b) 4-$NO_2C_6H_4COCl$/4-DMAP/CH_2Cl_2, 70%.



Scheme 9. (a) O_3, CH_2Cl_2, −78 °C, then Ph_3P, 50%; (b) Red-Al, THF, reflux (3 h), 76% (c) O_3, CH_2Cl_2, −78 °C; then excess Red-Al, THF, reflux (3 h), 33%.

were very close to those of the natural product reported in the literature.[10a,10d]

3. Conclusion

A 5-membered cyclic hydrazide containing an allylsilane functionality was readily synthesized by a facile, but rarely used aza-ene reaction. The allylsilane terminator allowed its further elaboration to a fused tetrahydropyrazole which may be regarded as a mono-nitrogen analog of the biologically potent necine bases. An in-depth analysis of the stereochemistry of the allylsilane-hydrazonium ion ring closure leading to the fused pyrazole was made possible by use of density functional theoretical study (B3LYP/6-21G*). The stereochemical information gathered from this work proved useful in the multi-step synthesis of two pyrrolizidine natural products (±)-supinidine and (±)-macronecine starting from a substituted 2-pyrrolidinone, readily available from the 5-membered cyclic hydrazide via an alkylation–reduction sequence.

4. Experimental

4.1. General

All melting points are uncorrected. Unless otherwise noted, all reactions were carried out under an inert atmosphere in flame-dried flasks. Solvents and reagents were dried and purified by distillation before use as follows: tetrahydrofuran, toluene, and benzene from sodium benzophenone ketyl; dichloromethane from P_2O_5; DMSO from CaH_2; Et_3N, pyridine from solid KOH; and MeOH, EtOH from Mg. After drying, organic extracts were evaporated under reduced pressure and the residue was chromatographed on silica gel (Acme's, particle size 100–200 mesh) using EtOAc, petroleum ether (60–80 °C) mixture as eluent unless specified otherwise. TLC was recorded using precoated plate (Merck, silica gel 60 F_{254}).

4.1.1. 5-(Trimethylsilyl)-3-hydroxy-1-pentene (10). To a stirred solution of vinylmagnesium bromide (124 mL of 1.3 M in THF, 161 mmol) at −20 °C under argon was added a solution of 3-(trimethylsilyl)propanal[11] (18.90 g, 145 mmol) in THF (75 mL) over a period of 30 min. The reaction mixture was stirred at room temperature overnight and quenched by the addition of ammonium chloride solution (150 mL, sat. aq) at 0 °C. The organic layer was separated and the aqueous layer was extracted with ether (200 mL). The combined ether extract was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the crude product afforded the title compound **10** (18.4 g, 80.6%) as a colorless oil; bp 97–98 °C/5 Torr; mp (3,5-dinitrobenzoate) 53–54 °C; [Found: C, 51.01; H, 5.63; N, 8.01. $C_{15}H_{20}N_2O_6Si$ requires C, 51.12; H, 5.72; N, 7.95%]; R_f [2% EtOAc/petroleum ether (60–80 °C)] 0.38; ν_{max} (liquid film) 3360, 2960, 2930, 1420, 1250, 920, 860, 835 cm^{-1}; δ_H NMR (200 MHz, $CDCl_3$) 5.93–5.76 (1H, m), 5.23–5.09 (2H, m), 4.00 (1H, td, J=12.2, 6.2 Hz), 1.60–1.57 (1H, br s), 1.53–1.47 (2H, m), 0.60–0.44 (2H, m), 0.00 (9H, s); δ_C (50 MHz, $CDCl_3$) 140.8 (CH), 114.7 (CH_2), 75.3 (CH), 32.1 (CH_2), 12.1 (CH_2), −1.9 (3 CH_3).

4.1.2. (*E*)-7-(Trimethylsilyl)-4-heptenoic acid (12). A stirred mixture of **10** (18 g, 113.9 mmol), triethyl orthoacetate (22.9 g, 141.5 mmol) and a catalytic amount of propionic acid (0.30 mL) in toluene (150 mL) was heated at reflux for 8 h in an oil bath under argon. Toluene was removed by distillation and the temperature of oil bath gradually increased to 155 °C over a period of 1.5 h. The reaction mixture was cooled to room temperature and distilled to give ethyl (*E*)-7-(trimethylsilyl)-4-heptenoate (**11**) (21 g, 81%) as a colorless oil; bp 88 °C/0.2 Torr; R_f [petroleum ether (60–80 °C)] 0.87; ν_{max} (liquid film) 2980, 2950, 2900, 1745, 1450, 1375, 1250, 1180, 970, 860, 835 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.60–5.33 (2H, m), 4.11 (2H, q, J=7.2 Hz), 2.36–2.23 (4H, m), 2.06–1.86 (2H, m), 1.25 (3H, t, J=7.2 Hz), 0.57–0.51 (2H, m), −0.03 (9H, s); δ_C (50 MHz, $CDCl_3$) 173.1 (C), 134.3 (CH), 126.3 (CH), 60.1 (CH_2), 34.3 (CH_2), 27.7 (CH_2), 26.6 (CH_2), 16.3 (CH_2), 14.1 (CH_3), −1.7 (3 CH_3). To a stirred solution of **11** (20 g, 87.7 mmol) in methanol (80 mL) was added a solution of 10% methanolic sodium hydroxide (30 mL) dropwise at room temperature. After 2 h the reaction mixture was concentrated in vacuo and diluted with water (30 mL). The aqueous layer was cooled in ice bath, acidified with dilute hydrochloric acid and extracted with ether (150 mL). The combined ether extract was washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo. Distillation of the residue gave the title compound **12** (16 g, 91%) as a colorless thick oil; bp 135 °C (bath) / 0.5 Torr; [Found: C, 60.03; H, 9.95. $C_{10}H_{20}O_2Si$ requires C, 59.94; H, 10.06%]; ν_{max} (liquid film) 2960, 2920, 1715, 1410, 1250, 970, 860, 835 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.58–5.28 (2H, m), 2.45–2.26 (4H, m), 2.02–1.94 (2H, m), 0.60–0.52 (2H, m), −0.02 (9H, s); δ_C (50 MHz, $CDCl_3$) 179.8 (C), 134.7 (CH), 126.0 (CH), 34.1 (CH_2), 27.4 (CH_2), 26.7 (CH_2), 16.3 (CH_2), −1.6 (3 CH_3).

4.1.3. Methyl (*E*)-7-(trimethylsilyl)-4-heptenoylhydrazocarboxylate (13). To a mixture of sodium hydride (7 g, 82.5 mmol, 28% dispersion in oil) in benzene (100 mL) at 0 °C was added a solution of **12** (15 g, 75 mmol) in benzene (50 mL). The mixture was stirred for 30 min before addition of oxalyl chloride (8.16 mL, 93.2 mmol) at 0 °C, followed

by pyridine (4 drops). After 3.5 h, the reaction mixture was filtered through a sintered filter under argon and the filtrate was concentrated in vacuo. The residue was diluted with dichloromethane (50 mL) and was slowly added to a stirred solution of methyl hydrazinocarboxylate (8.80 g, 97.5 mmol), Et_3N (10.6 g, 105.9 mmol) in dichloromethane (100 mL). After 12 h, the reaction mixture was poured into water (150 mL) and extracted with ether (200 mL). The combined ether extract was washed with water (30 mL), brine (60 mL), dried (Na_2SO_4) and concentrated in vacuo to give the title compound **13** (18 g, 88%) as a white crystalline solid, mp 76 °C [ether–pet.ether (40–60 °C)]; [Found: C, 52.74; H, 8.88; N, 10.25. $C_{12}H_{24}N_2O_3Si$ requires C, 52.94; H, 8.88; N, 10.28%]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.53; ν_{max} (film) 3285, 3170, 3020, 2940, 2895, 1715, 1655, 1520, 1430, 1300, 1280, 1260, 1245, 1235, 1050, 970, 865, 840 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.34 (1H, br s), 6.71 (1H, br s), 5.60–5.53 (1H, m), 5.46–5.39 (1H, m), 3.78 (3H, s), 2.38–2.27 (4H, m), 2.06–1.98 (2H, m), 0.60–0.55 (2H, m), 0.00 (9H, s); δ_C (50 MHz, $CDCl_3$) 172.2 (C), 156.9 (C), 135.1 (CH), 126.1 (CH), 53.1 (CH_3), 34.0 (CH_2), 27.9 (CH_2), 26.7 (CH_2), 16.3 (CH_2), −1.6 (3 CH_3).

4.1.4. *N*-Carbomethoxyamino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (14). To a stirred suspension of active MnO_2 (38.8 g, 0.40 mol) in dichloroethane (100 mL) was slowly added a solution of **13** (8.4 g, 30.8 mmol) in dichloroethane (50 mL) at 0 °C under argon and the resulting suspension was sonicated (using BRANSONIC (R) 5210 E-MTH, frequency 47 KHz) for 4 h. The reaction mixture was then filtered through sintered filter and the residue washed with hot ethyl acetate (150 mL). The filtrate was concentrated in vacuo to give the title compound **14** (7.5 g, 89%), which was sufficiently pure for the next step. A part of this solid was recrystallized [Et_2O/petroleum ether (40–60 °C)] for analytical purpose, mp 89 °C; [Found: C, 53.36; H, 8.08; N, 10.37. $C_{12}H_{22}N_2O_3Si$ requires C, 53.30; H, 8.20; N, 10.36%]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.34; ν_{max} (KBr) 3170, 3000, 2950, 2900, 1720, 1695, 1650, 1540, 1455, 1430, 1410, 1315, 1295, 1280, 1250, 1230, 1180, 1145, 1095, 1060, 1040, 1020, 980, 970, 865, 855 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.41 (br s); 5.69 (1H, dt, $J=15.0$, 8.2 Hz), 5.13 (1H, dd, $J=15.0$, 8.8 Hz), 4.69–4.55 (0.3×1 H for *Z*-isomer, m), 4.21–4.05 (0.7×1H, m), 3.73 (3H, s), 2.47–2.39 (2H, m), 2.32–2.24 (1H, m), 1.81–1.74 (1H, m), 1.50 (2H, d, $J=6.9$ Hz), 0.00 (9H, s); δ_C (75 MHz, $CDCl_3$) for *E*-isomer 173.7 (C), 155.6 (C), 133.2 (CH), 126.3 (CH), 62.0 (CH_3), 52.6 (CH), 28.0 (CH_2), 24.7 (CH_2), 22.8 (CH_2), −2.1 (CH_3); δ_C for *Z*-isomer (partial): 131.8 (CH), 125.5 (CH), 55.6 (CH), 24.4 (CH_2), 18.7 (CH_2); *m/z* (ES) 271.1 (100 MH^+), 293.1 (56% MNa^+).

4.1.5. Methyl (3*S, 3a*S**)-3-ethenylhexahydro-6-oxo-1*H*-pyrrolo-[1,2-b]pyrazole-1-carboxylate (17a).** To a mixture of sodium hydride (92 mg, 1.16 mmol, 28% dispersion in oil) in THF (5 mL) at 0 °C was added a solution of **14** (200 mg, 0.74 mmol) in THF (2 mL). The mixture was stirred for 1 h at room temperature before addition of methoxymethyl chloride (0.3 mL, 3.98 mmol) at 0 °C and stirring was continued for 30 min at 0 °C. After 2 h, the reaction mixture was quenched by addition of ammonium chloride solution (5 mL, sat. aq) and extracted with ether (15 mL). The combined ether extract was washed with brine (5 mL), dried (Na_2SO_4) and concentrated in vacuo to afford *N*-carbomethoxy, *N*-methoxyamino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (**15**) (210 mg, 90%) as a light yellow thick oil; δ_H (200 MHz, $CDCl_3$) 5.70–5.50 (1H, m), 5.30–4.55 (3H, m), 4.30–4.18 (1H, m), 3.70–3.68 (3H, m), 3.37 (3H, br s), 2.50–2.10 (3H, m), 1.90–1.60 (1H, m), 1.50–1.30 (2H, m), −0.02 (9H, s). To a stirred solution of **15** (210 mg, 0.67 mmol) in dichloromethane (5 mL), $BF_3 \cdot OEt_2$ (0.2 mL, 1.68 mmol) was added at −20 °C under argon and stirred for 1 h and then it was allowed to attain room temperature. After 4 h, the reaction mixture was poured into brine (5 mL) and extracted with dichloromethane (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue after preparative layer chromatography on silica gel [10% EtOAc/petroleum ether (60–80 °C)] afforded the title compound **17a** (72 mg, 51%) as a light yellow thick oil. For analytical purpose, this compound was further purified by preparative HPLC [Lichrosob (R) Si 60 (7 mm) column (Merc), ethyl acetate–hexane solvent system]; ν_{max} GC-FTIR (270 °C) 2964, 1772, 1737, 1450, 1366, 1176, 925 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.70–5.61 (1H, m, C1′–H), 5.25–5.19 (2H, m, C2′-2*H*), 3.84–3.79 (1H, m, C2–H*H*), 3.79 (3H, s, OC*H*$_3$), 3.60–3.54 (2H, m, C3a–*H*, C2–*H*H), 2.67–2.64 (1H, m, C5–H*H*), 2.56–2.51 (1H, m, C3–*H*), 2.46–2.38 (2H, m, C5–*H*H, C4–H*H*), 2.01–1.91 (1H, m, C4–*H*H); δ_C (100 MHz, $CDCl_3$) 178.7 (C), 157.3 (C), 133.3 (CH), 119.2 (CH_2), 62.7 (CH), 53.9 (CH_2), 53.7 (CH_3), 50.3 (CH), 27.9 (CH_2), 18.8 (CH_2); *m/z* [GC–MS (JLB.COL. SPB1 30M PRG: 130–240 10/MN)] 210 (34 M^+), 155 (35), 151 (30), 127 (100), 123 (48), 101 (38), 68 (35), 59 (39), 55 (38), 41 (47%).

4.1.6. 5-[3-(Trimethylsilyl)-1-propenyl]-2-pyrrolidinone (19). To a mixture of sodium hydride (2.1 g, 24.50 mmol, 28% dispersion in oil) in THF (20 mL) at 0 °C was added a solution of **14** (5.5 g, 20.4 mmol) in THF (20 mL). The mixture was stirred for 1 h at room temperature before addition of methyl iodide (6.37 mL, 102.2 mmol, freshly distilled) at 0 °C and stirring was continued for 30 min at that temperature. After 2 h at room temperature the reaction mixture was quenched by addition of ammonium chloride solution (30 mL, sat. aq) and extracted with ether (90 mL). The combined ether extract was washed with brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo. The crude product was purified by silica gel chromatography [10% EtOAc/petroleum ether (60–80 °C)] to afford *N*-carbomethoxy, *N*-methylamino-5-[3-(trimethylsilyl)-1-propenyl]-2-pyrrolidinone (**18**) (5 g, 86%) as a light yellow thick oil; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.58; ν_{max}($CHCl_3$): 3480, 3285, 2956, 2888, 1688, 1500, 1399, 1251, 1399, 1251, 1150, 1064, 1021, 970, 851 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.74–5.54 (1H, m), 5.19–5.03 (1H, m), 4.34–4.22 (0.3×1H, m, for *Z*-isomer), 4.14– 4.01(0.7×1H, m), 3.74–3.60 (3H, m), 3.14–3.00 (3H, m), 2.40–2.10 (3H, m), 1.90–1.60 (1H, m), 1.52–1.40 (2H, m), −0.04 (9H, s). To liquid NH_3 (~140 mL) was added Li metal (200 mg, 28.57 mmol) and stirred. Within 2 min the color of the solution became blue. To this solution was added a solution of **18** (2.40 g, 8.45 mmol) in ether (12 mL). The color of the solution became grey within 1 min. It was quenched

immediately with dry ethanol (12 mL). The reaction mixture was left for hours so as to allow ammonia to evaporate and then ethanol was removed in vacuo. It was then diluted with water (20 mL) and extracted with ether (60 mL). The combined organic layers were concentrated in vacuo. The residue after silica gel chromatography [20% EtOAc/petroleum ether (60–80 °C)] afforded the title compound **19** (1.6 g, 96%) as a light yellow oil; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.32; ν_{max} (liquid film) 3788, 3215, 3094, 2957, 2893, 1698, 1416, 1344, 1255, 1152, 970, 852 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.65–5.57 (1H, m), 5.26–5.18 (1H, m), 4.13–4.06 (0.83×1H, m), 2.36–2.27 (2H, m), 1.81–1.72 (2H, m), 1.48 (2H, dd, $J=8.1$, 1.1 Hz), 0.00 (9H, s); for *Z*-isomer (partial) 4.50–4.40 (0.17×1H, m); δ_C for *E*-isomer (75 MHz, $CDCl_3$) 178.1 (C), 129.3 (CH), 128.9 (CH), 56.7 (CH), 30.1 (CH_2), 28.8/28.7 (CH_2), 22.5 (CH_2), −2.0 (CH_3); for *Z*-isomer (partial) 127.8 (CH), 50.8 (CH), 30.4 (CH_2), 28.8/28.7 (CH_2), 19.0 (CH_2); *m/z* (EI) 197 (9.6, M^+), 182 (17.5), 166 (5.0), 110 (5.3), 97 (6.0), 84 (15.7), 82 (9.4), 80 (7.4), 75 (25.1), 74 (13.3), 73 (100%, Me_3Si); HRMS (ES): MH^+, found 198.1309. $C_{10}H_{20}NOSi$ requires 198.1308.

4.1.7. Methyl 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1*H*-pyrrolyl]ethanoate (20). To a stirred solution of **19** (3.9 g, 19.7 mmol) in THF (40 mL) was added BuLi (7.5 mL of 2.5 M, 18.76 mmol) at −78 °C and stirred for 30 min. Then it was allowed to attain room temperature and stirring was continued for an additional 1 h. Then methyl bromoacetate (1.86 mL, 19.7 mmol) was added followed by HMPA (2 mL). After 4 h, the reaction mixture was quenched with ammonium chloride solution (10 mL, sat. aq) and extracted with ether (30 mL). The combined ether extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude residue by column chromatography [15% EtOAc/petroleum ether (60–80 °C)] gave the title compound **20** (3.5 g, 74%, based on recovered starting material) as a pale yellow thick oil; R_f [5% EtOAc/petroleum ether (60–80 °C)] 0.32; ν_{max} (liquid film) 3477, 2956, 2893, 1751, 1702, 1547, 1427, 1254, 1208, 1063, 1016, 978, 850 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 5.67 (1H, dt, $J=15.0$, 8.2 Hz), 5.06 (1H, dd, $J=15.0$, 9.0 Hz), 4.30 (1H, d, $J=17.5$ Hz), 4.14–4.12 (0.85×1H, td, $J=8.0$, 7.4 Hz), 3.71 (3H, s), 3.65 (1H, d, $J=17.5$ Hz), 2.45–2.39 (2H, m), 2.32–2.23 (1H, m), 1.79–1.67 (1H, m), 1.49 (2H, d, $J=8.2$ Hz), 0.00 (9H, s); for *Z*-isomer (partial) 4.62–4.50 (0.15×1H, m), 3.63 (1H, d, $J=17.5$ Hz); δ_C for *E*-isomer (50 MHz, $CDCl_3$:CCl_4, 3:1) 175.1 (C), 169.1 (C), 132.8 (CH), 127.4 (CH), 61.5 (CH), 51.8 (CH_3), 41.5 (CH_2), 30.0/29.9 (CH_2), 26.5 (CH_2), 22.8 (CH_2), −2.0 (3 CH_3); for *Z*-isomer (partial) 175.2 (C), 169.3 (C), 131.8 (CH), 126.3 (CH), 54.7 (CH), 30.0/29.9 (CH_2), 26.1 (CH_2), 18.8 (CH_2); HRMS (ES): MH^+, found 270.1521. $C_{13}H_{24}NO_3Si$ requires 270.1520.

4.1.8. 2-[2-Oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1*H*-pyrrolyl]ethanoicacid (21). To a stirred solution of **20** (4.2 g, 15.6 mmol) in methanol (90 mL) was slowly added a solution of 10% methanolic sodium hydroxide (9 mL) at room temperature. After 2.5 h the reaction mixture was concentrated in vacuo and diluted with water (20 mL). The aqueous layer was washed with ether (20 mL) to remove any organic impurities and then the aqueous layer was cooled and acidified with dilute hydrochloric acid and extracted with ether (60 mL). The combined ether layer was washed with brine (20 mL), dried (Na_2SO_4) and concentrated in vacuo to give the title compound **21** (3.40 g, 85%) as a white crystalline solid; mp 100 °C, [50% EtOAc/petroleum ether (60–80 °C)]; [Found: C, 56.45; H, 8.28; N, 5.46. $C_{12}H_{21}NO_3Si$ requires C, 56.44; H, 8.29; N, 5.84%]; ν_{max} (KBr) 3879, 3823, 3722, 3628, 3437, 3378, 3253, 2964, 2708, 1749, 1640, 1556, 1455, 1410, 1340, 1259, 1187, 1035, 978 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 6.39 (1H, br s), 5.71 (1H, dt, $J=15.0$, 8.2 Hz), 5.06 (1H, dd, $J=15.0$, 9.1 Hz), 4.29 (1H, d, $J=17.7$ Hz), 4.14 (0.86×1H, td, $J=8.1$, 7.3 Hz), 3.67 (1H, d, $J=17.7$ Hz), 2.51– 2.42 (2H, m), 2.32–2.21 (1H, m), 1.80–1.67 (1H, m), 1.50 (2H, d, $J=8.1$ Hz), 0.0 (9H, s); For *Z*-isomer (partial) 4.59–4.56 (0.14×1H, m), 4.26 (d, $J=17.7$ Hz); δ_C (50 MHz, $CDCl_3$: CCl_4, 3:1) 176.2 (C), 171.6 (C), 133.3 (CH), 127.0 (CH), 61.9 (CH), 41.8 (CH_2), 29.9 (CH_2), 26.5 (CH_2), 22.9 (CH_2), −1.9 (3 CH_3); δ_C for *Z*-isomer (partial) 132.3 (CH), 125.9 (CH), 55.2 (CH), 18.9 (CH_2); HRMS (ES): MH^+, found 256.1362. $C_{12}H_{22}NO_3Si$ requires 256.1363.

4.1.9. Ethyl 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]-tetrahydro-1*H*-pyrrolyl]ethanethioate (22). To a stirred solution of **21** (1.48 g, 5.8 mmol) in dichloromethane (15 mL) was added DMAP (64 mg), ethanethiol (1.72 mL, 23.28 mmol) and DCC (2.4 g, 11.64 mmol) at 0 °C. After 5 min it was warmed to room temperature and stirred for 3 h. Then the precipitated urea derivative was filtered off and the filtrate was concentrated to one fourth of the total volume in vacuo. The precipitate reappeared, was filtered again to make it free from any further precipitate of urea derivative. The filtrate was then diluted with dichloromethane (20 mL), washed twice with 0.5 N hydrochloric acid followed by sodium bicarbonate (30 mL, sat. aq) and dried (Na_2SO_4). The solvent was removed in vacuo. The crude product was purified by column chromatography [10% EtOAc/petroleum ether (60–80 °C)] to give the title compound **22** (1.32 g, 76%) as a colorless thick oil; R_f [10% EtOAc/petroleum ether (60–80 °C)] 0.3; ν_{max}($CHCl_3$) 3509, 3137, 2942, 2857, 2132, 1699, 1451, 1636, 1354, 1305, 1254, 1139, 1151, 1081, 1039, 955, 891, 848 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.65 (1H, dt, $J=15.0$, 8.2 Hz), 5.05 (1H, dd, $J=15.0$, 9.0 Hz), 4.42 (1H, d, $J=17$ Hz), 4.20–4.0 (1H, m), 3.74 (1H, d, $J=17$ Hz), 2.89 (2H, q, $J=7.4$ Hz), 2.50–2.20 (3H, m), 1.85–1.65 (1H, m), 1.48 (2H, d, $J=8.1$ Hz), 1.25 (3H, t, $J=7.4$ Hz), 0.00 (9H, s); For *Z*-isomer (partial) 4.60–4.40 (m), 4.41 (d, $J=17$ Hz), 3.71 (d, $J=17$ Hz); δ_C (50 MHz, $CDCl_3$/CCl_4 3:1) 195.7 (C), 175.0 (C), 133.0 (CH), 127.0 (CH), 61.7 (CH), 49.8 (CH_2), 29.7 (CH_2), 26.4 (CH_2), 22.9 (CH_2), 22.9 (CH_2), 14.6/ 14.5 (CH_3), −1.9 (3 CH_3); δ_C for *Z*-isomer (partial) 132.1 (CH), 125.9 (CH), 54.9 (CH), 34.9 (CH_2), 29.9 (CH_2), 26.2 (CH_2), 25.4 (CH_2), 18.9 (CH_2), 14.6/14.5 (CH_3); HRMS (ES): MH^+, found 300.1448. $C_{14}H_{26}NO_2SiS$ requires 300.1448.

4.1.10. (1*S, 2*S**, 7a*S**)-1-Ethenyl-2-hydroxy-5-oxohexahydro-1*H*-pyrrolizine (24).** To a stirred solution of **22** (440 mg, 1.47 mmol) and 10% Pd–C (120 mg) in dichloromethane (50 mL) was added Et_3SiH (0.70 mL, 4.42 mmol) at room temperature under argon atmosphere. Stirring was continued for 25 min. The catalyst was filtered

off through a sintered funnel and the residue washed with dichloromethane (10 mL). The filtrate was concentrated in vacuo and purified quickly by chromatography [50% EtOAc/petroleum ether (60–80 °C)] to give 2-[2-oxo-5-[3-(trimethylsilyl)-1-propenyl]tetrahydro-1*H*-pyrrolyl]ethanal (**23**) (330 mg, 94%) as a colorless thick oil; ν_{max} (liquid film) 2946, 2623, 1707, 1666, 1548, 1451, 1251, 1156 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 9.54 (1H, m), 5.65 (1H, dt, $J=15.0$, 7.9 Hz), 5.06 (1H, dd, $J=15.0$, 9.0 Hz), 4.25 (1H, d, $J=$ 18.4 Hz), 4.15–4.00 (1H, m), 3.82 (1H, d, $J=18.4$), 2.5–2.2 (3H, m), 1.90–1.60 (1H, m), 1.50 (2H, d, $J=8.2$ Hz), 0.02 (9H, s). To a stirred solution of **23** (130 mg, 0.54 mmol) in dichloromethane (2 mL) was added $BF_3{\cdot}OEt_2$ (0.20 mL, 1.63 mmol) at −20 °C. The mixture was stirred for 1 h and then it was allowed to attain room temperature. After 4 h, the mixture was poured into brine (2 mL) and extracted with dichloromethane (15 mL). The combined organic layers were dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by preparative thin layer chromatography [25%, 50% EtOAc/petroleum ether (60–80 °C)] to afford the title compound **24** (40 mg, 44%) contaminated with three other diastereomers (LCMS) as a semi solid mass. Preparative HPLC [Lichrosob (R) Si 60 (7 mm) column (Merc), (50% EtOAc/hexane + 2% MeOH)] gave pure **24** as a white solid, mp 100.2 °C (MeOH); R_f (EtOAc) 0.15; ν_{max} (KBr) 3667, 3083, 2929, 1673, 1428, 1292, 1211, 1174, 1091, 931, 864, 790, 668, 574 cm^{-1}; δ_H (500 MHz, D_2O) 5.62 (1H, ddd, $J=$ 17, 10, 8 Hz, C1′–H), 5.09 (1H, d, $J=17$ Hz, C2′–H*H*), 5.05 (1H, d, $J=10$ Hz, C2′–*H*H), 4.28–4.20 (1H, m, C2–*H*), 3.74–3.67 (1H, m, C7a–*H*), 3.37 (1H, dd, $J=11.5$, 8.5 Hz, C3–H*H*), 3.03 (1H, dd, $J=11.5$, 7 Hz, C3–*H*H), 2.61–2.51 (1H, m, C6–H*H*), 2.30–2.23 (1H, m, C6–*H*H), 2.15–2.10 (1H, m, C7–H*H*), 2.09–2.07 (1H, m, C1-*H*), 1.78–1.69 (1H, m, C7-*H*H); δ_C (125 MHz, D_2O) 177.7 (C, C-5), 134.7 (CH, C-1′), 119.0 (CH_2, C-2′), 77.1 (CH, C-2), 64.6 (CH, C-7a), 57.6 (CH, C-1), 47.7 (CH_2, C-3), 33.9 (CH_2, C-6), 25.3 (CH_2, C-7); HRMS (FAB): MH^+, found 168.1029. $C_9H_{14}NO_2$ requires 168.1025.

4.1.11. (1*S, 2*S**, 7a*S**)-5-Oxo-1-vinylhexahydro-1*H*-pyrrolizine-2yl 4-nitrobenzoate (26).** To a stirred solution of **24** (crude product containing three other diastereomers, 120 mg, 0.718 mmol), triphenylphosphine (756.0 mg, 2.88 mmol) and 4-nitrobenzoic acid (478 mg, 2.85 mmol) in THF (20 mL) was added slowly a solution of diethyl azodicarboxylate (DEAD, 0.45 mL, 2.80 mmol) at 0 °C. The resulting yellow solution was allowed to attain to room temperature, stirred in an aluminum foil-covered flask for 30 h and then concentrated in vacuo. The resulting thick oil was diluted with dichloromethane (30 mL), washed with sodium bicarbonate solution (20 mL, sat. aq), brine (20 mL) and dried (Na_2SO_4). Solvent was removed under reduced pressure and the crude product was purified by column chromatography [20%, 40% EtOAc/petroleum ether (60–80 °C)] to afford 190 mg of solid product, which was further purified by preparative thin layer chromatography [40% EtOAc/petroleum ether (60–80 °C)] to give the title compound **26** (120 mg, 53%) as a yellowish white solid; mp 103–104 °C [EtOAc/petroleum ether (60–80 °C)]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.69; ν_{max} (liquid film) 3439, 3075, 2934, 2886, 2732, 1723, 1688, 1602, 1524, 1414, 1347, 1276, 1113, 1059, 1002, 931, 852, 772, 749, 712 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.33–8.26 (2H, m), 8.20–8.14 (2H, m), 5.89–5.71 (2H, m), 5.28–5.19 (2H, m), 4.27–4.11(1H, m), 4.04 (1H, dd, $J=13.8$, 5.3 Hz), 3.27 (1H, d, $J=13.8$ Hz), 2.83–2.70 (1H, m), 2.56–2.31 (2H, m), 1.94–1.78 (2H, m); δ_C (50 MHz, $CDCl_3$) 175.2 (C), 163.6 (C), 150.7 (C), 134.9 (C), 130.6 (2 CH), 123.6 (CH), 119.6 (CH_2), 79.0 (CH), 63.1 (CH), 54.3 (CH), 49.0 (CH_2), 33.9 (CH_2), 24.8 (CH_2); HRMS (EI): M^+, found 316.1051. $C_{16}H_{16}N_2O_5$ requires 316.1059.

4.1.12. (1*S, 2*R**, 7a*S**)-5-Oxo-1-vinylhexahydro-1*H*-pyrrolizine-2yl 4-nitrobenzoate (27).** To a stirred solution of **24** (crude product containing three other diastereomers, 30 mg, 0.179 mmol) in dichloromethane (5 mL) was added DMAP (11 mg, 0.09 mmol), pyridine (0.06 mL, 0.776 mmol) and 4-nitrobenzoyl chloride (109.3 mg, 0.55 mmol) and stirred for 5 h at room temperature. Then it was poured into dichloromethane (50 mL), washed with sodium bicarbonate solution (30 mL, sat. aq), 1 N hydrochloric acid (30 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4) and concentrated in vacuo. The crude product was then purified by preparative thin layer chromatography [40% EtOAc/petroleum ether (60–80 °C)] to afford the title compound **27** (40 mg, 70.5%) as a yellowish white solid; mp 101–102 °C [50% EtOAc/etroleum ether (60–80 °C)]; R_f [40% EtOAc/petroleum ether (60–80 °C)] 0.66; ν_{max} (KBr pellet) 3071, 2959, 2896, 1727, 1684, 1605, 1524, 1461, 1404, 1352, 1279,1167, 114, 1006, 931, 871 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 8.29 (2H, d, $J=8.6$ Hz), 8.15 (2H, d, $J=8.7$ Hz), 5.94–5.64 (1H, m), 5.59–5.41 (1H, m), 5.38–5.19 (2H, m), 3.95–3.77 (1H, m), 3.75–3.65 (2H, m), 2.85–2.32 (4H, m), 2.05–1.70 (1H, m); δ_C (50 MHz, $CDCl_3$) 175.2 (C), 164.0 (C), 150.7 (C), 134.5 (C), 133.5 (CH), 130.7 (CH), 123.5 (CH), 119.0 (CH_2), 80.3 (CH), 63.2 (CH), 55.6 (CH), 46.9 (CH_2), 32.8 (CH_2), 24.9 (CH_2); HRMS (EI): M^+, found 316.1053. $C_{16}H_{16}N_2O_5$ requires 316.1059.

4.1.13. (7a*S)-3-Oxo-1-2,3,5,7a-tetrahydro-1*H*-pyrrolizine-7-carbaldehyde (29).** To a stirred solution of olefin **26** (50 mg, 0.158 mmol) in dichloromethane (10 mL) ozone was bubbled at −78 °C until a faint blue color persisted. Triphenylphosphine (50 mg, 0.190 mmol, 1.2 equiv) was then added at that temperature, and the reaction mixture was allowed to attain room temperature. After 12 h, the mixture was concentrated in vacuo and crude product was purified by preparative thin layer chromatography [EtOAc] to afford the title compound **29** (12 mg, 50%) as a white crystalline solid; mp 106–107 °C [EtOAc/petroleum ether (60–80 °C)]; R_f (EtOAc) 0.14; ν_{max} (CH_2Cl_2) 3812, 3748, 3379, 2925, 1678, 1411, 1230, 1062, 802, 658, 552 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 9.78 (1H, br s), 6.88 (1H, br s), 4.84 (1H, br s), 4.66 (1H, br d, $J=18.8$ Hz), 3.87 (1H, br d, $J=18.8$ Hz), 2.85–2.60 (2H, m), 2.42–2.20 (1H, m), 2.10–1.75 (1H, m); δ_C (50 MHz, $CDCl_3$) 187.0, 178.4, 146.3, 146.2, 65.0, 50.3, 33.3, 29.2; HRMS (EI): M^+ found 151.0629. $C_8H_9NO_2$ requires 151.0633.

4.1.14. Supinidine (8). To a stirred solution of **29** (10 mg, 0.066 mmol) in THF (5 mL) was added Red-Al (65+ wet% in toluene, 1 mL, excess) slowly at −78 °C. After 5 min the clear solution was allowed to attain room temperature and stirred for 0.5 h, during which the color changed from yellow to red. The resulting solution was then heated at

reflux for 3 h. The mixture was cooled to room temperature and quenched with water (0.4 mL), 2 N sodium hydroxide (0.3 mL) and water (0.6 mL) and then it was diluted with THF (3 mL) and stirred for 5 min. The resulting solution was filtered, concentrated and crude product was purified by preparative thin layer chromatography [SiO_2, 10/10/1 CH_2Cl_2 /MeOH/NH_4OH] to give the title compound (**8**) (7 mg, 76%) as yellow oil, mp (picrate) 123–124 °C [ethanol] (lit.[9e] 124.5–125 °C); R_f (CH_2Cl_2: MeOH: NH_4OH, 10:10:1) 0.25; ν_{max} (CH_2Cl_2) 3371, 3300, 2957, 1613, 1455, 1338, 1193, 1087, 1050, 894, 857, 800 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 5.48 (1H, br s), 4.25–4.07 (3H, m), 3.86 (1H, d, $J=15$ Hz), 3.30 (1H, br d, $J=15$ Hz), 3.11–3.01 (1H, m), 2.74 (1H, O*H*, br s), 2.57–2.45 (1H, m), 2.03–1.88 (1H, m), 1.80–1.67 (2H, m), 1.57–1.41 (1H, m); δ_C (50 MHz, $CDCl_3$) 144.2, 120.7, 70.9, 61.8, 59.6, 56.4, 30.2, 25.7.

4.1.15. Macronecine (9). To a stirred solution of olefin **26** (80 mg, 0.253 mmol) in dichloromethane (10 mL) ozone was bubbled at −78 °C until a faint blue color persisted. Then solvent was removed at −30 °C; THF (8 mL) was added to it at −78 °C and was followed by Red-Al (65+ wet% in toluene, 5 mL, excess) and the cold bath was allowed to attain room temperature. The resulting reaction mixture was stirred at room temperature for 0.5 h during which time the solution color changed from yellow to red. The red solution was heated to reflux for 3 h. The mixture was cooled to room temperature, quenched with water (0.6 mL), 2 N sodium hydroxide (0.5 mL) and water (1 mL). Then the reaction mixture was diluted with THF (3 mL) and stirred for 5 min. The resulting solution was filtered, concentrated to 2 mL and the crude product was purified by preparative thin layer chromatography [SiO_2, 10/10/1 CH_2Cl_2/MeOH/NH_4OH as developing solvent] to give the title compound (**9**) (13 mg, 33%) as a white solid, mp 107–108 °C (lit.[10a] 109–110 °C); R_f (10/10/1 CH_2Cl_2/MeOH /NH_4OH,) 0.18; ν_{max} (CH_2Cl_2) 3356, 2949, 1452, 1319, 1091, 1037, 764, 613, 564 cm^{-1}; δ_H ($CDCl_3$, 200 MHz) 4.54–4.36 (1H, m), 4.11 (2H, br s), 3.85–3.71 (2H, m), 3.60–3.39 (1H, m), 3.18 (1H, d, $J=11$ Hz), 3.04–2.80 (1H, m), 2.73–2.40 (2H, m), 2.04–1.63 (4H, m), 1.63–1.39 (1H, m); δ_C (50 MHz, $CDCl_3$) 75.1, 63.9, 63.0, 60.4, 54.9, 52.5, 31.2, 25.4; HRMS (ES): MH^+ found 158.1175. $C_8H_{16}NO_2$ requires 158.1175.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2004.11.046

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Multiblock copolymer synthesis via controlled radical polymerization in aqueous dispersions. Part 1: Synthesis of *S-tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamates

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Abstract—In a novel two- or three-step synthetic route, *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) is reacted at low temperature with various alkyl chloroformates to form various *S-tert*-alkyl-*N*,*N*-alkoxycarbonylmethyl-dithiocarbamate RAFT agents. Also an alternative and novel synthetic route towards *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate), is proposed.

1. Introduction

In a forthcoming series of papers, the synthesis of multiblock copolymers via controlled radical polymerization in aqueous dispersions will be discussed. These polymers can be used, for example, as compatibilizers for polymer blends and composites, or as pressure-sensitive adhesives, which can be applied to the substrates directly from the waterborne latex. Various techniques have been reported in literature for the synthesis of (multi)block copolymers, for example, anionic polymerization,[1] polycondensation of telechelic polymers,[2,3] the iniferter method[4,5] and more recently several techniques allowing controlled (or 'living') radical polymerization.[6–10] However, of these techniques only the RAFT process allows the well-controlled synthesis of (multi)block copolymers in aqueous dispersions.[9,11–14] Therefore, the RAFT process has been utilized in this work. The number of polymerization steps needed to create multiblock copolymers is dependent on the number of RAFT moieties per controlling molecule/polymer chain. Most of the research in block copolymer synthesis via the RAFT process has been performed employing mono- and bifunctional RAFT agents.[15–24] The concept of this work, however, has been to employ multifunctional RAFT agents, which allow the synthesis of multiblock copolymers in one or two polymerization steps, depending on the nature of the Z group (see Fig. 1). If Z in compounds **1** (dithiocarboxylate) or **2** (trithiocarboxylate) is a low molecular weight moiety (e.g., butyl), then two polymerization steps are required to obtain a (multi)block copolymer. If Z is a macromolecular moiety, then only one polymerization step is required. Recently, the synthesis of sequence ordered polystyrene via compound **2** was reported by Motokucho.[25] However, these authors reported that the synthesis of

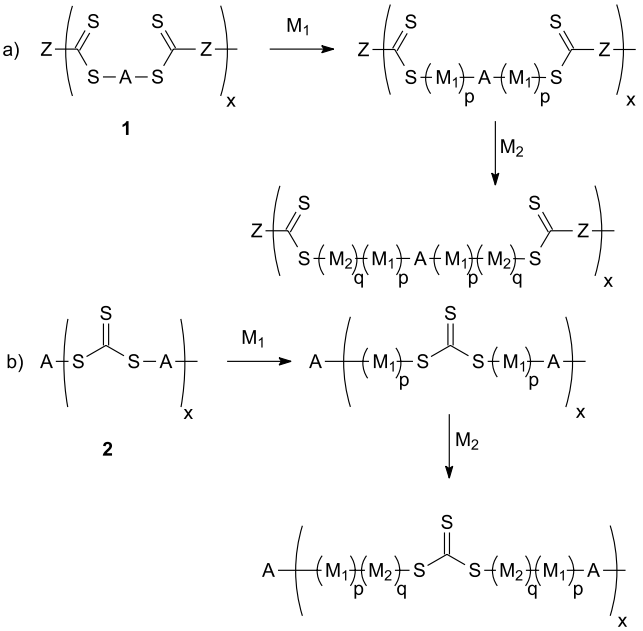

Figure 1. Multiblock copolymer synthesis via a multifunctional RAFT agent. (a) Multiblock copolymer synthesis starting from a symmetrical, multifunctional RAFT agent **1**. (b) Multiblock copolymer synthesis starting from a symmetrical multifunctional trithiocarbonate **2**.

Keywords: Block copolymer synthesis; Alkyl chloroformates; Dithiocarbamates; Living radical polymerization.
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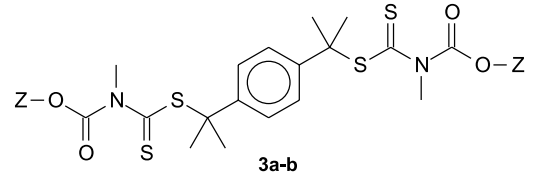
compound **2** is cumbersome. Moreover, only primary alkyl leaving groups have been used, leading to relatively high polydispersities of the resulting polymers.

In this work, the *S*-alkyl-*N*,*N*-alkoxycarbonylmethyldithiocarbamate RAFT moiety has been employed, for three major reasons. The first reason is that this type of RAFT agent has a high transfer constant.[25–32] The second reason involves the incorporation of a macromolecule into the RAFT agent during synthesis: the classical synthetic routes towards RAFT agent synthesis[10,33,34] imply the incorporation of a macromolecule into the RAFT agent during the first synthesis step. Since RAFT agent synthesis generally involves three reaction steps, this renders purification of the macromolecular RAFT agent extremely difficult. However, in this paper a novel synthetic route towards *S*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamate RAFT agents is reported that allows the incorporation of macromolecules during the final reaction step. The third reason for choosing the *S*-alkyl-*N*,*N*-alkoxycarbonylmethyldithiocarbamate moiety is related to the synthesis of multifunctional RAFT agents: the classical synthetic routes towards RAFT agents generally involve low to medium yield reaction steps, which subsequently implies a low final yield. The synthetic route that is reported in this paper allows the synthesis of a linear, symmetrical multifunctional RAFT agent, via the step-growth polymerization principle.

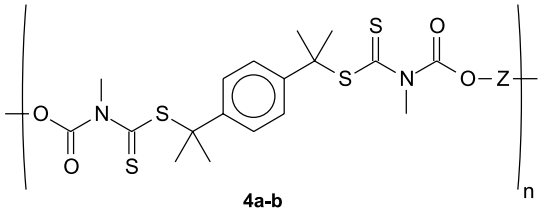
The RAFT agents that have been used in our study on the polymerization of acrylic monomers are depicted in Figure 2. Bifunctional RAFT agents **3** [*S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*,*N*-alkoxycarbonylmethyldithiocarbamate)] were synthesized because the mini-emulsion polymerization of acrylic monomers mediated with an *S*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamate RAFT agent has not yet been described. These polymerizations



3a-b

3a: Z = -$CH_2CH_2CH_2CH_3$

3b: Z = poly(ethylene-*co*-butylene)- (Kraton L1203)



4a-b

4a: Z = -$(CH_2)_{10}$-

4b: Z = -poly(ethylene-*co*-butylene)- (Kraton L2203)

Figure 2. Bi- and multifunctional *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamates studied in this work. Bifunctional RAFT agents **3**, with varying length of the Z group are used to study the viability of the *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamate moiety to control polymerization of various acrylates in solution and emulsion. RAFT agents **4**, either with a low molecular weight or a macromolecular Z group are studied on their ability to synthesize multiblock copolymers.

will be discussed in two forthcoming papers. Compounds **4** [poly(*S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*,*N*-alkoxycarbonylmethyldithio-carbamate))] are the multifunctional RAFT agents. The synthesis of multiblock copolymers with this compound will be discussed in two future papers. These compounds do not suffer from the disadvantages of the traditional RAFT agents. Whereas the more classical RAFT agents exhibit a dark red to pink color and an extremely bad smell, the *S*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamates described in this work are only slightly yellow and have a faint, sweet smell.

The novel, extremely versatile synthetic route is based on two bifunctional precursors, which upon condensation form the RAFT moiety. This approach avoids the cumbersome three-step reaction towards most RAFT agents and reduces the total number of synthetic steps needed. Moreover, this synthetic route allows the incorporation of a tertiary leaving group in high yield. The novel synthetic route is based on the route proposed by Allainmat et al.,[35] which implies the reaction of a chloroformate with a primary *S*-alkyl dithiocarbamate. This route is depicted in Figure 3, applied to the RAFT agents that have been synthesized in this work. Employing this route, the synthesis of a macromolecular or a multifunctional RAFT agent can be performed in a maximum of three convergent reaction steps: the synthesis of bifunctional dithiocarbamate **5**, the synthesis of chloroformates **6b** and **7a–b** (**6a**, that is, butyl chloroformate, is commercially available), and the (poly)condensation reaction of dithiocarbamate **5** with chloroformates **6a–b** or **7a–b**. Unfortunately, Allainmat et al.[35] only reported the use of primary *S*-alkyl dithiocarbamates, and not of tertiary *S*-alkyl dithiocarbamates in this synthetic route. In the following sections the syntheses of compound **5**, **6b** and **7a–b** are described in detail. Then, the synthetic route proposed by Allainmat et al.[35] is modified and applied to the synthesis of *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamates.

Two of the RAFT agents, of which the synthesis is described in this paper, are based on either Kraton® L-1203 or on Kraton® L-2203. Kraton is the trade name of fully hydrogenated, linear poly(butadiene), carrying primary hydroxyl groups on either one (L-1203) or both (L-2203) chain ends. The number average molar mass of both polymers, according to the manufacturer, is 4000 g mol^{-1}. Both non-crystalline Kraton grades have a glass transition temperature below −50 °C, and, because of their low molar masses, both compounds are viscous liquids.

2. Results and discussion

2.1. Synthesis of *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate)

For the synthesis of *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate), that is, compound **5**, the route reported by Monde et al.[36] was employed. Using this method, sodium alkylthiolate salts were reacted with various isothiocyanates, resulting in excellent yields while short reaction times were employed. To the best of our knowledge, however, no reports are available on the reaction of tertiary thiolate salts with isothiocyanates.

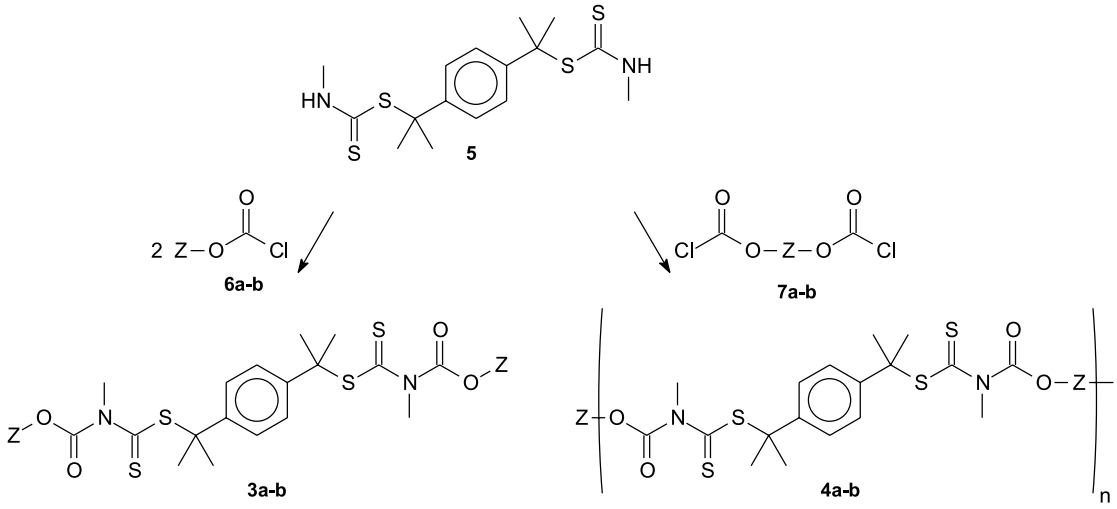


Figure 3. Allainmat's synthetic route applied to the RAFT agents that have been studied in this work. Bifunctional dithiocarbamate **5** is reacted with monofunctional chloroformate **6a–b** to form bifunctional RAFT agents **3a–b**. By using a bifunctional chloroformate **7a–b**, a polycondensation reaction of this compound with bifunctional dithiocarbamate **5** allows the synthesis of multifunctional RAFT agent **4a–b**.

However, we successfully modified Monde's route, thereby enabling it to synthesize tertiary *S*-alkyl dithiocarbamates. This method, however, requires the use of tertiary sodium thiolate salts. These compounds were synthesized according to the procedure reported by Lee et al.[37] This procedure involves the reaction of a tertiary alkyl alcohol with thiourea, and subsequent hydrolysis to form the sodium thiolate salt.

The entire synthetic route towards compound **5** is depicted in Figure 4. In the first reaction step, diol **8**, thiourea and hydrobromic acid were reacted according to the procedure reported by Lee et al.,[37] to form bifunctional dithiouronium salt **9**. The method reported by Lee et al.,[37] then implies the hydrolysis of bifunctional dithiouronium salt **9** to the dithiol with 2 equiv of aqueous sodium hydroxide. However, as was mentioned above, the route proposed by Monde et al.,[36] implies the addition of a sodium thiolate salt to an alkyl isothiocyanate. The tertiary dithiol, formed via Lee's procedure,[37] should therefore be hydrolyzed to dithiolate salt **10** in a separate reaction step. We found that it was also possible to hydrolyze dithiouronium salt **9** directly to dithiolate anion **10**, using 6 equiv of aqueous sodium hydroxide. Moreover, a methanolic solution of methyl isothiocyanate could be added to the dithiolate anion **10** solution without isolating the dithiolate sodium salt first. After addition of methyl isothiocyanate to the reaction mixture, dithiocarbamate **5** readily precipitated out of the solution and could be collected easily by filtration. After recrystallization, the product was pure and compound **5** was obtained in an overall yield of 60%. With this approach, we thus succeeded in reducing the number of reaction steps required for this synthesis from three to two.

2.2. Chloroformate synthesis

In this work, we opted for the use of a phosgene solution in toluene. To ensure safe reaction conditions, all reactions involving a phosgene solution were performed under strict exclusion of air by having a stream of argon passing through the reaction mixture at all times. All gases that left the reactor were passed through a solution of sodium hydroxide in order to destroy phosgene and hydrogen chloride passing along with the argon. Various mono- and bifunctional (macromolecular) alcohols were treated with a 20% phosgene solution in toluene. The reaction mechanism and the various synthesized chloroformates are depicted in Figure 5. It should be noted that the formation of the

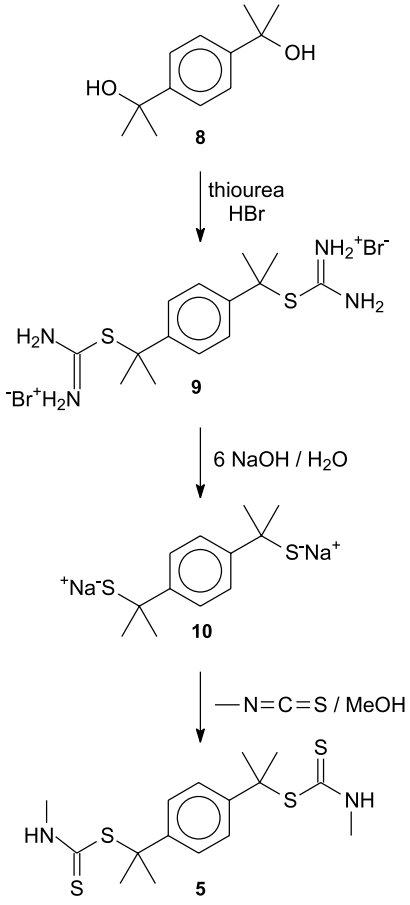


Figure 4. Novel synthetic route towards *S-tert*-alkyl-*N*-alkyldithiocarbamates.

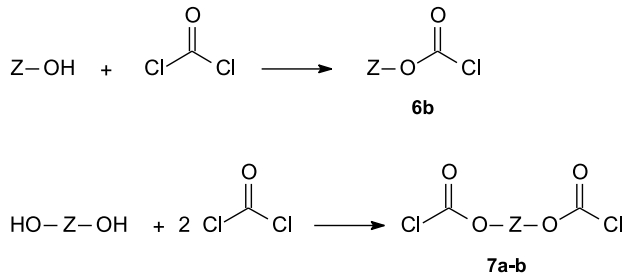


Figure 5. Chloroformate synthesis employing a 20% phosgene solution in toluene. A slight excess of phosgene must be used in order to prevent the reaction between the chloroformate and the alcohol to form a carbonate.

respective carbonates or polycarbonates, formed by a reaction of two alcohol molecules with one phosgene molecule, cannot be entirely avoided, since for safety reasons only a slight excess of phosgene was used. After the reaction, in all cases the yields were close to 100%. In the case of Kraton® chloroformate **6b**, a minor amount of di(Kraton®) carbonate was found after the reaction with GPC analysis. However, this is only a few percent, and could not be observed in the ^{1}H NMR and ^{13}C NMR spectra, due to the low end-group concentration in the sample. The reaction of various alcohols with a phosgene solution was performed with and without the use of a proton trap, but no differences could be observed in reaction yield or product purity.

2.3. Synthesis of *S*-alkyl-*N*,*N*-alkoxycarbonyl-methyldithiocarbamates

After describing the synthesis of all the required compounds for the (poly)condensation reaction between bifunctional dithiocarbamate **5** and various mono- and bifunctional chloroformates, we will focus on the condensation reaction itself. As was reported earlier, Allainmat et al., only used primary *S*-alkyl-*N*-alkyldithiocarbamates in this reaction.[35] Although not much difference in reactivity towards chloroformates was expected between primary and tertiary *S*-alkyl-*N*-alkyldithiocarbamates, we found that the reaction pathway did require some optimization, especially in the reaction of dithiocarbamate **5** with bifunctional chloroformates.

The synthetic route towards bifunctional *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylmethyl-dithiocarbamates is depicted schematically in Figure 6, together with the optimal reaction conditions. Dithiocarbamate **5** was reacted with monofunctional chloroformates **6a**–**b** to form bifunctional RAFT agents **3a**–**b**. In this reaction, triethylamine was used to trap the hydrogen chloride that is formed upon reaction. Triethylamine hydrochloride precipitated from the solution, thus forcing the reaction equilibrium towards the reaction products. The highest yield (85–90%) was obtained when performing the reaction at −20 °C in THF for 48 h, using 5 equiv of triethylamine as the proton trap. The remaining 10–15% of the obtained crude reaction mixture was compound **11a**–**b**, which resulted from addition of only one chloroformate molecule to dithiocarbamate **5**. The extended reaction times that were required can be explained by the fact that the reaction in Figure 6 proceeds via intermediate *N*-alkoxycarbonyl triethylammonium chloride, which is formed by the reaction of triethylamine with a chloroformate, and in which the carbonyl group is activated for reaction with **5**. The *N*-alkoxycarbonyl triethylammonium chloride salt is only moderately soluble in tetrahydrofuran, and precipitated partially out of the solution. This salt gradually redissolved and thus ensured complete reaction.

The full potential of the synthetic route introduced above is shown when it is applied to the synthesis of multifunctional RAFT agents. As was mentioned earlier, it is possible to synthesize multifunctional RAFT agents starting from *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) **5**, and bifunctional chloroformates **7a**–**b** via a polycondensation reaction. The reaction scheme is presented in Figure 7. In a first series of experiments, equimolar quantities of 1,4-butanediol bischloroformate

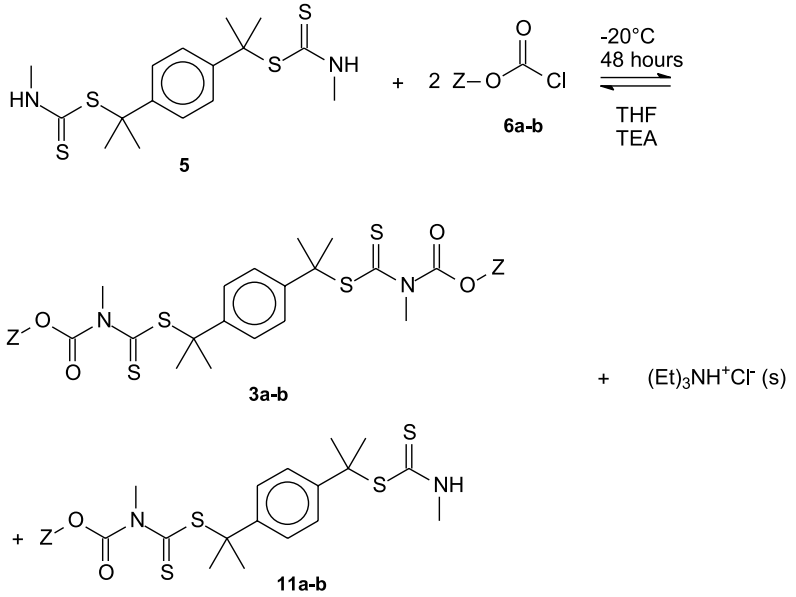


Figure 6. Synthesis of bifunctional RAFT agents. The reaction proceeds optimally when performed at −20 °C over 48 h, employing 5 equiv of the proton trap.

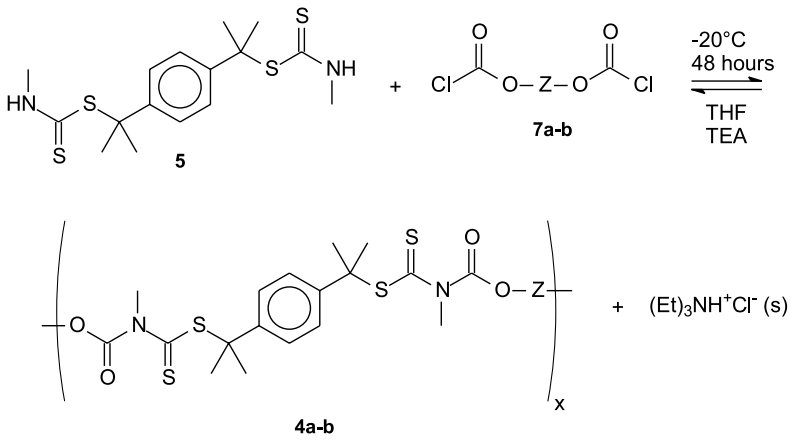


Figure 7. Synthesis of multifunctional RAFT agents. The reaction proceeds optimally when performed at −20 °C over 48 h, employing 5 equiv of the proton trap. However, the chain length of the Z group has a major influence on the conversion of the functional groups.

(commercially available) and bifunctional dithiocarbamate **5** were reacted at −20 °C, together with a sixfold excess of triethylamine. However, after 48 h, no reaction had taken place. Here, the bifunctional *N*-alkoxycarbonyl triethylammonium dichloride salt was formed as an intermediate of this reaction, but this compound was virtually insoluble in tetrahydrofuran. Thus, the reaction was fully inhibited, due to the absence of activated bischloroformate in the solution. However, by employing 1,10-decanediol bischloroformate **7a** instead, a polycondensation reaction occurred. In this reaction again the dichloride salt was formed, but in this molecule the *N*-alkoxycarbonyl triethylammonium moieties were further separated from each other, and the more apolar character of this compound enhanced its solubility in tetrahydrofuran. Therefore, solubility was less affected, and only partial precipitation took place. The dichloride salt derived from 1,10-decanediol bischloroformate **7a** gradually redissolved during the reaction, allowing the synthesis of a multifunctional RAFT agent.

In a similar fashion, macromolecular multifunctional RAFT agent poly(Kraton®-RAFT) was synthesized from Kraton® L-2203 bischloroformate **7b** and bifunctional dithiocarbamate **5**. Here also, a dichloride salt was formed upon reaction of Kraton® bischloroformate **7b** with triethylamine, but this was not a problem here, due to the small influence the end-groups had on the solubility of the macromolecule in the reaction medium.

3. Conclusions

Employing the RAFT process always implies the synthesis of the organic chain transfer agents that are necessary to mediate the RAFT polymerization. However, for the objective of this work, the classical synthetic routes towards RAFT agents were not useful. It was shown that there is one type of RAFT moiety which can be synthesized in a different way than the classical synthetic routes towards RAFT agents, allowing the introduction of a macromolecule in the chain, and allowing the synthesis of a multifunctional RAFT agent: the versatile *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamate moiety. We have successfully developed a two- or three-step synthetic route (depending on the targeted compound) towards these compounds, based on a procedure reported by Allainmat et al.[35] We have modified this procedure in such a way that it now allows the synthesis of *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylalkyldithiocarbamates. Also, we have developed a novel synthetic route towards *S*-*tert*-alkyl-*N*-alkyldithiocarbamates, as the synthetic routes reported in literature were only suitable for the synthesis of primary and secondary *S*-alkyl-*N*-alkyldithiocarbamates. This novel route successfully combines the synthetic route towards tertiary thiols reported by Lee et al.,[37] with the synthetic route towards primary *S*-alkyl-*N*-alkyldithiocarbamates reported by Monde et al.,[36] to synthesize *S*-*tert*-alkyl-*N*-alkyldithiocarbamates in two steps with a good overall yield. These compounds are intermediates in the synthesis of *S*-*tert*-alkyl-*N*,*N*-alkoxycarbonylmethyldithiocarbamates.

4. Experimental

4.1. Materials and methods

Thiourea, α,α,α′,α′-tetramethyl-1,4-benzenedimethanol, HBr 48% in water, sodium hydroxide, methylisothiocyanate, a 20% phosgene solution in toluene, 1,10-decanediol, triethylamine and *n*-butyl chloroformate were purchased from Aldrich, and were used as received. Kraton® L-1203 and L-2203 were purchased from Kraton BV, Amsterdam and were used as received. All solvents were purchased from Biosolve BV, and were dried and purified before use over a Grubbs apparatus, that is, an apparatus in which the solvent is passed under pressure over an alumina catalyst in order to dry and deoxygenate the solvent, except for methanol, which was used as received. Dichloromethane was used as received for column chromatography. All glassware was dried overnight at 150 °C before use, except in the synthesis of *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate).

NMR analysis was performed on a Varian Gemini-2000 300 MHz or a Varian Mercury-Vx 400 MHz spectrometer. Samples of the various compounds were dissolved in deuterated chloroform (Cambridge Isotope Laboratories).

GPC analysis was carried out using a Waters model 510 pump, a model 410 refractive index detector (at 40 °C) and a model 486 UV detector (at 254 nm) in series. Injections were done by a Waters model WISP 712 autoinjector, using an injection volume of 50 μL. The columns used were a PLgel guard (5 μm particles) 50×7.5 mm column, followed by two PLgel mixed-C or mixed-D (5 μm particles) 300×7.5 mm columns at 40 °C in series. Tetrahydrofuran (Biosolve, stabilised with BHT) was used as eluent at a flow rate of 1.0 mL min^{-1}. Calibration has been done using polystyrene standards (Polymer Laboratories, $\bar{M}_n = 580$ to 7.1×10^6 g mol^{-1}). Data acquisition and processing were performed using Waters Millennium32 (v3.2 or 4.0) software. Before injection, the samples were filtered over a 13 mm×0.2 μm PTFE filter, PP housing (Alltech).

HPLC-ESI MS analysis was carried out on an Agilent Technologies 1100 series system, using a G1311A quaternary pump, a G1313A autosampler, a G1315B UV-DAD detector at 254 nm and an Agilent MDS type SL G1946D mass spectrometer with atmospheric pressure electrospray ionization. All data were processed with HP Chemstation software. The column used was a Supersphere 100RP-18E; 150×3 mm; dp 4 μm (Bischoff) using a methanol (HPLC grade, Biosolve)/water 50:50 to methanol gradient in 25 min at a flow of 0.4 mL min^{-1} at 25 °C. Samples were dissolved in methanol (HPLC grade, Biosolve) at a concentration of 10 mg mL^{-1}. Typical injection volumes were 1 μL.

MALDI-TOF MS analysis was carried out on a Voyager DE-STR from Applied Biosystems. The matrix used was *trans*-2-[3-(4-*tert*-butylphenyl)-2-methyl-2-propenylidene] malononitrile, which was synthesized according to the procedure reported by Ulmer et al.[38] Sodium, potassium or lithium trifluoroacetate (Aldrich, 98%) was added to the compounds as cationic ionization agent at a typical concentration around 1 mg mL^{-1}. The matrix was dissolved in THF (Biosolve) at a concentration of 40 mg mL^{-1}. In a typical MALDI experiment, the matrix, salt and polymer solution were premixed in the ratio: 5 μL sample: 5 μL matrix: 0.5 μL salt. Approximately, 0.5 μL of the obtained mixture was hand spotted on the target plate. All the spectra were acquired on the Voyager DE-STR in the reflector mode.

4.1.1. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) (5). Thiourea (17.2 g, 0.23 mol) and α,α,α′,α′-tetramethyl-1,4-benzenedimethanol (20.0 g, 0.10 mol) were mixed and added slowly with stirring to HBr 48% (41.7 g, 0.25 mol) in a 250 mL flask. The slurry was heated to 50 °C with an oil bath for 5 min, after which the slurry solidified. The white solid was cooled down, filtered, washed with a 0.1 M aqueous HBr solution, and dried under vacuum. The solid was then crushed to powder. A solution of NaOH (24.7 g, 0.62 mol) in water (50 mL) was prepared in a 250 mL three-necked flask, and heated to 40 °C with an oil bath. The white powder was added to the NaOH solution and was left to stir at 40 °C for 2 h. After this, the solution had become clear and red. The solution was filtered over a Büchner funnel and the filtrate was transferred to a 250 mL three-necked flask under Ar atmosphere, equipped with a dropping funnel and a cooler, and the solution was cooled to 5 °C using an ice bath. Methyl isothiocyanate (15.8 g, 0.22 mol) was dissolved in the minimum amount of methanol needed, and this solution was added dropwise to the red thiolate solution. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) **5** readily precipitated out as a white solid. The resulting slurry was left to stir for 1 h to ensure complete reaction, and was then filtered over a Büchner funnel and washed with cold water. The white solid was recrystallized twice from ethanol and dried under vacuum. The overall yield was 60%. ^{1}H NMR: δ 1.83 (s, 12H, C–(CH_3)$_2$), 2.95 (d, J=4.7 Hz, 6H, NH–CH_3), 6.65 (s broad, 2H, N–*H*), 7.64 (s, 4H, aromatic H). ^{13}C NMR: δ 29.92 (C–CH_3), 33.18 (NH–(CH_3)$_2$), 54.37 (C–(CH_3)$_2$), 127.27 (aromatic, 2-, 3-, 5-, 6-C), 143.96 (aromatic, 1-, 4-C), 196.01 (C=S). LC–MS (ESI): m/z calcd for $(M+Na)^+$ $C_{16}H_{24}N_2S_4Na$ 395.07; found 395.01.

4.1.2. Kraton® chloroformate (6b). A 250 mL three-necked flask was equipped with a stirrer, a 100 mL dropping funnel with stopper and 2 septa equipped with needles. The flask was placed under Ar atmosphere through the first septum, and the second septum was connected to a washing bottle containing a 1 M aqueous NaOH solution, to destroy all phosgene escaping from the reaction vessel. Phosgene solution (2.5 g, 5.2 mmol) was injected into the flask through the septum, using a 10 mL syringe. The flask was then cooled to 0 °C with an ice bath. Monohydroxyfunctional Kraton® L-1203 ($\bar{M}_n = 4000$ g mol^{-1}, 20.0 g, 5 mmol) was dissolved in toluene (30 mL) and the solution was brought into the dropping funnel, and slowly added to the phosgene solution. The mixture was left to stir at 0 °C for 4 h. The mixture was then purged with Ar for 2 h to remove the excess phosgene. Toluene was removed under reduced pressure. Kraton® chloroformate was used without further purification. Yield 98% (calculated from ^{1}H NMR). ^{1}H NMR: δ (ppm) 0.80–1.80 (m, polymer chain H), 4.36 (t, J=7.0 Hz, –CH_2–O(CO)Cl). ^{13}C NMR: δ 10.60–39.20 (polymer chain C), 71.16 (–CH_2–O(CO)Cl), 151.10 (C=O).

4.1.3. 1,10-Decanediol bischloroformate (7a). A 250 mL three-necked flask was equipped with a stirrer, a 100 mL dropping funnel with stopper and 2 septa equipped with needles. The flask was placed under Ar atmosphere through the first septum, and the second septum was connected to a washing bottle containing a 1 M aqueous NaOH solution, to destroy all phosgene escaping from the reaction vessel. Phosgene solution (33.0 g, 67 mmol) was injected into the flask through the septum, using a 50 mL syringe. The flask was then cooled to 0 °C with an ice bath. 1,10-Decanediol (5.8 g, 33 mmol) was dissolved in a minimum amount of THF and the solution was brought into the dropping funnel, and slowly added to the phosgene solution. The mixture was left to stir at 0 °C for 4 h. The mixture was then purged with Ar for 2 h to remove the excess phosgene. Toluene was removed under reduced pressure. 1,10-Decanediol bischloroformate was used without further purification. Yield 98% (calculated from ^{1}H NMR). ^{1}H NMR: δ 1.20–1.90 (m, –CH_2–(CH_2)$_8$–CH_2–), 4.38 (t, J=6.7 Hz, –CH_2–(CH_2)$_8$–CH_2–). ^{13}C NMR: δ 25.36–29.13 (–CH_2–(CH_2)$_8$–CH_2–), 72.22 (–CH_2–(CH_2)$_8$–CH_2–), 150.44 (C=O).

4.1.4. Kraton® bischloroformate (7b). A 250 mL three-necked flask was equipped with a stirrer, a 100 mL dropping

funnel with stopper and 2 septa equipped with needles. The flask was placed under Ar atmosphere through the first septum, and the second septum was connected to a washing bottle containing a 1 M aqueous NaOH solution, to destroy all phosgene escaping from the reaction vessel. Phosgene solution (5.4 g, 11 mmol) was injected into the flask through the septum, using a 10 mL syringe. The flask was then cooled to 0 °C with an ice bath. Bishydroxyfunctional Kraton® L-2203 ($\bar{M}_n = 4000$ g mol^{-1}, 20.0 g, 5 mmol) was dissolved in toluene (30 mL) and the solution was brought into the dropping funnel, and slowly added to the phosgene solution. The mixture was left to stir at 0 °C for 4 h. The mixture was then purged with Ar for 2 h to remove the excess phosgene. Toluene was removed under reduced pressure. Kraton® bischloroformate was used without further purification. Yield 98% (calculated from ^{1}H NMR). ^{1}H NMR: δ 0.80–1.80 (m, polymer chain H), 4.36 (t, $J=7.0$ Hz, –CH_2–O(CO)Cl). ^{13}C NMR: δ 10.60–39.20 (polymer chain C), 71.16 (–CH$_2$–O(CO)Cl), 151.10 (C=O).

4.1.5. Butyl-RAFT agent (3a). Butyl-RAFT agent will be further used as the common name for *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*,*N*-butoxycarbonylmethyldithiocarbamate).

N-Butyl chloroformate (3.1 g, 23 mmol) was dissolved in THF (10 mL) in a 100 mL double enveloped flask, equipped with a stirrer and a 50 mL dropping funnel, and placed under Ar atmosphere. The mixture was cooled to −20 °C using a cryostate. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) (4.0 g, 11 mmol) and triethylamine (5.4 g, 54 mmol) were dissolved in a minimum amount of THF. This solution was added dropwise to the *n*-butyl chloroformate solution with stirring. This mixture was left to stir at −20 °C for 48 h, after which the mixture was brought to room temperature. Triethylamine hydrochloride was filtered off, and THF was removed under reduced pressure. The resulting yellow oil was purified by column chromatography using dichloromethane as the eluent and yielded butyl-RAFT **3a** as a yellow solid. Yield 85%. ^{1}H NMR: δ 0.92 (t, $J=7.3$ Hz, 6H, –CH_2–CH_2–CH_2–CH_3), 1.43 (m, 4H, –CH_2–CH_2–CH_2–CH_3), 1.70 (m, 4H, –CH_2–CH_2–CH_2–CH_3), 1.88 (s, 12H, C–$(CH_3)_2$), 3.51 (s, 6H, N–CH_3), 4.26 (t, $J=6.6$ Hz, 4H, –CH_2–CH_2–CH_2–CH_3), 7.40 (s, 4H, aromatic H). ^{13}C NMR: δ 13.64 (–CH_2–CH_2–CH_2–CH_3), 19.12 (–CH_2–CH_2–CH_2–CH_3), 28.83 (C–$(CH_3)_2$), 30.52 (–CH_2–CH_2–CH_2–CH_3), 38.35 (C–$(CH_3)_2$), 56.15 (N–CH_3), 67.42 (–CH_2–CH_2–CH_2–CH_3), 126.05 (aromatic, 2-, 3-, 5-, 6-C), 142.84 (aromatic, 1-, 4-C), 153.97 (C=O), 202.97 (C=S). LC–MS (ESI): *m*/*z* calcd for $(M+Na)^+$ $C_{26}H_{40}N_2S_4O_4Na$ 595.84; found 595.76. HRMS (MALDI-TOF MS): *m*/*z* calcd for $(M+K)^+$ $C_{26}H_{40}N_2S_4O_4K$ 611.151; found 611.135.

4.1.6. Kraton®-RAFT agent (3b). Kraton®-RAFT agent will be further used as the common name for *S*-(1,4-phenylenebis(propane-2,2-diyl)) bis(*N*,*N*-Kratoncarbamoylmethyldithiocarbamate).

Kraton® chloroformate (20.0 g, 5 mmol) was dissolved in THF (30 mL) in a 250 mL double enveloped flask, equipped with a stirrer and a 50 mL dropping funnel, and placed under Ar atmosphere. The mixture was cooled to −20 °C using a cryostate. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) (0.9 g, 2.5 mmol) and triethylamine (1.3 g, 13 mmol) were dissolved in a minimum amount of THF. This solution was added dropwise to the Kraton® chloroformate solution with stirring. This mixture was left to stir at −20 °C for 48 h, after which the mixture was brought to room temperature. Triethylamine hydrochloride was filtered off, and THF was removed under reduced pressure. Yield 86%. The resulting yellow viscous oil was not further purified and was used as such in polymerizations. ^{1}H NMR: δ 0.80–1.80 (m, polymer chain H), δ 1.96 (s, 12H, C–$(CH_3)_2$), 3.57 (s, 6H, N–CH_3), 4.35 [t, $J=6.9$ Hz, 4H, –O–CH_2–), 7.47 (s, 4H, aromatic H). ^{13}C NMR: δ 10.24–38.77 (polymer chain C, C–$(CH_3)_2$), 56.20 (N–CH_3), 67.78 (–O–CH_2–), 126.10 (aromatic, 2-, 3-, 5-, 6-C), 142.84 (aromatic, 1-, 4-C), 153.98 (C=O), 206.22 (C=S).

4.1.7. Poly(decyl-RAFT) agent (4a). Poly(decyl-RAFT) agent will be further used as the common name for poly(*S*-1,4-phenylenebis(propane-2,2-diyl)) bis(*N*,*N*-1,10-decoxycarbonylmethyl-dithiocarbamate)).

1,10-Decanediol bischloroformate (2.3 g, 11 mmol) was dissolved in THF (10 mL) in a 100 mL double enveloped flask, equipped with a stirrer and a 50 mL dropping funnel, and placed under Ar atmosphere. The mixture was cooled to −20 °C using a cryostate. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) (4.0 g, 11 mmol) and triethylamine (6.7 g, 66 mmol) were dissolved in the minimum amount of THF. This solution was added dropwise to the 1,10-decanediol bischloroformate solution with stirring. This mixture was left to stir at −20 °C for 48 h, after which the mixture was brought to room temperature. Triethylamine hydrochloride was filtered off, and THF was removed under reduced pressure. The resulting viscous yellow oil was further purified by preparative SEC. Yield 70%. ^{1}H NMR: δ 1.20–2.10 (m, –CH_2–$(CH_2)_8$–CH_2–, C–$(CH_3)_2$), 3.51 (s, N–CH_3), 4.25 (t, $J=7.0$ Hz, –CH_2–$(CH_2)_8$–CH_2–), 7.40 (s, aromatic H). ^{13}C NMR: δ 22.63–32.42 (–CH_2–$(CH_2)_8$–CH_2–, C–$(CH_3)_2$), 38.37 (C–$(CH_3)_2$), 56.14 (N–CH_3), 67.39 (–CH_2–$(CH_2)_8$–CH_2–), 126.38 (aromatic, 2-, 3-, 5-, 6-C), 142.97 (aromatic, 1-, 4-C), 154.07 (C=O), 203.12 (C=S). GPC (before purification): $\bar{M}_n = 1800$ g mol^{-1}, PDI = 1.80. GPC (after purification and isolation of the high molecular weight fraction): $\bar{M}_n = 3700$ g mol^{-1}, PDI = 1.59.

4.1.8. Poly(Kraton®-RAFT) agent (4b). Poly(Kraton®-RAFT) agent will be further used as the common name for poly(*S*-(1,4-phenylenebis (propane-2,2-diyl)) bis(*N*,*N*-Kratoncarbamoylmethyldithiocarbamate)).

Kraton® bischloroformate (4.0 g, 1 mmol) was dissolved in THF (20 mL) in a 100 mL double enveloped flask, equipped with a stirrer and a 50 mL dropping funnel, and placed under Ar atmosphere. The mixture was cooled to −20 °C using a cryostate. *S*-(1,4-Phenylenebis(propane-2,2-diyl)) bis(*N*-methyldithiocarbamate) (0.37 g, 1 mmol) and triethylamine (0.51 g, 5 mmol) were dissolved in a minimum amount of THF. This solution was added dropwise to the Kraton® chloroformate solution with stirring. This mixture was left

to stir at −20 °C for 48 h, after which the mixture was brought to room temperature. Triethylamine hydrochloride was filtered off, and THF was removed under reduced pressure. Yield 80% (GPC). The resulting yellow oil was not further purified and was used as such in polymerizations. ^{1}H NMR: δ 0.80–1.80 (m, polymer chain H), 1.95 (s, 12H, C–(CH_3)$_2$), 3.59 (s, 6H, N–CH_3), 4.36 (t, J=7.0 Hz, 4H, –O–CH_2–), 7.45 (s, 4H, aromatic H). ^{13}C NMR: δ 10.20–38.70 (polymer chain C, C–(CH_3)$_2$), 56.21 (N–CH_3), 67.83 (–O–CH_2–), 126.08 (aromatic, 2-, 3-, 5-, 6-C), 142.84 (aromatic, 1-, 4-C), 153.95 (C=O), 206.18 (C=S). GPC: $\bar{M}_n = 21,600$ g mol^{-1}, PDI=1.60.

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Ziziphine N, O, P and Q, new antiplasmodial cyclopeptide alkaloids from *Ziziphus oenoplia* var. *brunoniana*

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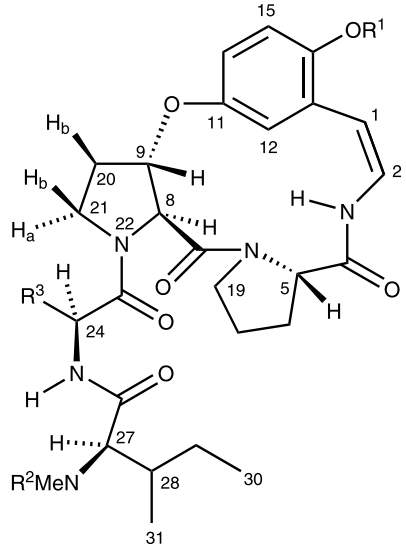
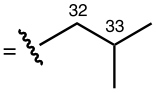
Abstract—Bioassay-guided fractionation of the EtOAc extract of the roots of Thai *Ziziphus oenoplia* var. *brunoniana* resulted in the isolation of four new 13-membered cyclopeptide alkaloids of the 5(13) type, ziziphine N–Q. The structures of the new metabolites were elucidated on the basis of spectroscopic analyses and the stereochemical assignments were established by comparison with other related compounds of known stereochemistry. Ziziphine N and Q exhibited significant antiplasmodial activity against the parasite *Plasmodium falciparum* with the inhibitory concentration (IC_{50}) values of 3.92 and 3.5 μg/mL, respectively. Ziziphine N and Q also demonstrated weak antimycobacterial activity against *Mycobacterium tuberculosis* with the same MIC value of 200 μg/mL.

1. Introduction

The Rhamnaceous *Ziziphus* (formerly known as *Zizyphus*) species have been investigated due to the rich source of new and/or bioactive cyclopeptides.[1–3] To date over 170 cyclopeptides have been published[1–3] which can be classified into five groups of the 4(13)-, 5(13)-, 4(14)-, 5(14)- and 4(15)-type of compounds.[3] Among these, 81 cyclopeptide alkaloids have been reported from various *Ziziphus* species and these include 35 13-membered, 39 14-membered and seven 15-membered ring cyclopeptides.[2] Some *Ziziphus* plants have been found to possess biological activities, for example sedative,[4] hypoglycemic,[5] antibacterial and antifungal activities.[6] *Ziziphus oenoplia* (L.) Mill. is a thorny sprawling bush, widely spread and used traditionally as a folk medicine in Thailand for its antiinfectious, antidiabetic and diuretic activities.[7–8] Previous phytochemical studies of this plant species resulted in the isolation of cyclopeptides of the 5(13)-zizyphine-A type (zizyphine A–C,[9] F,[10] I[11] and K),[12] 4(14)-amphibine-B type (zizyphine H),[2,13] 4(14)-amphibine-F type (zizyphine G),[10]





1 Ziziphine N: $R^1 = R^2 = Me$, R^3 =

2 Ziziphine O: $R^1 = Me$, $R^2 = H$, $R^3 = CH_2CH(CH_3)_2$
3 Ziziphine P: $R^1 = H$, $R^2 = Me$, $R^3 = CH_2CH(CH_3)_2$
4 Ziziphine Q: $R^1 = R^2 = Me$, $R^3 = CH(CH_3)_2$
5 Zizyphine A: $R^1 = R^2 = Me$, $R^3 = CH(CH_3)CH_2CH_3$

Keywords: *Ziziphus oenoplia* var. *brunoniana*; Rhamnaceae; Cyclopeptide alkaloid; Ziziphine N–Q; Antiplasmodial activity; Antimycobacterial activity.
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4(14)-frangulanine-type (frangufoline),[14] 4(15)-mucronine-A type (abyssinine A–B and zizyphine D–E)[9] and 5(14)-amphibine-B type (amphibine B and mauritine D).[14] It should be noted that the structures of zizyphine J, L and M have not been presented.[1–3,12] In continuation of the search for bioactive substances of new structural type from Thai natural resources,[15–17] we have found that the root extract of the Thai *Z. oenoplia* (L.) Mill. var. *brunoniana* (Cl. ex Brand.) Tard exhibited a significant in vitro antimalarial potential against *Plasmodium falciparum*. In this paper we describe the isolation and structure elucidation of four new 13-membered cyclopeptide alkaloids of the 5(13)-type, ziziphine N–Q (**1**–**4**) from the roots of this plant species.

2. Results and discussion

The pulverized, dried root of *Z. oenoplia* var. *brunoniana* was successively extracted with *n*-hexane, EtOAc and MeOH. The resulting fractions were tested for antiplasmodial activity and the EtOAc extract, which exhibited antiplasmodial activity, was subjected to further investigation. Bioassay-directed fractionation and chromatographic separation of this extract resulted in the isolation of four new 13-membered cyclopeptide alkaloids of the 5(13) type, ziziphine N–Q (**1**–**4**).

The major metabolite, ziziphine N (**1**), a colorless solid, mp 117–119 °C, displayed a pseudomolecular ion at *m/z* 612 $[M+H]^+$ in the EIMS, and the molecular formula $C_{33}H_{49}N_5O_6$ was established by HRFABMS (*m/z* 612.3769 $[M+H]^+$, $\Delta+0.8$ mmu). Compound **1**, as well as the metabolites **2**–**4**, gave a very faint positive coloration with Dragendorff's reagent and a blue coloration with anisaldehyde-H_2SO_4 reagent. The ^{1}H NMR spectrum of **1** (Table 1) displayed signals corresponding to two olefinic protons, three aromatic protons, one methoxyl and a number of methine and methylene protons. While the ^{13}C NMR spectrum showed 33 carbon signals and DEPT analysis provided signals for four methyls, one *N*,*N*-dimethyl, one methoxyl, seven methylenes, 12 (including one oxygenated and two olefinic) methines and seven quaternary carbons,

Table 1. ^{1}H and ^{13}C NMR spectral data for compounds **1**–**4** in $CDCl_3$

	δ_H*				δ_C			
	1	2	3	4	1	2	3	4
1	5.82 d (8.9)	5.92 d (8.8)	5.89 d (8.6)	5.94 d (8.7)	106.6	106.6	105.9	106.6
2	6.79 dd (11.9, 8.9)	6.92 dd (11.5, 8.8)	6.90 dd (11.5, 8.6)	6.94 dd (8.7, 11.5)	121.3	121.6	121.5	121.6
3	8.22 d (11.9)	8.33 d (11.5)	8.33 d (11.5)	8.34 d (11.5)				
4					167.5	167.7	168.0	167.7
5	4.39 dd (8.9, 3.5)	4.53 dd (9.1, 3.8)	4.52 dd (9.0, 3.8)	4.51 m	61.8	62.0	62.0	62.1
7					171.3	171.6	171.7	171.5
8	4.26 d (5.4)	4.38 d (5.7)	4.34 d (5.7)	4.39 d (5.7)	62.5	62.7	62.8	62.6
9	5.09 ddd (8.8, 7.4, 5.4)	5.24 ddd (8.9, 7.1, 5.7)	5.18 ddd (7.8, 7.5, 5.7)	5.25 dt (6.7, 5.7)	78.3	78.5	78.4	78.5
11					150.6	151.2	150.7	150.9
12	6.65 br s	6.73 br s	6.68 d (2.0)	6.83 br s	110.4	110.7	110.2	110.7
13					123.7	124.0	122.6	124.0
14					151.0	150.8	148.0	151.2
15	6.75 d (9.6)	6.83 d (8.1)	6.85 d (8.8)	6.85 m	113.6	113.7	117.7[a]	113.5
16	6.70 d (9.6)	6.80 d (8.1)	6.73 dd (8.8, 2.0)	6.85 m	116.8	116.9	118.8[a]	116.9
17a	2.10 m	2.20 m	2.20 m	2.25 m	28.8	29.0	29.0	29.0
17b	1.83 m	1.95 m	1.95 m	2.00 m				
18a	1.83 m	1.95 m	1.95 m	2.00 m	24.6	24.9	24.9	24.9
18b	1.68 m	1.60 m	1.95 m	1.85 m				
19a	4.12 m	4.25 m	4.20 m	4.21 m	47.6	47.8	47.9	47.8
19b	3.17 m	3.25 m	3.23 m	3.32 m				
20a	2.25 m	2.50 m	2.45 m	2.45 m	32.4	32.7	32.6	32.6
20b	2.33 m	2.35 m	2.35 m	2.35 m				
21a	4.12 m	4.25 m	4.20 m	4.21 m	45.1	45.3	45.3	45.5
21b	3.49 m	3.60 m	3.60 m	3.63 m				
23					171.0	171.2	171.3	170.8
24	4.66 dt (8.1, 7.8)	4.47 dt (8.6, 7.4)	4.74 q (8.5)	4.51 m	47.6	47.8	48.0	54.9
25	6.81 d (8.1)	7.50 d (8.6)	6.95[a]	6.90[b]				
26					171.6	173.4	172.2	172.1
27	2.45 d (5.4)	2.83 d (4.6)	2.55 d (5.3)	2.58 d (5.5)	74.0	69.8	74.4	74.5
28	1.68 m	1.75 m	1.80 m	1.85 m	34.0	38.2	34.3	34.3
29a	1.39 m	1.50 m	1.50 m	1.55 m	26.6	25.3	27.0	26.9
29b	1.08 m	1.15 m	1.20 m	1.20 m				
30	0.80 t (6.7)	0.90 d (6.5)	0.90 t (6.8)	0.93 t (6.8)	11.7	11.7	12.0	11.9
31	0.75 d (6.5)	0.86 d (6.5)	0.85 d (6.6)	0.95 d (6.2)	14.1	15.8	14.5	14.7
32a	1.42 m	1.50 m	1.45 m	2.00 m	40.5	40.9	40.6	30.8
32b	1.39 m	1.50 m	1.45 m					
33	1.52 m	1.75 m	1.65 m	0.93 d (6.6)	24.4	24.6	24.7	18.5[f]
34	0.80 d (6.5)	0.90 d (6.5)	0.89 d (6.8)	0.90 d (6.6)	22.9[c]	23.0[d]	23.1[e]	19.0[f]
35	0.80 d (6.5)	0.90 d (6.5)	0.89 d (6.8)		21.4[c]	21.8[d]	21.6[e]	
OMe	3.66 s	3.77 s		3.79 s	55.7	55.9		55.9
NMe	2.12 s	2.36 s	2.22 s	2.24 s	42.8	36.0	43.2	43.0

*The *J* values are in Hz in parentheses. [a,b]Partially obscured signal. [c–f]Signals under the same superscript may be reversed.

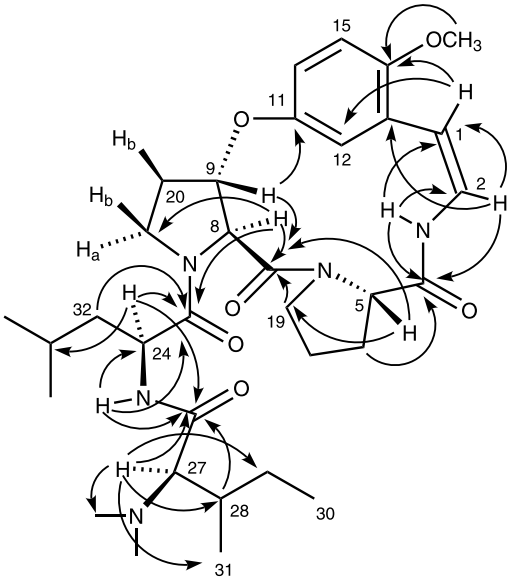

Figure 1. Selected HMBC correlations for **1**.

four of which corresponded to the carbonyl groups (Table 1).

Analysis of the ^{1}H–^{1}H COSY and ^{1}H–^{13}C HMQC spectra of **1** and comparison with the reported value[3,18] led to the assignments of the spin systems for amino acid units of proline, 3-oxygenated proline, leucine and *N*,*N*-dimethylisoleucine. The presence of a *meta*-oxygenated *Z*-styrylamino group suggested that **1** was a 13-membered cyclopeptide alkaloid which was further supported by its UV spectrum (266 and 319 nm).[19] Its IR spectrum showed the presence of amino (3399 cm^{-1}), amide (1693, 1653, 1641 cm^{-1}), styryl double bond (1625 cm^{-1}) and phenol ether (1223 and 1054 cm^{-1}) functionality. Connections among these subgroups were provided by analysis of HMBC and NOESY spectra (Figs. 1 and 2, respectively). Thus the resonance at δ 8.22 of *m*-oxystyrylamino-NH at the 3-position showed HMBC cross peaks with C-1, C-2 and C-4. Correlations of H-2 to C-1, C-4 and C-13 and H-1 to C-12 were also observed. The correlations of H-5, H-8 and H-9 to C-7 revealed the connection between the proline and β-oxyproline amino acids. Furthermore, HMBC correlation from H-9 to C-11 confirmed that the β-oxyproline unit was attached to the aryl group. The cross-peak of the methoxyl signal at δ 3.66 with a quaternary aromatic carbon signal of C-14 at δ 151.0 in HMBC spectrum confirmed that the methoxyl group was placed at C-14 of the 13-membered cyclopeptide feature. The overlapping of the aromatic proton signals in the ^{1}H NMR spectroscopic data recorded in $CDCl_3$ were clearly resolved when the spectrum was recorded in DMSO-d_6 (see Section 3). The strong NOE effect displayed between the methoxyl group and H-15 in the NOESY experiment (Fig. 2) in DMSO-d_6 further supported the placement of the methoxyl group at C-14. The H-8 proton and the leucyl protons H-24 showed connectivities with C-23 in which the latter signal proton also exhibited cross-peaks with C-26 and C-33 in HMBC spectrum. NOE interactions observed between H-24 and H-21 in the NOESY spectrum further revealed that the position of the leucine unit was attached to the hydroxyproline amino acid. The HMBC correlations of NH-25 to C-24 and C-26, and of the isoleucyl proton H-27 to C-26, C-29, C-31 and *N*,*N*-dimethyl carbon were also observed. Thus the connections between the leucyl group and the hydroxyprolyl *N* as well as the isoleucyl *N* were established.

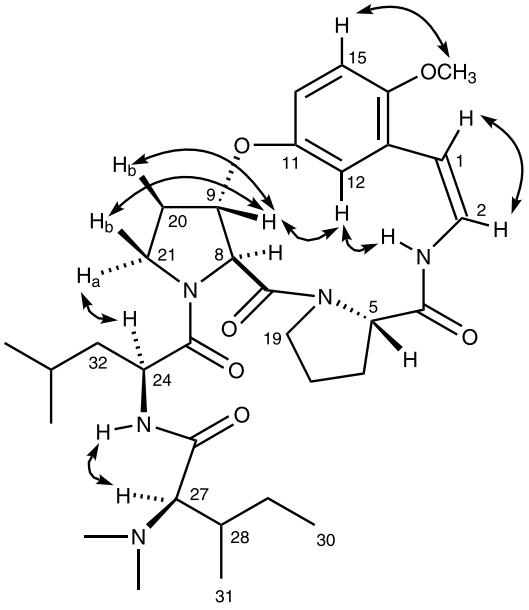

Figure 2. Key NOESY correlations for **1**.

The mass spectrum of compound **1** followed the typical fragmentation pattern of a zizyphine A-type 13-membered cyclopeptide alkaloid.[1] The base peak at *m*/*z* 114 represents the amine fragment which indicates that the end amino acid is *N*,*N*-dimethylisoleucine. Compound **1** and zizyphine A (**5**)[3,20] showed similar mass fragmentation patterns indicating their gross structural similarity. Based on these findings the structural framework of ziziphine N was proved to be **1**, which differs from that of zizyphine A (**5**) in having a leucine instead of an isoleucine amino acid attached to the hydroxyproline unit of the macrocyclic ring system.

The *Z*-geometry of the 1,2-double bond was established on the basis of the coupling constant value of 8.9 Hz for H-1 and H-2. The relative stereochemistry at the C-5 position of the amino acid (proline) and the C-8 and C-9 positions of the β-hydroxyproline units were determined by analysis of ^{1}H NMR coupling constants and NOESY interactions (Fig. 2). The small vicinal coupling constant value 5.4 Hz of the methine protons H-8 and H-9 indicated a *trans* configuration.[21,22] No significant NOE observed in NOESY spectrum between these two protons also supported the *trans* relationship between H-8 and H-9.[21] Strong NOE enhancements between NH-3 and the aromatic proton H-12 and between the later proton and H-9 were observed. Moreover the coupling constant value between H-2 and NH-3 (J=11.9 Hz) implied that they were in *trans* coplanar position.[21] No NOE interaction shown between H-5 and NH-3 revealed the opposite orientation of these two protons. Strong correlations were observed between H-9 and both H-20b and H-21b, but not with H-20a and H-21a, indicating

that H-9, H-20b and H-21b were on the same side of the pyrrolidine ring. The ^{1}H and ^{13}C NMR spectroscopic data of **1** were very similar to those of the natural zizyphine A (**5**),[3,23] except for those of the leucine moiety in the former and the isoleucine in the latter, suggesting the relative stereochemistry of these two compounds to be the same. Since the total synthesis of **5** was achieved and it was identical to the natural zizyphine A in all respects,[24] and since the amino acid units of the acyclic part attached to N-22 were those of L-isoleucine and L-*N*,*N*-dimethylisoleucine, the configuration of the corresponding amino acid units (leucine and *N*,*N*-dimethylisoleucine) of **1** could possibly be L. Furthermore, the ^{1}H and ^{13}C NMR spectroscopic data of the leucine unit (C-23, C-24 and C-32 to C-35) of **1** were very similar to those of mucronine D, the structurally related 13-membered cyclopeptide alkaloid isolated from *Z. mucronata* and the absolute configuration of the amino acids of which was determined as L by degradation of the alkaloid and analysis of the amino acids.[25] In addition, the ^{1}H and ^{13}C NMR spectroscopic data of the *N*,*N*-dimethylisoleucine moiety (C-26 to C-31 and $N(CH_3)_2$) in **1** were also very similar to those of compound **5**.[3,23] The stereochemistry of the two acyclic amino acid moieties was thus tentatively inferred to be L. Therefore, the absolute configuration of ziziphine N is as shown in **1**.

Ziziphine O (**2**) was obtained as a colorless solid, mp 106–108 °C. On the basis of its HRFABMS (*m*/*z* 598.3604, $[M+H]^+$, Δ −0.1 mmu) the molecular formula of **2** was established as $C_{32}H_{47}N_5O_6$. The UV and IR absorption spectra of **2** were similar to those of **1** suggesting the presence of styrylamine chromophore of 13-membered cyclopeptide alkaloid.[19] The ^{1}H NMR spectrum of **2** (Table 1) were almost identical to that of **1**; the different features are the signals at δ 7.50 (H-25), δ 2.83 (H-27) and δ 1.75 (H-28). Furthermore, the singlet signal at δ 2.36, integrating for three protons, corresponded to one *N*-methyl group instead of two as found in **1**. The main differences between the ^{13}C NMR spectra of **1** and **2** (Table 1) are those of C-26, C-27, C-28 and the *N*-methyl carbon which are in agreement with a structural change in the region of the isoleucine residue. The HMBC and NOESY information revealed that the two compounds possessed the same molecular framework. α-Cleavage at the terminal amino acid led to the base peak at *m*/*z* 100 in EIMS data also provided the evidence for the presence of a *N*-methylisoleucine unit. Thus the structure of **2** was deduced to be the *N*-desmethyl analogue of ziziphine N.

The minor cyclopeptide alkaloid, ziziphine P (**3**), was obtained as a colorless solid, mp 127–129 °C. The molecular formula $C_{32}H_{47}N_5O_6$ was derived from the HRFABMS where the $[M+H]^+$ ion was observed at *m*/*z* 598.3590 (Δ −1.5 mmu). Its 1D (^{1}H and ^{13}C NMR (Table 1), DEPT and 2D (COSY, HMQC, HMBC and NOESY) spectral data were very similar to those of **1** except for the absence of the methoxyl signal, indicating that **3** was another ziziphine N analogue. The IR and molecular composition revealed that **3** contained a phenolic group as compared with **1**. The structure of **3** was, therefore, established as the *O*-desmethyl analogue of ziziphine N.

Ziziphine Q (**4**), isolated as a colorless solid, was found to have a molecular formula of $C_{32}H_{47}N_5O_6$ by HRFABMS (*m*/*z* 598.3607, $[M+H]^+$, Δ +0.2 mmu). Its UV and IR spectroscopic data suggested that **4** also possessed a 13-membered cyclopeptide. The ^{1}H and ^{13}C NMR spectroscopic data (Table 1) of **4** closely resembled to those of ziziphine N (**1**) except for the presence of a valine unit [δ_H 4.51 (H-24), δ_C 54.9 (C-24); δ_H 2.00 (H-32), δ_C 30.8 (C-32); δ_H 0.93 (H-33), δ_C 18.5 (C-33) and δ_H 0.90 (H-34), δ_C 19.0 (C-34)] instead of leucine amino acid residue. The absence of one methylene unit observed in the DEPT spectrum of **4** as compared with **1** also supported that compound **4** possessed a valine group. The identical HMBC and NOESY data of **4** in comparison with those of **1** confirmed that the valinyl group in **4** was located in the same position as those found for the leucine moiety in compound **1**. Thus ziziphine Q possessed the structure **4** with valine as the amino acid residue bound to the hydroxyproline of the macrocyclic ring and connected to the isoleucyl residue. In fact ziziphine **4** was a derivative of zizyphine K, a compound obtained from a Pakistani *Z. oenoplia*.[12] The only difference was that the hydroxyl group in zizyphine K was replaced by a methoxyl group at C-14 to give **4**. The structure of **4** was, therefore, concluded to be *O*-methyl zizyphine K.

Rhamnaceous cyclopeptide alkaloids are generally composed of L-amino acids and *trans*-β-hydroxy-L-proline, including zizyphine A-type alkaloid.[3] Due to the similarity of the ^{1}H and ^{13}C NMR spectral data and levorotatory optical rotations of compounds **2**–**4** as compared with **1**, it is thus concluded that ziziphine O–Q share the same stereochemistry as that of ziziphine N and zizyphine A.

Many 13-membered cyclopeptides constructed with a variation of amino acid residues have been reported.[1–3] However, to our knowledge those with leucine and isoleucine residues are rare. Ziziphine N–Q (**1**–**4**) are additional members of the 5(13)-membered cyclopeptides which belong to the zizyphine A-type. It should be noted that while ziziphine N (**1**) was the major alkaloid of the Thai *Z. oenoplia* var. *brunoniana*, zizyphine A and its analogues were not detected.

All isolates **1**–**4** were tested in vitro for antimalarial potential against *P. falciparum*.[26,27] No activity was observed in ziziphine O (**2**) and P (**3**). On the other hand, ziziphine N (**1**) and Q (**4**) demonstrated significant antiplasmodial activity with the IC_{50} values of 3.92 and 3.5 μg/mL, respectively. The cyclopeptides **1** and **4** also exhibited weak antituberculosis activity against *Mycobacterium tuberculosis*[28] with the same MIC value of 200 μg/mL, whilst cyclopeptides **2** and **3** were found inactive in the same test. All metabolites did not show cytotoxicity to KB and BC cell lines[29] at IC_{50} value of 20 μg/mL. Based on these observations, the preliminary structure–activity relationship regarding these alkaloids was tentatively summarized that both the methoxyl and the *N*,*N*-dimethylamino groups in **1** and **4** are crucial for the activity. In addition, substitution of leucine unit in **1** with valine moiety in **4** showed similar trend of biological activities. To the best of our knowledge, this is the first report of in vitro antiplasmodial and antimycobacterial activities from the Rhamnaceous plants.

3. Experimental

3.1. General experimental procedures

Melting points were determined using a Griffin melting point apparatus. Optical rotations were measured on a Jasco digital polarimeter. UV spectra were obtained on a Shimadzu UV-2401 PC spectrophotometer. IR spectra were recorded on a Perkin Elmer FT-IR Spectrum BX spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 300 FT-NMR spectrometer, operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). For the spectra taken in $CDCl_3$ and DMSO-d_6, the residual nondeuterated solvent signals at δ 7.24 and δ 2.49 and the solvent signals at δ 77.00 and δ 39.50 were used as references for ^{1}H and ^{13}C NMR spectra, respectively. EI and FAB mass spectra were run on a Thermo Finnigan Polaris Q and a Finnigan MAT 90 instruments. Column chromatography and TLC were carried out using Merck silica gel 60 (<0.063 mm) and precoated silica gel 60 F_{254} plates, respectively. Plates of silica gel PF_{254}, thickness 1.25 mm, were used for preparative TLC. Spots on TLC were visualized under UV light and by spraying with anisaldehyde-H_2SO_4 followed by heating.

3.2. Materials and methods

The roots of *Z. oenoplia* (L.) Mill. var. *brunoniana* (Cl. ex Brand.) Tard was collected from Chanae District, Naratiwat Province, Thailand, in April 1999 and a voucher specimen, (Mayuso Kuno 002) is deposited at the CMU Herbarium, Faculty of Science, Chiang Mai University, Thailand.

3.3. Extraction and separation

Pulverized, dry root (5.16 kg) of *Z. oenoplia* var. *brunoniana* was defatted with hexane and then extracted successively with EtOAc and MeOH at 50 °C for 48 h and the solvents were evaporated to yield the EtOAc (58.2 g) and MeOH (40.2 g) extracts, respectively. The EtOAc extract exhibited antiplasmodial activity, whereas the MeOH extract was found inactive. Thus, the EtOAc soluble fraction (44.7 g) was investigated extensively through serial fractionations by quick column chromatography,[30] eluted with a gradient system, to provide eight major fractions. Fraction seven (7.10 g) which was active to the antiplasmodial test was subjected to column chromatography employing solvent gradient $CHCl_3$–MeOH and eight subfractions (1–8) were collected. A portion of subfraction 2 (87 mg) was further chromatographed, eluting with EtOAc, to give ziziphine N (**1**, 43 mg) and ziziphine Q (**4**, 10 mg). Ziziphine O (**2**, 29 mg) and ziziphine P (**3**, 25 mg) were obtained after repeated column chromatography of subfractions 3 (110 mg, eluting with $CHCl_3$–MeOH, 98:2) and subfraction 4 (132 mg, eluting with $CHCl_3$–MeOH, 97:3), respectively. Other fractions contained small quantities of the isolated cyclopeptide alkaloids **1**–**4** and other type of compounds.

3.3.1. Ziziphine N (1). Colorless solid, mp 117–119 °C; $[\alpha]_D^{30} = -326.6$ (*c* 0.18, $CHCl_3$); UV (EtOH) λ_{max} 266 (log ε 4.40), 319 nm (log ε 4.28); IR ν_{max} (KBr) 3399, 2960, 2926, 2826, 2783, 1693, 1653, 1641, 1625, 1511, 1223, 1054, 772 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.44 (1H, d, J=10.6 Hz, NH-3), 8.11 (1H, d, J=8.0 Hz, NH-25), 6.98 (1H, d, J=9.0 Hz, H-15), 6.81 (1H, dd, J=9.0, ca. 2.0 Hz, H-16), 6.77 (1H, dd, J=10.6, 7.6 Hz, H-2), 6.71 (1H, d, ca. 2.0 Hz, H-12), 5.86 (1H, d, J=7.6 Hz, H-1), 5.03 (1H, ddd, J=8.5, 7.3, 6.1 Hz, H-9), 4.62 (1H, dt, J=8.0, 6.0 Hz, H-24), 4.27 (1H, d, J=6.1 Hz, H-8), 4.15 (1H, m, H-19a), 4.03 (2H, m, H-5 and H-21a), 3.71 (3H, s, OCH_3), ca. 3.40 (1H, m, H-19b), ca. 3.30 (1H, m, H-21b), 2.70 (1H, d, J=10.2 Hz, H-27), 2.50 and 2.20 (2×1H, each m, H-20), 2.15 (2×3H, s, $N(CH_3)_2$), 2.10 and 1.75 (2×1H, each m, H-17), 1.80 (3H, m, H-18 and H-28), 1.60 and 1.15 (2×1H, each m, H-29), 1.40 and 1.20 (2×1H, each m, H-32), 1.10 (1H, m, H-33), 0.86 (3H, d, J=6.2 Hz, H-35),[a] 0.85 (3H, d, J=6.4 Hz, H-34),[a] 0.80 (3H, t, J=7.3 Hz, H-30), 0.71 (3H, d, J=6.4 Hz, H-31), ('a' stands for the assignments may be reversed for signals with the same superscript); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.0 (C-7 and C-23), 169.8 (C-26), 167.8 (C-4), 150.9 (C-11), 150.6 (C-14), 123.8 (C-13), 121.9 (C-2), 116.5 (C-16), 113.6 (C-15), 111.6 (C-12), 107.5 (C-1), 79.1 (C-9), 70.6 (C-27), 62.4 (C-8), 62.2 (C-5), 55.7 (OCH_3), 47.8 (C-19), 47.5 (C-24), 44.7 (C-21), 41.3 (N-CH_3), 39.5 (C-32), 32.3 (C-28 and C-20), 28.6 (C-17), 24.9 (C-29), 24.6 (C-18), 24.2 (C-33), 23.1 (C-34), 21.1 (C-35), 15.5 (C-31), 10.3 (C-30); EIMS *m/z* 612 $[M+H]^+$ (60), 596 (15), 582 (95), 568 (65), 554 (90), 497 (45), 496 (45), 454 (55), 358 (2), 216 (2), 114 (100), 86 (5), 70 (10); HRFABMS (positive ion mode) *m/z* 612.3769 $[M+H]^+$ (calcd for $C_{33}H_{49}N_5O_6$+H, 612.3761).

3.3.2. Ziziphine O (2). Colorless solid, mp 106–108 °C; $[\alpha]_D^{31} = -380.2$ (*c* 0.15, $CHCl_3$); UV (EtOH) λ_{max} 268 (log ε 4.01), 319 nm (log ε 3.89); IR (KBr) ν_{max} 3399, 2964, 2935, 2879, 2797, 1686, 1654, 1639, 1625, 1509, 1418, 1223, 1053, 771 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; EIMS *m/z* 598 $[M+H]^+$ (0.3), 597 (0.6), 554 (7), 511 (1), 455 (5), 412 (8), 385 (2), 358 (6), 100 (100), 70 (9); HRFABMS (positive ion mode) *m/z* 598.3604 $[M+H]^+$ (calcd for $C_{32}H_{47}N_5O_6$+H, 598.3605).

3.3.3. Ziziphine P (3). Colorless solid, mp 127–129 °C; $[\alpha]_D^{31} = -385.4$ (*c* 0.15, $CHCl_3$); UV (MeOH) λ_{max} 265 (log ε 4.73), 321 nm (log ε 4.59); IR (KBr) ν_{max} 3450, 3394, 2960, 2935, 2877, 2783, 1686, 1642, 1513, 1429, 1210, 1053, 786 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; EIMS *m/z* 598 $[M+H]^+$ (0.1), 554 (0.1), 540 (0.2), 397 (0.1), 365 (0.1), 344 (0.1), 114 (100), 57 (7); HRFABMS (positive ion mode) *m/z* 598.3590 $[M+H]^+$ (calcd for $C_{32}H_{47}N_5O_6$+H, 598.3605).

3.3.4. Ziziphine Q (4). Colorless solid, mp 140–142 °C; $[\alpha]_D^{29} = -345.0$ (*c* 0.16, $CHCl_3$); UV (MeOH) λ_{max} 265 (log ε 3.64), 319 nm (log ε 3.50); IR (KBr) ν_{max} 3586, 3396, 2962, 2927, 2782, 1689, 1640, 1509, 1418, 1222, 1054 cm^{-1}; ^{1}H (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$), see Table 1; FABMS (positive ion mode) *m/z* 598 $[M+H]^+$ (38), 358 (4), 310 (1), 241 (1), 193 (6), 165 (2), 114 (100), 70 (6); HRFABMS (positive ion mode) *m/z* 598.3607 $[M+H]^+$ (calcd for $C_{32}H_{47}N_5O_6$+H, 598.3605).

3.4. Bioassay procedure

Antiplasmodial activity was evaluated against the parasite *P. falciparum* (K1, multidrug resistant strain), which was cultured continuously according to the method of Targer and Jensen.[26] Quantitative assessment of antiplasmodial activity in vitro was determined by means of the microculture radioisotope technique based upon the method described by Desjardins.[27] The inhibitory concentration which causes 50% reduction in parasite growth as indicated by the in vitro uptake of 3[*H*]-hypoxanthine by *P. falciparum*. An IC_{50} value of 1 ng/mL was observed for the standard compound, artemisinine, in the same test system. The antimycobacterial activity was assessed against *M. tuberculosis* H_{37}Ra using the Microplate Alamar Blue Assay.[28] Standard drugs, isoniazid and kanamycin sulfate, the reference compounds for the antimycobacterial assay, showed MIC of 0.6 and 2.5 μg/mL, respectively. The cytotoxicity of compounds **1**–**4** was determined, employing the colorimetric method as described by Skehan et al.[29] The reference substance, ellipticine, exhibited activities towards BC and KB cells with IC_{50} of 1.33 and 1.46 μg/mL, respectively.

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Enantioselective synthesis of *m*-carboranylalanine, a boron-rich analogue of phenylalanine

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Abstract—The enantiomers of the highly lipophilic α-amino acid *m*-carboranyl-alanine [3-(1,7-dicarba-*closo*-dodecaborane(12)-1-yl)-2-aminopropanoic acid], a carborane containing analogue of phenylalanine, have been synthesised via hydroxyamination of the *N*-acyl derivative formed from 3-(*m*-carboranyl)propionic acid [3-(1,7-dicarba-*closo*-dodeca-borane(12)-1-yl)-2-propanoic acid] and Oppolzer's camphor sultam. The enantiomeric excess of both enantiomers of the amino acid was >98%. (*S*)-Configuration was assigned to the (+)-enantiomer (CH_3OH, 589 nm).

1. Introduction

The carboranes $C_2B_{10}H_{12}$ exhibit remarkable chemical stability and are generally biologically inactive.[1] The high boron content of organic compounds substituted with polyhedral boron clusters make them interesting for use in Boron Neutron Capture Therapy (BNCT) of cancer, and has attracted much interest in recent years. For this purpose, numerous carborane-containing derivatives of biomolecules have been synthesised.[2–6] Until recently, only a few cases, besides the BNCT application, have been described where use has been made of the carborane cages as hydrophobic pharmacophores in biologically active molecules. One example of the most explored compounds is *o*-carboranyl-alanine, the *o*-carboranyl analogue of phenylalanine, which has been used to replace phenylalanine and tyrosine in a number of biologically active peptides. This work has recently been reviewed.[7] Research on the use of carboranes as hydrophobic pharmacophores has recently intensified,[8–11] particularly by Endo.[12–16] The carborane containing amino acid *o*-carboranylalanine [3-(1,2-dicarba-*closo*-dodecaborane(12)-1-yl)-2-aminopropanoic acid] (**1**), a highly lipophilic carboranyl analogue of phenylalanine, was first reported in racemic form) independently by Brattsev and Stanko[17] and Zakharkin et al.[18] Later several syntheses of optically active (**1**) have been reported.[19]

We have previously developed enantioselective routes to a number of other carboranyl amino acids with differing liphophilicity (Fig. 1): *o*-carboranylalanine (**1**)[19c,f,g] and its methyl derivative (**2**),[20] as well as 5-(1,2-dicarba-*closo*-dodecaborane(12)-1-yl)-2-aminopentanoic acid (**3**),[21] its methylated analogue (**4**)[21] and the hydrophilically substituted derivative (**5**)[22] of (**4**). Related compounds recently prepared, by asymmetric synthesis, in our laboratory are the enantiomers of [3-(1,2-dicarba-*closo*-dodecaborane(12)-1-yl)-2-amino-propanoic acid] (**6**), a *p*-carboranyl analogue of phenyl-alanine.[20]

We recently observed a new intramolecular self-degradation reaction of (**1**) and (**2**) to form the corresponding diastereomeric *nido*-analogues in water and methanol solutions. The reaction was studied in some detail for (**1**) and was found to be pH-dependent with a rate maximum at the pH of the isoelectric point ($p_i=4.9$).[19f,g,23] This degradation reaction might limit the use of (**1**) in biological experiments.

In this report we describe an enantioselective route to *m*-carboranylalanine (**7**). The amino acids *p*- and *m*-carboranylalanine, although having similar steric demands as *o*-carboranylalanine, will differ in lipophilicity ($o<m<p$) due to the differences in dipole moment of the cages.

2. Results and discussion

The amino acids were synthesised using Oppolzer's sultam

Keywords: *m*-Carboranylalanine; Absolute configuration; Carborane; Boron neutron capture therapy; Asymmetric synthesis; Highly lipophilic amino acid.
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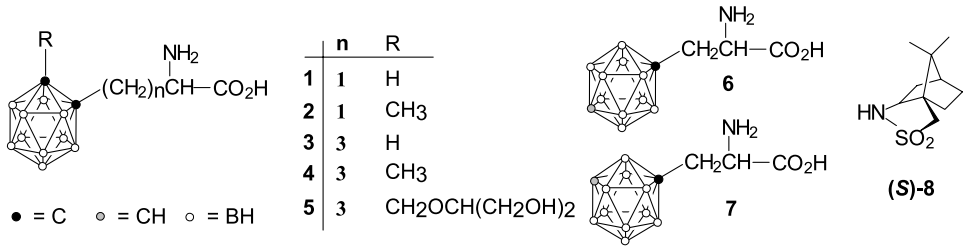
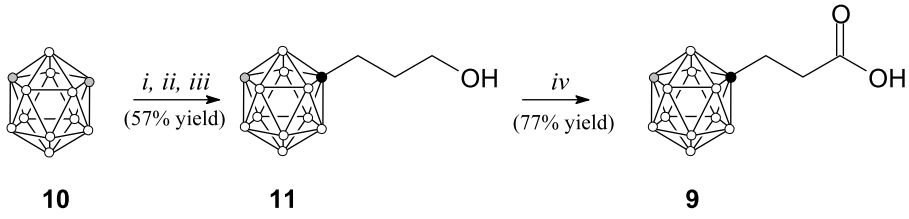


Figure 1.

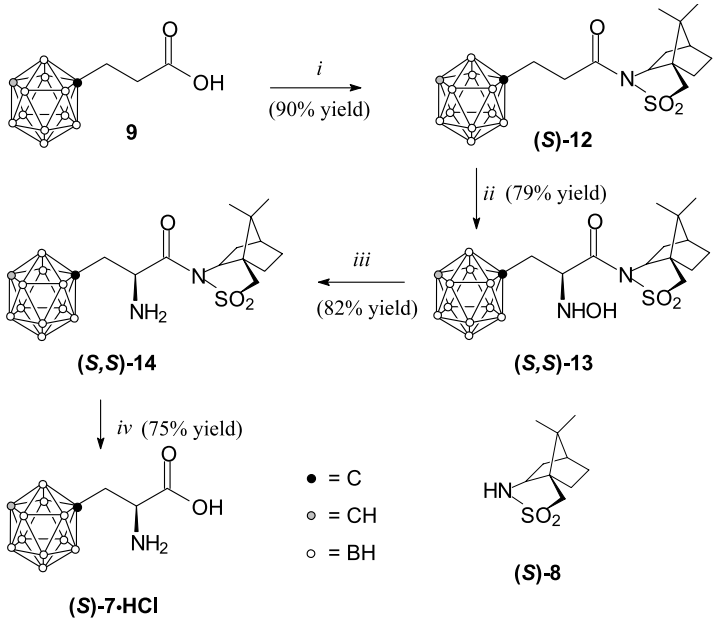


Scheme 1. (i) BuLi, TBDMS-Cl; (ii) BuLi, oxetane; (iii) $(n\text{-}C_4H_9)_4NF$; (iv) CrO_3, H_2SO_4/acetone.

methodologies for introduction of the chirality by hydroxyamination reactions of *N*-acyl derivatives of the sultam [(*S*)-**8**] or its enantiomer (Fig. 1).[24]

The synthesis of (*S*)-*m*-carboranylalanine, [(*S*)-**7**], required the *m*-carboranylpropanoic acid (**9**). *m*-Carborane (**10**) was protected using *tert*-butyldimethylsilyl chloride (TBDMSCl) (Scheme 1). Alkylation of the crude reaction mixture with trimethylene oxide and subsequent deprotection with tetrabutylammonium fluoride (TBAF) afforded the 1-(3-hydroxypropyl)-*m*-carborane (**11**) in 57% yield from *m*-carborane. Small amounts of 1,7-(3-hydroxypropyl)-*m*-carborane were isolated as well as unreacted *m*-carborane, which could be recovered. The 1-(3-hydroxypropyl)-*m*-carborane (**11**) was oxidised, using Jones' reagent (CrO_3/H_2SO_4), to the corresponding 3-(*m*-carboranyl)propionic acid (**9**) in 77% yield.

For further introduction of the chirality in the final product, Oppolzer's sultam methodologies were used.[24] The 3-(*m*-carboranyl)propionic acid (**9**) was reacted with camphor sultam [(*S*)-**8**] in the presence of dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) to afford [(*S*)-**12**] in 90% yield (Scheme 2). The enolate of the *N*-acylsultam [(*S*)-**12**] was treated with 1-chloro-1-nitrosocyclohexane to afford the hydroxyaminosultam [(*S*,*S*)-**13**] in 79% yield. *N*/*O*-Hydrogenolysis of the hydroxyaminosultam (Zn-dust HCl/acetic acid) provided the *N*-(α-aminoacyl)sultam [(*S*,*S*)-**14**] in 82% yield. Removal of the chiral auxiliary in LiOH/THF afforded



Scheme 2. (i) (*S*)-**8**, DCC, DMAP, CH_2Cl_2; (ii) $NaN(TMS)_2$, 1-chloro-1-nitroso-cyclohexane,THF; (iii) a. Zn-dust, HOAc/HCl, b. $NaHCO_3$; (iv) a. LiOH, b. HCl.

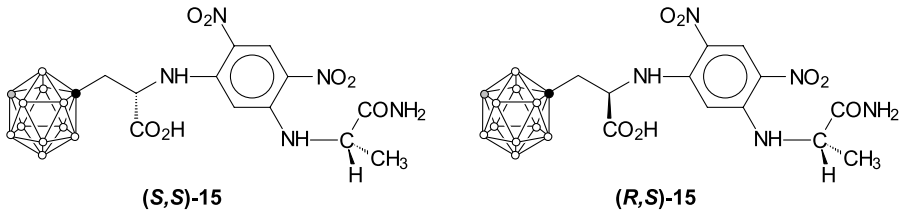


Figure 2.

(*S*)-*m*-carboranylalanine [(*S*)-**7**], which was isolated as the hydrochloride salt. The same procedure was applied for the preparation of the other enantiomer [(*R*)-**7**].

The enantiomeric purities of [(*S*)-**7**] and [(*R*)-**7**] were determined by chromatographic separation by HPLC of the diastereomeric derivatives [(*S*,*S*)-**15**] and [(*R*,*S*)-**15**], respectively (Fig. 2), formed by reaction with Marfey's reagent, *N*-α-(2,4-dinitro-5-fluoro-phenyl)-(*S*)-alanine-amide.[25] This method has been verified as a reliable method for the determination of enantiomeric purities of other carboranylamino acids.[19f,g,20–22,26] The enantiomeric excess of both [(*S*)-**7**] and [(*R*)-**7**] were found to be >98%.

The assignment of absolute configurations of the amino acid **7** is based on the stereochemical outcome of previously reported hydroxyamination reactions[24] and is supported by the fact that for the amino acids (**1**),[19f,g,26] (**3**)[21] and (**4**)[21] (with known absolute configurations) the derivatives formed by reacting the (*S*)-enantiomers with Marfey's reagent all show the same chromatographic elution order as [(*S*,*S*)-**15**]. The hydrochloride of [(*S*)-**7**] is dextrorotatory in methanol at 589 nm.

3. Conclusion

In summary we have shown that both enantiomers of the highly lipophilic amino acid [3-(1,7-dicarba-*closo*-dodecaborane(12)-1-yl)-2-aminopropanoic acid] (*m*-carboranylalanine), can be prepared in high enantiomeric excess.

4. Experimental

4.1. General instructions

The ^{1}H, ^{13}C, and ^{11}B NMR spectra were recorded in $CDCl_3$ (7.26 ppm ^{1}H, 77.0 ppm ^{13}C) or CD_3OD (3.35 ppm ^{1}H, 49.0 ppm ^{13}C) on a Varian XL-300 spectrometer operating at 300, 75.4, and 96.2 MHz, respectively. Boron trifluoride-diethyl ether was used as an external standard for the boron spectra. IR spectra were obtained with a Perkin–Elmer 1600 FT-IR spectrometer. In the determination of enantiomeric purities of the amino acids according to the method by Marfey, the separation of the diastereomeric derivatives was performed on a 250 mm×4.6 mm Spherisorb ODS1 10 μm column using a Waters HPLC system equipped with a Waters 991 Photodiode Array Detector (340 nm) and a Millenium 2010 Chromatographic Manager. Solvents A (0.01 M potassiumdihydrogen phosphate) and B (acetonitrile/water (50/7, v/v)) with the gradient system 25% B to 50% B were used as the eluting system. For flash chromatography, Merck Silica Gel 60 (230–400 mesh) was used. TLC was performed using Merck Silica 60 F_{254} gel. Melting points are uncorrected and were obtained using a Büchi capillary melting point apparatus. Solvents were dried and distilled according to standard methods.

4.2. Synthesis

4.2.1. 1-(3-Hydroxypropyl)-*m*-carborane (11). *m*-Carborane (**10**) (5.01 g, 35 mmol) was dissolved in anhydrous THF (60 ml) under N_2 and cooled to 0 °C. *n*-Butyllithium (21.5 ml, 35 mmol), as a 1.6 M solution in hexane was added and the reaction mixture was stirred at 0 °C for 1 h and then allowed to warm to RT. *tert*-Butyl-dimethylsilyl chloride (5.22 g, 35 mmol) was added and the reaction mixture was refluxed overnight and then quenched with H_2O (30 ml). The THF was evaporated under reduced pressure and the remaining residue was extracted with diethyl ether (3×30 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the diethyl ether was evaporated under reduced pressure. The remaining residue was dissolved in anhydrous THF (25 ml) under N_2 and cooled to 0 °C. *n*-Butyllthium (21.5 ml 35 mmol), as a 1.6 M solution in hexane, was added and the reaction mixture was stirred at 0 °C for 1 h. Trimethylene oxide (2.20 ml, 35 mmol) was added, the reaction mixture was refluxed overnight and then quenched with 1 M aqueous HCl (30 ml). The THF was evaporated under reduced pressure and the remaining residue was extracted with diethyl ether (3×30 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the diethyl ether was evaporated under reduced pressure. The remaining residue was dissolved in anhydrous THF (40 ml) and cooled to −78 °C, under N_2. Tetrabutylammonium fluoride (31.9 ml, 35 mmol), as a 1.1 M solution in THF, was added dropwise and the reaction mixture was stirred at −78 °C for 1 h and then quenched with H_2O (50 ml). The THF was evaporated under reduced pressure and the remaining residue was extracted with diethyl ether (3×40 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the diethyl ether was evaporated under reduced pressure. Purification by column chromatography on silica (diethyl ether/pentane 1:2) gave **11** (4.03 g, 19.9 mmol), 57%, R_f=0.19. An analytical sample was obtained, as a white solid, by recrystallisation from hexane. Mp=84–85 °C; ^{1}H NMR ($CDCl_3$) δ 1.54–1.64 (m, 2H, CH_2–CH_2–CH_2), 1.99–2.09 (m, 2H, C–CH_2–CH_2), 2.91 (brs, 1H, CH_{cage}), 3.47 (dd, J=6.4 Hz, 2H, CH_2–OH); ^{13}C NMR ($CDCl_3$) δ 32.3 ($CH_2\beta$), 32.9 ($CH_2\gamma$), 54.4 (CH_{cage}), 61.3 ($CH_2\alpha$), 77.2 (C_{cage}); ^{11}B NMR ($CDCl_3$) δ −4.2, −11.1, −14.7, −16.4; IR (KBr) ν: 3288 (m, br), 2958 (w), 2602 (s), 1451 (w), 1059 (s), 1007 (m), 729 (m) (cm^{-1}); Anal. calcd for $C_5H_{18}B_{10}O$: C, 29.69; H, 8.97; Found: C, 29.76; H, 8.94.

4.2.2. 3-(*m*-Carboranyl)propionic acid (9). 1-(3-Hydroxypropyl)-*m*-carborane (**11**) (2.04 g, 10.1 mmol) was dissolved in acetone (60 ml) and cooled to 0 °C. CrO_3 (4.08 g, 40.8 mmol) was dissolved in 3 M aqueous H_2SO_4 (20 ml) and added dropwise over a period of 30 min. The reaction mixture was stirred at 0 °C for 3 h and then quenched with H_2O (60 ml). The acetone was evaporated under reduced pressure and the aqueous residue was extracted with diethyl ether (3×60 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the diethyl ether was evaporated under reduced pressure. The remaining residue was dissolved in 2 M aqueous NaOH, filtered through celite, and the filtrate was acidified with conc. HCl. Filtration gave 3-(*m*-carboranyl)propionic acid (1.69 g, 7.82 mmol) 77%. An analytical sample was obtained, as a white solid, by recrystallisation from hexane. Mp=136–137 °C; ^{1}H NMR ($CDCl_3$) δ 2.28–2.34 (m, 2H, $CH_2\beta$), 2.41–2.48 (m, 2H, $CH_2\alpha$), 2.93 (brs, 1H, CH_{cage}); ^{13}C NMR ($CDCl_3$) δ 30.6 ($CH_2\alpha$), 33.3 ($CH_2\beta$), 54.6 (CH_{cage}), 77.2 (C_{cage}) 176.9 (C=O); ^{1}B NMR ($CDCl_3$) δ −4.5, −10.8, −14.6, −16.2; IR (KBr) ν: 3062 (w), 2598 (s), 1702 (s), 1431 (w), 1320 (w), 1229 (w) (cm^{-1}); Anal. calcd for $C_5H_{16}B_{10}O_2$: C, 27.77; H, 7.46; Found: C, 27.92; H, 7.39.

4.2.3. (2*S*)-*N*-[3′-(1″-7″-Dicarba-*closo*-dodecaborane-(12)-1″-yl)propanoyl] bor-nane-10,2-sultam [(*S*)-12]. 3-(*m*-Carboranyl)propionic acid (**9**) (1.00 g, 4.63 mmol) was dissolved in anhydrous CH_2Cl_2 (30 ml) under N_2. Sultam (0.96 g, 4.65 mmol), DCC (1.00 g, 4.87 mmol), and DMAP (30 mg), dissolved in anhydrous CH_2Cl_2 were added and the reaction mixture was stirred at RT overnight. The precipitate was filtered off and the CH_2Cl_2 was evaporated under reduced pressure. Purification by column chromatography (diethyl ether/pentane 1:2) gave the title compound (1.73 g, 4.19 mmol) 90%, R_f=0.13. An analytical sample was obtained, as a white solid, by recrystallisation from MeOH. Mp=206–207 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.34–1.40 (m, 2H, CH_2–CH_2–CH), 1.87–1.91 (m, 3H, CH_2–CH_2–CH), 2.05–2.07 (m, 2H, CH–CH_2–CH), 2.32–2.38 (m, 2H, O=C–CH$_2$–CH_2), 2.76–2.82 (m, 2H, O=C–CH$_2$), 2.91 (brs, 1H, CH_{cage}), 3.46 (AB, 2H, J=14 Hz, δ=23 Hz, CH_2–SO_2), 3.82 (dd, 1H, J=5, 8 Hz, N–CH); ^{13}C NMR ($CDCl_3$) δ 199 (CH_3), 20.8 (CH_3), 26.4 (CH_2), 32.8 (CH_2), 35.2 (CH_2), 38.3 (CH_2), 44.6 (CH), 47.8 (C), 48.6 (C), 52.8 (CH_2), 54.4 (CH_{cage}), 65.2 (CH), 169.5 (C=O); ^{11}B NMR ($CDCl_3$) δ −4.0, −10.8, −14.0, −16.2; IR (KBr) ν: 2958 (w), 2598 (s), 1681 (s), 1394 (m), 1329 (s), 1267 (w), 1237 (m), 1220 (m), 1164 (w), 1135 (m), 1116 (m), 533 (m) (cm^{-1}); $[\alpha]^{25}_{589}$=+73.1 (c=1.00 $CHCl_3$); Anal. calcd for $C_{15}H_{31}B_{10}NO_3S$: C, 43.56; H, 7.55; N, 3.39; Found: C, 43.76; H, 7.62; N, 3.46.

4.2.4. (2*R*)-*N*-[3′-(1″-7″-Dicarba-*closo*-dodecaborane-(12)-1″-yl)propanoyl]-born-ane-10,2-sultam [(*R*)-12]. The title compound was prepared according to the same procedure as described for [(*S*)-**12**]. Mp=207 °C. Spectral data were in accordance with [(*S*)-**12**]. $[\alpha]^{25}_{589}$=−73.0 (c=1.00 $CHCl_3$).

4.2.5. (2*S*,2*S*′)-*N*-(3′-(1″,7″-Dicarba-*closo*-dodecaborane(12)-1″-yl)-2′-(hydroxy-amino)-propanoyl)-bornane-10,2-sultam [(*S*,*S*)-13]. The sultam [(*S*)-**12**] (250 mg, 0.60 mmol) was dissolved in anhydrous THF (5 ml) and cooled to −78 °C under N_2. Sodium *N*-bis(trimethylsilyl)amide (0.65 ml, 0.65 mmol), as a 1.0 M solution in THF, was added dropwise and the reaction mixture was stirred at −78 °C for 1 h. 1-Chloro-1-nitrosocyclohexane (0.62 ml, 0.80 mmol), as a 1.3 M solution in THF, was added and the reaction mixture was stirred at −78 °C for 2 h and then quenched with 1 M aqueous HCl (5 ml). The THF was evaporated under reduced pressure and the aqueous solution was neutralised with saturated aqueous Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2 (3× 15 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the CH_2Cl_2 was evaporated under reduced pressure. Purification by column chromatography on silica (toluene/MeCN/Et_3N 95:5:1) gave the title compound (201 mg, 0.47 mmol) 79%, R_f=0.15. An analytical sample was obtained, as a white solid, by recrystallisation from MeOH. Mp=215–218 °C; ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3H, –CH_3), 1.18 (s, 3H, –CH_3), 1.35–1.42 (m, 2H, –CH_2–CH_2–CH), 1.88–1.94 (m, 2H, –CH$_2$–CH_2–CH), 2.07–2.19 (m, 4H, –(C=O)–CH–CH_2, CH–CH_2–CH–, –C–CH_2–CH$_2$–), 2.63 (dd, J=4, 15 Hz, 1H, –(C=O)–CH–CH_2–), 2.91 (brs, 1H, CH_{cage}), 3.51 (AB, J=14 Hz, δ=23 Hz, 2H, CH_2–SO_2–), 3.91 (dd, J=5, 8 Hz, 1H, N–CH–CH$_2$–CH–), 4.09 (dd, J=5, 8 Hz, 1H, (C=O)–CH–), 4.51 (brs, 1H, NHOH), 6.06 (brs, 1H, NHOH); ^{13}C NMR ($CDCl_3$) δ 19.9 (C–CH_3), 20.5 (C–CH_3), 26.4 (–CH$_2$–CH_2–CH–), 32.7 (–CH$_2$–CH_2–CH–), 34.9 (cage-CH_2), 38.0 (–CH–CH_2–CH–), 44.5 (CH$_2$–CH$_2$–CH), 47.9 (C–(CH_3)$_2$–), 49.0 (CH$_2$–C–CH–), 53.0 (–CH_2–SO_2), 55.1 (CH_{cage}), 63.8 (C=O)–CH), 65.3 (N–CH–CH$_2$–CH–), 77.2 (C_{cage}), 170.7 (C=O); ^{11}B NMR ($CDCl_3$) δ −4.1, −10.8, −14.4, −15.9; $[\alpha]^{25}_{589}$=+62.5 (c=1.02 $CHCl_3$); IR (KBr) ν: 2958 (w), 2602 (s), 1718 (m), 1645 (s), 1303 (s), 1254 (w), 1167 (w), 1139 (w), 119 (w), 1064 (m), 552 (m), 538 (m); Anal. calcd for $C_{15}H_{32}B_{10}N_2O_4S$: C, 40.52; H, 7.25; N, 6.30; Found: C, 40.74; H, 7.29; N, 6.13.

4.2.6. (2*R*,2*R*′)-*N*-(3′-(1″,7″-Dicarba-*closo*-dodecaborane(12)-1″-yl)-2′-(hydroxy-amino)propanoyl)-bornane-10,2-sultam [(*R*,*R*)-13]. The title compound was prepared according to the same procedure as described for [(*S*,*S*)-**13**]. Mp=216–218 °C. Spectral data were in accordance with [(*S*,*S*)-**13**]. $[\alpha]^{25}_{589}$=−62.8 (c=1.02 $CHCl_3$).

4.2.7. (2*S*,2*S*′)-*N*-(3′(1″,7″-dicarba-*closo*-dodecaborane(12)-1″-yl)-2′-aminopropan-oyl)-bornane-10,2-sultam [(*S*,*S*)-14]. The hydroxyamino compound [(*S*,*S*)-**13**] (200 mg, 0.45 mmol) was dissolved in acetic acid/conc. HCl 11:1 (6 ml) and cooled to 4 °C, under N_2. Zn dust (0.54 g, 8.31 mmol) was added and the reaction mixture was stirred at 4 °C for 3 days. The mixture was filtered through glass wool and concentrated under reduced pressure. The residue was partly dissolved in CH_2Cl_2, neutralised with aqueous $NaHCO_3$, and filtered. The residue was extracted with CH_2Cl_2 (3×10 ml), the combined organic layers were dried over Na_2SO_4, filtered, and the CH_2Cl_2 was evaporated under reduced pressure to give the title compound (157 mg, 0.37 mmol) 82%. An analytical sample was obtained, as a white solid, by recrystallisation from MeOH/H_2O. Mp=232–233 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 1.35–1.46 (m, 2H, CH_2–CH_2–CH), 1.50 (brs, 2H, NH_2), 1.88–1.93 (m, 4H, CH_2–CH_2–CH, CH_2–CH–C=O),

2.06–2.11 (m, 2H, CH–CH_2–CH), 2.62 (dd, $J=6$, 15 Hz, 1H, CH_2–CH–C=O), 2.91 (brs, 1H, CH_{cage}), 3.51 (AB, $J=$ 14 Hz, $\delta=21$ Hz, 2H, CH_2–SO_2), 3.89 (m, 2H, CH–C=O, N–CH); ^{13}C NMR δ 19.8 (CH_3), 20.8 (CH_3), 26.3 (CH_2), 32.7 (CH_2), 38.0 (CH_2), 39.3 (CH_2), 44.5 (CH), 47.8 (C), 48.9 (C), 52.9 (CH_2), 54.1 (CH), 55.1 (CH_{cage}), 65.1 (CH), 77.2 (C_{cage}), 172.4 (C=O); ^{11}B NMR ($CDCl_3$) δ −3.9, −10.8, −13.8, −15.3; IR, cm^{-1} ($CHCl_3$): 3621, 3434 (NH_2), 3019, 2975, 2400, 1691, 1219, 1047; $[\alpha]^{25}{}_{589}=$ +69.9 ($c=0.99$ $CHCl_3$); Anal. calcd for $C_{15}H_{32}B_{10}N_2O_3S$: C, 42.04; H, 7.53; N, 6.54: Found: C, 42.29; H, 7.58; N, 6.44.

4.2.8. (2*R*,2*R*′)-*N*-(3′(1″,7″-dicarba-*closo*-dodecaborane(12)-1″-yl)-2′-amino-pro-panoyl)-bornane-10,2-sultam [(*R*,*R*)-14]. The title compound was prepared according to the same procedure as described for [(*S*,*S*)-**14**]. Mp= 233–234 °C. Spectral data were in accordance with [(*S*,*S*)-**14**]. $[\alpha]^{25}{}_{589}=-70.4$ ($c=0.99$ $CHCl_3$).

4.2.9. (*S*)-*m*-Carboranylalanine hydrochloride [(*S*)-7·HCl]. The sultam [(*S*,*S*)-**14**] (36 mg, 0.084 mmol) was dissolved in THF (2 ml). 1 M LiOH (0.30 ml) was added and the reaction mixture was stirred at RT overnight. The THF was evaporated under reduced pressure and the aqueous mixture was acidified with 3 M aqueous HCl and stirred for 1 h. Filtration gave (*S*)-*m*-carboranylalanine hydrochloride, as a white solid, in 75% yield (46 mg, 0.17 mmol). ^{1}H NMR (CD_3OD) δ 2.18 (dd, 1H, $J=6$, 16 Hz, C$H_2\beta$), 2.30 (dd, 1H, $J=5$, 16 Hz, C$H_2\beta$), 3.98 (t, $J=6$ Hz, 1H, C$H\alpha$); ^{13}C NMR δ −40.2 (CH_2), 53.8 (CH), 171.1 (C=O); $[\alpha]^{25}{}_{589}=+5.3$ ($c=0.95$ CH_3OH).

4.2.10. (*R*)-*m*-Carboranylalanine hydrochloride [(*R*)-7·HCl]. The title compound was prepared according to the same procedure as described for the enantiomer. Spectral data were in accordance with [(*S*)-**7·HCl**]. $[\alpha]^{25}{}_{589}=-4.8$ ($c=0.95$ CH_3OH).

4.3. Determination of enantiomeric purity

To ca. 1 mg of amino acid hydrochloride, [(*S*)-**7·HCl**] or [(*R*)-**7·HCl**], was added Marfey's reagent (0.200 ml, 1% solution in acetone) followed by 1.0 M aqueous $NaHCO_3$ (0.080 ml). The reaction vial was closed and heated at 40 °C for 1 h. The reaction was quenched by the addition of 1 M aqueous HCl (0.080 ml), diluted with DMSO (0.50 ml) and analysed by HPLC using the solvent system A/B.

Acknowledgements

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Enantioselective syntheses of two 5, 9*E* diastereomers of 223V, an alkaloid from the poison frog *Dendrobates pumilio*

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Abstract—Enantioselective syntheses of two 5, 9*E* diastereomers (**1** and **2**) of **223V** (**3**) are described. Neither corresponded on GC–MS and GC-FTIR analyses to alkaloid **223I**, previously tentatively proposed to be a 5,8-disubstituted indolizidine of the unusual 5, 9*E* relative stereochemistry. Synthetic (−)-(5, 9*Z*)-5-*n*-propyl-8-*n*-butylindolizidine (**3**) corresponds on GC–MS and GC-FTIR analyses to the natural indolizidine **223V** found in a *pumilio* from 'Split Hill', Panama.

1. Introduction

5,8-Disubstituted indolizidines represent a major class of alkaloids found in skins of poison frogs.[1] Over 60 such alkaloids have been proposed. Some structures are tentative, being based only on their GC–MS, dominated by a base peak due to α-cleavage of the 5-substituent, followed by a *retro*-Diels–Alder loss to yield a characteristic fragment at *m/z* 96.[2] Several of the 5,8-disubstituted indolizidines have been isolated from frog skin in sufficient quantities to allow structure confirmation by NMR spectral analysis. These include (−)-**203A**,[13] (−)-**205A**,[14] (−)-**207A**,[15] **233D**,[13] (−)-**235B′** and (+)-**235B″** (formerly **235B**).[14,15] Structures are shown in Figure 1. The structures of (−)-**207A**, (−)-**235B′**, and (+)-**235B″** have been confirmed by enantioselective synthesis.[3,16,17] The relative stereochemistry of **205A** is depicted on the basis of comparison with synthetic racemic material.[18] The structure and absolute stereochemistry of natural **209I**[15] was confirmed (unpublished results) by comparison to synthetic racemic material,[19] and the synthetic (−)-unnatural enantiomer.[20] Several laboratories have reported syntheses of (−)-**209B**.[18,21,22] Virtually all alkaloids of this class possess a 5, 9*Z* structure as shown by a characteristic sharp and intense Bohlmann

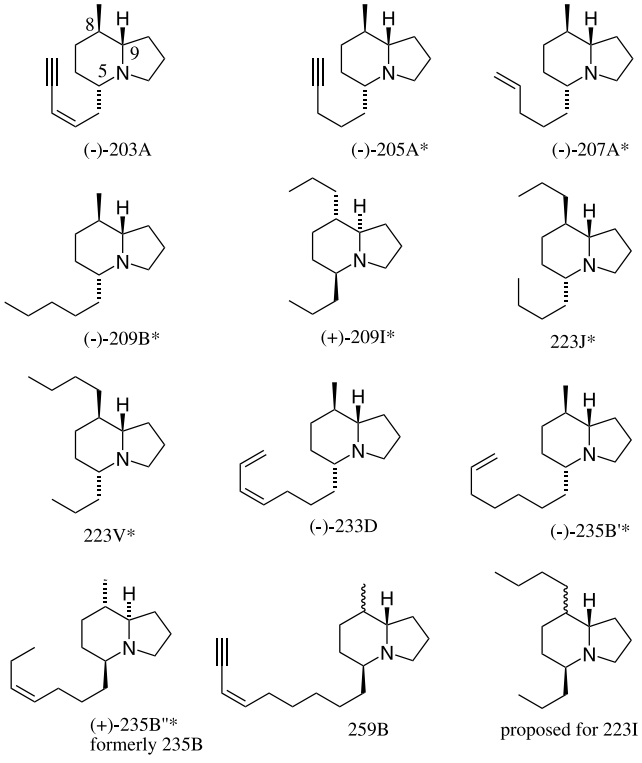

Figure 1. Alkaloids of the 5,8-disubstituted indolizidine class: structures of **203A**, **205A**, **207A**, **233D**, **235B′** and **235B″** were established by NMR spectral analysis, while structures indicated by an asterisk have been synthesized (see text). Absolute configurations have been established for the indicated alkaloids.

Keywords: Enantioselective syntheses; Diastereomers; Alkaloid.
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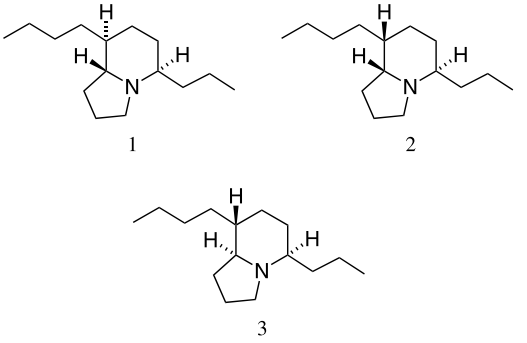
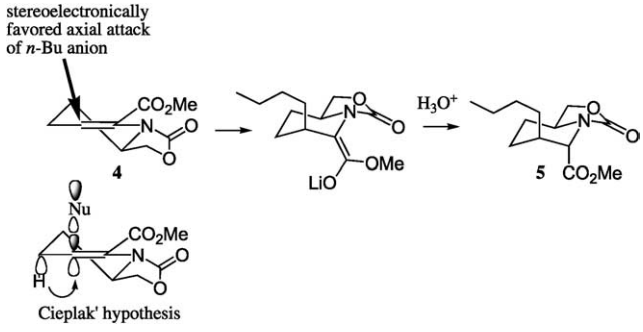
band near 2790 cm^{-1} in their GC-FTIR spectra.[2] Only two alkaloids have been tentatively proposed to be (5, 9*E*)-5,8-disubstituted indolizidines, based on GC–MS and a weak absorbance in the Bohlmann band region on GC-IR.[1] One of these is alkaloid **259B** from one population of *Dendrobates pumilio* with an EI-MS showing the α-cleavage expected of a 5-C_9H_{13}-8-CH_3-indolizidine, followed by *retro*-Diels–Alder cleavage of the fragment at *m/z* 138 to yield a significant diagnostic ion at *m/z* 96. The second was alkaloid **223I** from another population of the poison frog *D. pumilio*, tentatively proposed to have a (5, 9) *E*-5-propyl-8-butylindolizidine structure even though the diagnostic peak in EI-MS at *m/z* 96 was much weaker than expected.

In this paper, we would like to report the enantioselective syntheses of two 8-epimers of (5, 9*E*) 5-propyl-8-butyl-indolizidine (**1**, **2**) and comparison to alkaloid **223I**. In addition, a previously synthesized (−)-(5, 9*Z*) 5-propyl-8-butylindolizidine[3] (**3**) has now been shown to be identical in GC–MS and GC-FTIR to alkaloid **223V** from yet another population of the same poison frog, *D. pumilio* from 'Spilit Hill', Panama.



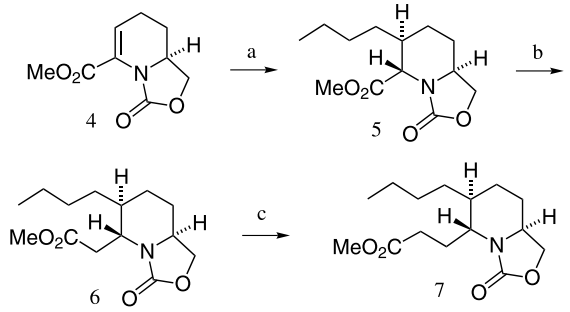
2. Results and discussion

The stereoselective synthesis of **3** has been described.[3] The synthesis of **1** began with the enaminoester **4**,[4] which was treated with lithium dibutylcuprate to afford the adduct **5** as a single isomer.[5] The stereoselectivity of this addition reaction can be explained by the stereoelectronic effect[6] and Cieplak's hypothesis[7] as shown below (Scheme 1).

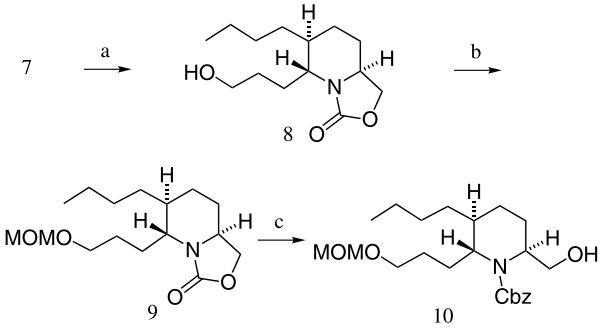


Scheme 1.

The carbon chain at the α-position of **5** was elongated by two Arndt–Eistert reactions to provide the two-carbon homologated ester **7**, which was converted to the methoxymethyl ether **9** by reduction of the ester moiety of **7** with Super-Hydride, followed by protection of the resulting alcohol **8** as shown in Schemes 2 and 3.

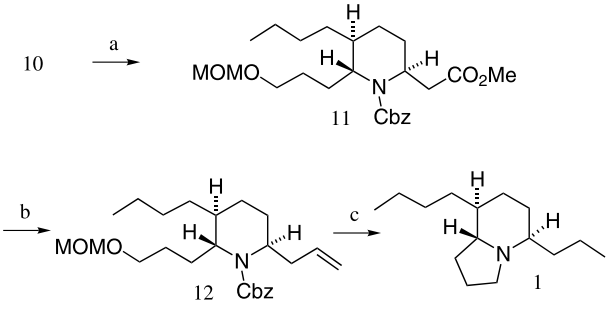


Scheme 2. (a) *n*-Bu_2CuLi, −78 to −10 °C (96%); (b) (1) LiOH, MeOH–H_2O, reflux; (2) $ClCO_2Et$, Et_3N, THF, 0 °C; (3) CH_2N_2; (4) $PhCO_2Ag$, Et_3N, MeOH, rt (80% in 4 steps); (c) same as (b) (86% in 4 steps).



Scheme 3. (a) Super-Hydride, THF, 0 °C (88%); (b) MOMCl, Hünig base, CH_2Cl_2, rt (87%); (c) (1) 2 M KOH/*i*-PrOH, 120 °C, sealed tube; (2) CbzCl, K_2CO_3, H_2O–CH_2Cl_2, rt (82% in 2 steps).

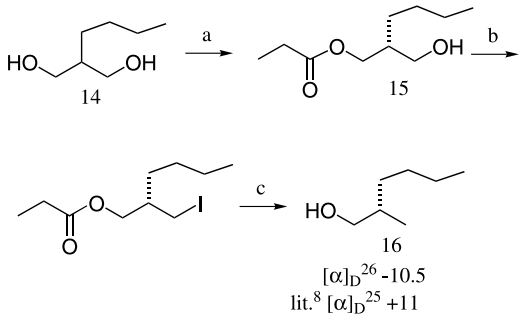
Hydrolysis of the oxazolizinone ring in **9** with KOH in a sealed tube, and protection of the resulting amino alcohol with CbzCl provided the alcohol **10**. Two-step oxidation of the alcohol **10** followed by Arndt–Eistert reaction afforded the methyl ester **11** (Scheme 4), which was reduced with DIBAL. Wittig olefination of the resulting aldehyde intermediate provided the olefin **12**. Hydrogenation of the double bond and hydrogenolysis of the Cbz-protecting group of **12**, and then removal of the methoxymethyl group with acid followed by indolizidine formation from the



Scheme 4. (a) (1) Swern ox.; (2) $NaClO_2$, H_2O–*t*-BuOH, 0 °C–rt; (3) $ClCO_2Et$, Et_3N, THF, 0 °C; (4) CH_2N_2; (5) $PhCO_2Ag$, Et_3N, MeOH, rt (54% in 5 steps); (b) (1) DIBAL, CH_2Cl_2, −78 °C (2) Witting reagent (57% in 2 steps); (c) (1) 10% Pd–C, H_2, EtOAc, 1 atm; (2) conc. HCl, MeOH, reflux; (3) CBr_4, Ph_3P, CH_2Cl_2, rt then Et_3N (67% in 3 steps).

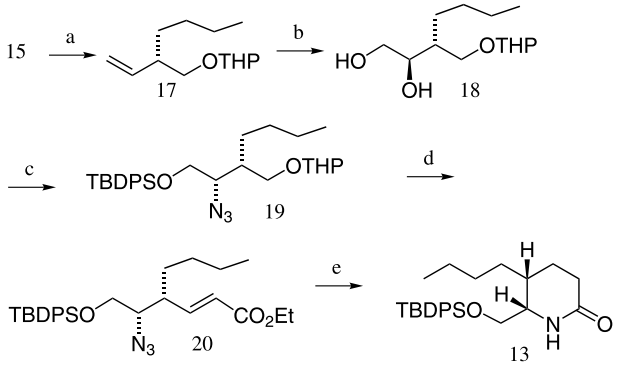
resulting amino alcohol via an intermediate bromide furnished the desired indolizidine **1** as shown in Scheme 4.

Synthesis of the indolizidine **2** was as follows: Lipase-mediated transesterification of the *meso*-diol **14** afforded the mono-propanoate **15**, which was transformed into the known 2-methyl-1-hexanol **16** via an intermediate iodide in a 3-step sequence as shown in Scheme 5. The enantiomeric excess of **15** was determined to be 95% ee using a GC chiral column and by comparison of the optical rotation of synthetic **16** with a reported value for the (+)-enantiomer.[8]



Scheme 5. (a) Lipase from *Pseudomonas cepacia* (Amano PS), vinyl propanoate MeCN (90%, 95% ee); (b) (1) MsCl, pyridine, CH_2Cl_2 (99%); (2) NaI, acetone (94%); (c) $LiAlH_4$, THF (69%).

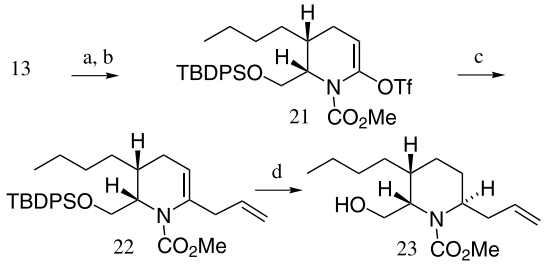
The mono-propanoate **15** was converted to the olefin **17**, which was subjected to $(DHQD)_2PYR$ ligand-induced Sharpless asymmetric dihydroxylation reaction[9] to give the diol **18** as shown in Scheme 6.



Scheme 6. (a) (1) DHP, PPTS, CH_2Cl_2; (2) K_2CO_3, MeOH; (3) Swern ox.; (4) $CH_3P^+Ph_3I^-$, *n*-BuLi, THF (80% in 4 steps) (b) $(DHQD)_2PYR$, K_2OsO_4, $K_3Fe(CN)_6$, K_2CO_3, H_2O–*t*-BuOH, 0 °C (84%); (c) (1) TBDPSCl, Et_3N, DMAP, CH_2Cl_2 (99%); (2) MsCl, Et_3N, CH_2Cl_2, 0 °C; (3) NaN_3, DMF 80 °C (73% in 2 steps); (d) (1) PPTS, EtOH, 60 °C; (2) Swern ox.; (3) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF (88% in 3 steps, 9:1 mixture of diastereomers); (e) 10% Pd–C, H_2, EtOAc, 4 atm (56%) isolated yield); only major diastereomers of **18**, **19**, and **20** are shown here.

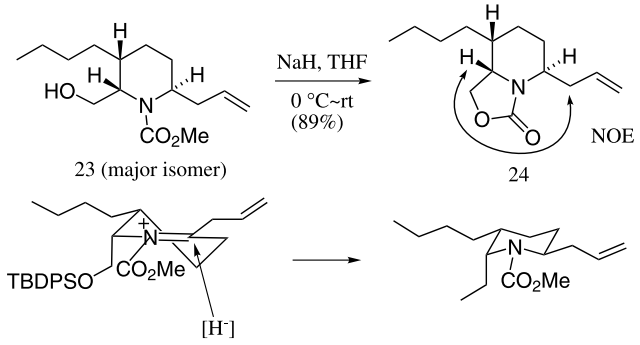
Protection of the primary hydroxyl group in **18** followed by substitution of the secondary hydroxyl group with NaN_3 via its mesylate provided azide **19**, which was transformed into the unsaturated ester **20**. Hydrogenation of **20** gave rise to 5,6-*cis*- and *trans*-piperidones. The desired 5,6-*cis*-piperidone **13** was isolated in 56% yield.

After conversion of **13** to the corresponding methyl urethane, the urethane was treated with Comins' triflating reagent[10] to yield the enoltriflate **21** as shown in Scheme 7.



Scheme 7. (a) *n*-BuLi, $ClCO_2Me$, THF, −78–0 °C (98%); (b) LiHMDS, 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine, THF, −78 to −40 °C (96%); (c) LiCl, allyltributyltin, $Pd(Ph_3P)_4$, THF, rt (92%); (d) TFA, $NaBH_3CN$, CH_2Cl_2, −45 °C (65% isolated yield, 2,6-*trans*/*cis* = 11:1).

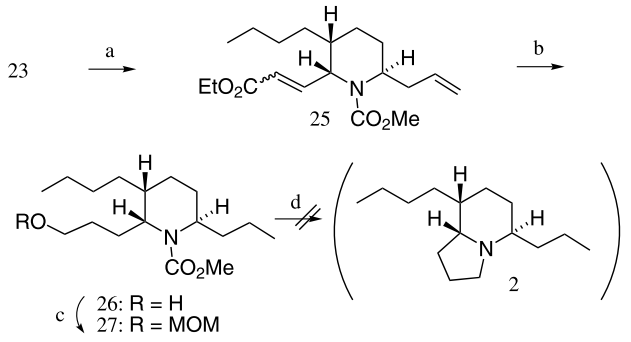
The triflate **21** was subjected to a Stille-type coupling reaction[11] using allyltributyltin to provide the olefin **22**. A stereoselective reduction of **22** with $NaBH_3CN$ under acidic conditions gave rise to the reduction product as an 11:1 mixture. The major isomer **23** was isolated in 65% yield. The stereochemistry of **23** was determined to be that of the desired 2,6-*trans* piperidine, based on the NOE spectrum of the corresponding oxazolizinone **24**. The stereochemical course of the attack of the hydride on the iminium salt generated from **22** under the acidic condition can be explained by $A^{(1,2)}$ strain and a stereoelectronic effect[6] as shown below (Scheme 8).



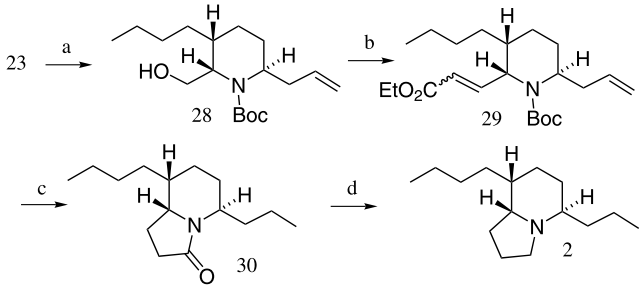
Scheme 8.

The carbon-chain on the 2-position of **23** was elongated by Swern oxidation followed by Horner–Emmons reaction to give **25**. Hydrogenation of **25** over Pd–C and reduction of the resulting ester with Super-Hydride afforded the alcohol **26** whose hydroxyl group was protected with methoxymethyl chloride in the presence of Hünig base to give **27**. Finally, the ether **27** was subjected to a 3-step indolizidine ring closure reaction, but no indolizidine formation was observed (Scheme 9).

A conversion of **23** to the desired indolizidine **2** was then attempted via the bicyclic lactam **30** as shown in Scheme 10. The methyl urethane **23** was converted to Boc-urethane **28** in two-step sequence and the carbon-chain on the 2-possition of **28** was elongated same as **25** in Scheme 9 to give rise to **29**. Hydrogenation of **29**, hydrolysis of the resulting ester, followed by removal of the Boc group with



Scheme 9. (a) (1) Swern ox.; (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (*E*/*Z*= 4:1, 87% in 2 steps); (b) (1) 10% Pd–C, H_2, EtOAc; (2) Super-Hydride, THF, 0 °C (96% in 2 steps); (c) MOMCl, Hünig base, CH_2Cl_2, rt (94%); (d) (1) *n*-PrSLi, HMPA–THF, 0 °C–rt; (2) conc. HCl, MeOH, reflux; (3) CBr_4, Ph_3P, then Et_3N, CH_2Cl_2, 0 °C.



Scheme 10. (a) (1) 2 M KOH/*i*PrOH, 120 °C sealed tube; (2) Boc_2O, NaOH, dioxane–H_2O (70% in 2 steps); (b) (1) Swern ox.; (2) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (*E*/*Z*=4: 1, 95% in 2 steps) (c) (1) 10% Pd–C, H_2, EtOAc, 1 atm; (2) LiOH, H_2O–EtOH, 60 °C; (3) TFA, CH_2Cl_2, rt; (4) DEPC, Et_3N, DMF, rt (91% in 4 steps); (d) $LiAlH_4$, THF, reflux (81%).

CF_3CO_2H and lactam formation using the Shioiri's reagent[12] gave rise to **30**. Reduction of the lactam moiety in **30** with $LiAlH_4$ furnished the desired indolizidine **2**.

3. Conclusion

The synthesis and properties of indolizidine **3** have been reported.[3] It proved on GC–MS {223 (M^+, 1), 222 (1), 180 (100), 166 (1), 138 (1), 136 (1), 126 (1), 124 (2), 110 (2), 108 (1), 96 (12), 70 (9), 55 (4)} and GC-FTIR (2968, 2938, 2880, 2787, 1459, 1377, 1133 cm^{-1}) analysis to be identical to natural indolizidine **223V**.

Synthesis of the 5, 9*E*-indolizidines **1** and **2** provided clear proof that alkaloid **223I** was not a 5, 9*E*-indolizidine. Both **1** and **2** had an appreciable *retro*-Diels–Alder fragment at *m*/*z* 96, while **223I** did not. The structure of natural **223I** should be revised, but further studies are required for the determination of the structure of natural product and results will be reported in due course.

4. Experimental

4.1. General

Melting points were determined with a Yanaco micro melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were taken on a Varian Gemini 300 or Unity Plus 500 spectrometer. ^1H NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in parts per million (ppm, δ) downfield from TMS and are referenced to $CHCl_3$ (7.26 ppm) as an internal standard. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded at the indicated field strength as solutions in $CDCl_3$ unless otherwise indicated. Chemical shifts are given in ppm, (δ) downfield from TMS and are referenced to the centre line of $CDCl_3$ (77.0 ppm) as an internal standard. Carbon signals were assigned by a DEPT pulse sequence, q=methyl, t=methylene, d=methine, and s=quaternary carbons. Infrared spectra (IR) were measured with a Perkin–Elmer 1600 series FT-IR spectrophotometer. Mass spectra (MS) and high-resolution mass spectra (HRMS) were measured on a JEOL JMS-AX505HAD mass spectrometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. Column chromatography was performed with Merck silica gel 60 (No 7734-5B) or (No 9385). GC–MS was performed with a Finnigan GCQ instrument fitted with a Restek Amine5x column (30 m×0.25 mm) and a program 100 °C (1 min hold time) to 280 °C at 10 °C. GC-FTIR spectra were obtained with a narrow band HP model 5981 GC-FTIR infrared spectrophotometer interfaced with both an HP MSD, model 5971 and an HP 5890 gas chromatograph using the same temperature program as above and fitted with the same column except 0.32 mm i.d.

4.1.1. (5*S*,6*S*,9*S*)-(+)-6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridine-5-carboxylic acid methyl ester (5). To a stirred solution of the enaminoester **4**[4] (950 mg, 4.82 mmol) in Et_2O (150 mL) was added a solution of the dibutyllithium cuprate, prepared from *n*-BuLi (1.6 M in hexane, 24 mL, 38.6 mmol) and CuI (3.44 g, 18.1 mmol) in Et_2O (60 mL) at −50 to −30 °C, and the resulting suspension was warmed to −10 °C for 1 h. The reaction was quenched with satd. NH_4Cl (aq). The aqueous mixture was diluted with CH_2Cl_2 (300 mL), and the resulting suspension was filtered. The filtrate was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (40 g, hexane/acetone=20:1–10:1) to give **5** (1.18 g, 96%) as a colorless oil.

IR (neat) 2935, 2863, 1745, 1255 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t-like, J=6.9 Hz, 1.30–1.39 (5H, m), 1.46–1.56 (3H, m), 1.63 (1H, m), 1.67 (1H, m), 2.20 (1H, br), 3.74 (3H, s), 3.90 (1H, t, J=8.5 Hz), 4.06 (1H, m), 4.35 (1H, s), 4.49 (1H, *t*, J=8.5 Hz); ^{13}C NMR (125 MHz) δ 13.89 (q), 22.38 (t), 23.62 (t), 24.04 (t), 29.50 (t), 30.22 (t), 34.08 (d), 51.66 (d), 52.29 (q), 55.90 (d), 69.00 (t), 157.62 (s), 171.19 (s); MS: 255 (M^+); HRMS: Calcd for $C_{13}H_{21}NO_4$ 255.1469; Found 255.1447; $[\alpha]_D^{26}$ +7.5° (*c* 0.92, $CHCl_3$).

4.1.2. (5*R*,6*S*,9*S*)-(−)-(6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)acetic acid methyl ester (6). To a stirred solution of **5** (590 mg, 2.31 mmol) in MeOH (9 mL) and H_2O (3 mL) was added $LiOH\cdot H_2O$ (200 mg, 4.73 mmol), and the resulting solution was refluxed for

2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl solution (aq). The aqueous mixture was extracted with EtOAc (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless paste, which was used directly in the next step. To a stirred solution of the above paste in THF (6 mL) were added $ClCO_2Et$ (0.29 mL, 3.03 mmol) and Et_3N (0.42 mL, 3.03 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL) and $Et_3N{\cdot}HCl$ was removed by filtration. The filtrate was evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above oil in Et_2O (10 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction was stirred at room temperature for 20 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (10 mL). To the MeOH solution were added $PhCO_2Ag$ (53 mg, 0.23 mmol) and Et_3N (0.64 mL, 4.63 mmol), and the resulting suspension was stirred at room temperature for 18 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=30:1–10:1) to give **6** (500 mg, 80%) as a colorless oil.

IR (neat) 2932, 2864, 1746, 1417, 1256 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7 Hz), 1.25–1.38 (5H, br m), 1.46–1.51 (2H, m), 1.53–1.66 (3H, m), 1.69–1.76 (1H, m), 2.57 (1H, dd, J=14.5, 7.7 Hz), 2.65 (1H, dd, J=14.5, 8.1 Hz), 3.67 (3H, s), 3.76–3.82 (1H, m), 3.88 (1H, dd, J=8.1, 6.9 Hz), 4.19 (1H, t-like, J=6.1 Hz), 4.40 (1H, t-like, J=8.1 Hz); ^{13}C NMR (125 MHz) δ 13.91 (q), 22.28 (t), 22.52 (t), 24.91 (t), 29.56 (t), 30.85 (t), 35.29 (d), 36.11 (t), 50.39 (d), 51.84 (q), 68.43 (t), 157.19 (s), 170.95 (s); MS: 269 (M^+); HRMS: Calcd for $C_{14}H_{23}NO_4$ 269.1626; Found 269.1648; $[\alpha]_D^{26}$ −12.7° (*c* 1.07, $CHCl_3$).

4.1.3. (5*R*,6*S*,9*S*)-(−)-3-(6-Butyl-3-oxohexahydrooxazolo[3,4-*a*]pyridin-5-yl)propionic acid methyl ester (7). To a stirred solution of **6** (445 mg, 1.65 mmol) in MeOH (6 mL) and H_2O (2 mL) was added $LiOH{\cdot}H_2O$ (141 mg, 3.33 mmol), and the resulting solution was refluxed for 2 h. After cooling, the MeOH was evaporated and the residue was acidified with 10% HCl solution (aq). The aqueous mixture was extracted with EtOAc (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless paste, which was used directly in the next step. To a stirred solution of the above oil in THF (6 mL) were added $ClCO_2Et$ (0.21 mL, 2.19 mmol) and Et_3N (0.30 mL, 2.19 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (20 mL) and $Et_3N{\cdot}HCl$ was removed by filtration. The filtrate was evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above oil in Et_2O (8 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction was stirred at room temperature for 25 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (8 mL). To the MeOH solution were added $PhCO_2$-Ag (48 mg, 0.21 mmol) and Et_3N (0.46 mL, 3.33 mmol), and the resulting suspension was stirred at room temperature for 20 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=15:1–12:1) to give **7** (405 mg, 86%) as a colorless oil.

IR (neat) 2932, 2864, 1743, 1253 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t, J=6.8 Hz), 1.22–1.34 (5H, m), 1.41–1.46 (1H, m), 1.48–1.63 (4H, br m), 1.70–1.80 (2H, m), 2.09–2.17 (1H, m), 2.33–2.43 (2H, m), 3.65 (3H, s), 3.69 (1H, dd, J=10.7, 4.5 Hz), 3.76–3.82 (1H, m), 3.89 (1H, dd, J=8.6, 5.6 Hz), 4.37 (1H, t-like, J=8.6 Hz); ^{13}C NMR (125 MHz) δ 13.94 (q), 22.42 (t), 22.55 (t), 25.27 (t), 26.39 (t), 29.73 (t), 30.90 (t), 31.07 (t), 36.13 (d), 50.06 (d), 51.62 (q), 53.67 (d), 68.36 (t), 157.79 (s), 173.73 (s); MS: 283 (M^+); HRMS: Calcd for $C_{15}H_{25}NO_4$ 283.1782; Found 283.1759; $[\alpha]_D^{26}$ −32.4° (*c* 0.87, $CHCl_3$).

4.1.4. (5*R*,6*S*,9*S*)-(−)-6-Butyl-5-(3-hydroxypropyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one (8). To a stirred solution of **7** (558 mg, 1.97 mmol) in THF (12 mL) was added a solution of Super-Hydride (1 M in THF, 4.4 mL, 4.4 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (25 g, hexane/acetone=10:1–2:1) to give **8** (444 mg, 88%) as a colorless oil.

IR (neat) 3427, 2931, 2864, 1733, 1063 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, t-like, J=6.4 Hz), 1.17–1.27 (6H, br m), 1.35–1.54 (7H, br m), 1.68–1.79 (2H, m), 2.90 (1H, br), 3.58 (2H, br), 3.64 (1H, m), 3.74 (1H, m), 3.83 (1H, m), 4.36 (1H, m); ^{13}C NMR (125 MHz) δ 13.87 (q), 22.12 (t), 22.49 (t), 25.31 (t), 27.37 (t), 29.04 (t), 29.65 (t), 30.86 (t), 35.61 (d), 50.09 (d), 53.51 (d), 61.89 (t), 68.44 (t), 157.88 (s); MS: 255 (M^+); HRMS: Calcd for $C_{14}H_{25}NO_3$ 255.1833; Found 255.1855; $[\alpha]_D^{26}$ −17.2° (*c* 1.05, $CHCl_3$).

4.1.5. (5*R*,6*S*,9*S*)-(−)-6-Butyl-5-(3-methoxymethoxypropyl)hexahydrooxazolo[3,4-*a*]pyridin-3-one (9). To a stirred solution of **8** (444 mg, 1.74 mmol) in CH_2Cl_2 (5 mL) were added MOMCl (0.29 mL, 3.83 mmol) and Hünig base (0.87 mL, 5 mmol), and the reaction mixture was stirred at room temperature for 48 h. The volatiles were evaporated and the residue was chromatographed on silica gel (25 g, hexane/acetone=10:1–7:1) to give **9** (438 mg, 87%) as a colorless oil.

IR (neat) 2931, 2868, 1746, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 0.80 (3H, t-like, J=6.8 Hz), 1.17–1.25 (6H, br m), 1.35–1.58 (7H, br m), 1.67–1.74 (2H, m), 3.26 (3H, s), 3.46 (2H, br), 3.62 (1H, br), 3.70 (1H, br), 3.79–3.80 (1H, m), 4.30–4.33 (1H, m), 4.52 (2H, s); ^{13}C NMR (125 MHz) δ 13.83 (q), 22.30 (t), 22.45 (t), 25.30 (t), 26.44 (t), 27.69 (t), 29.66 (t), 30.82 (t), 35.58 (d), 50.03 (d), 53.36 (d), 54.89 (q), 67.00 (t), 68.21 (t), 96.14 (t), 157.53 (s); MS: 299 (M^+); HRMS: Calcd for $C_{16}H_{29}NO_4$ 299.2095; Found 299.2098; $[\alpha]_D^{26}$ −18.4° (*c* 7.56, $CHCl_3$).

4.1.6. (2*R*,3*S*,6*S*)-(−)-3-Butyl-6-hydroxymethyl-2-(3-methoxymethoxypropyl)piperidine-1-carboxylic acid benzyl ester (10). A solution of 2 M KOH in *i*-PrOH

(25 mL) was added to **9** (432 mg, 1.44 mmol), and the resulting mixture was heated at 120 °C in a sealed tube for 48 h. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was extracted with $CHCl_3$ (10 mL×8). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in H_2O (6 mL) and $CHCl_3$ (15 mL) were added CbzCl (0.42 mL, 2.89 mmol) and K_2CO_3 (800 mg, 5.78 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 3 h. The organic layer was separated, and the aqueous layer was extracted with $CHCl_3$ (10 mL×5). The organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=18:1–13:1) to give **10** (483 mg, 82%) as a colorless oil.

IR (neat) 3456, 2931, 1680, 1112, 1040 cm^{-1}; ^1H NMR (500 MHz) δ 0.82 (3H, t-like, J=6.9 Hz), 1.20 (5H, br), 1.34–1.38 (3H, m), 1.45–1.57 (4H, br m), 1.74–1.90 (3H, br m), 3.28 (1H, br), 3.33 (3H, s), 3.46–3.51 (2H, m), 3.81 (3.89 (2H, m), 4.19–4.23 (1H, m), 4.52 (1H, br), 4.57 (2H, s), 5.05 (2H, ABq, J=12 Hz), 7.29–7.38 (5H, m); ^{13}C NMR (125 MHz) δ 14.09 (q), 22.80 (t), 23.72 (t), 24.29 (t), 26.47 (t), 27.54 (t), 29.95 (t), 31.67 (t), 37.10 (d), 55.08 (q), 55.74 (d), 57.36 (d), 64.27 (t), 67.08 (t), 67.24 (t), 96.29 (t), 127.85 (d), 127.89 (d), 128.31 (d), 136.28 (s), 156.17 (s); MS: 407 (M^+); HRMS: Calcd for $C_{23}H_{37}NO_5$ 407.2670; Found 407.2659; $[\alpha]_D^{26}$ −24.7° (*c* 1.22, $CHCl_3$).

4.1.7. (2*R*,3*S*,6*S*)-(−)-3-Butyl-6-methoxycarbonylmethyl-2-(3-methoxymethoxypropyl)-piperidine-1-carboxylic acid benzyl ester (11). To a stirred solution of $(COCl)_2$ (0.16 mL, 1.78 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.26 mL, 3.56 mmol) at −78 °C, and the resulting solution was stirred for 10 min. To the mixture was added a solution of **10** (483 mg, 1.19 mmol) in CH_2Cl_2 (1 mL×2) at −78 °C, and the reaction mixture was stirred for 30 min. Triethylamine (0.74 mL, 5.34 mmol) was added and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred suspension of $NaH_2PO_4 \cdot 2H_2O$ (1.85 g, 11.86 mmol), 2-methyl-2-butene (2.5 mL, 23.6 mmol), and the above oil in *t*-BuOH (10 mL) was added a solution of $NaClO_2$ (80%, 810 mg, 7.16 mmol) in H_2O (5 mL), and the resulting suspension was stirred at room temperature for 45 min. The reaction was quenched with satd. $NaHSO_3$ (aq) and 10% HCl (aq) at 0 °C, and the aqueous mixture was extracted with EtOAc (10 mL×10). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in THF (3 mL) were added $ClCO_2Et$ (0.15 mL, 1.54 mmol) and Et_3N (0.21 mL, 1.54 mmol) at 0 °C, and the resulting suspension was stirred at 0 °C for 1 h. The reaction mixture was diluted with Et_2O (10 mL) and $Et_3N \cdot HCl$ was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the above oil in Et_2O (5 mL) was added a solution of CH_2N_2 in Et_2O at 0 °C, and the reaction solution was stirred at room temperature for 20 h. The solvent was evaporated to give a pale yellow oil, which was dissolved in MeOH (6 mL). To the MeOH solution were added $PhCO_2Ag$ (54 mg, 0.24 mmol) and Et_3N (0.33 mL, 2.34 mmol), and the resulting suspension was stirred at room temperature for 16 h. The reaction mixture was diluted with EtOAc and the insoluble material was removed by filtration. The filtrate was evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=35:1–30:1) to give **11** (278 mg, 54%) as a colorless oil.

IR (neat) 2931, 1740, 1039 cm^{-1}; ^1H NMR (500 MHz) δ 0.83–0.86 (3H, m), 1.22–1.95 (16H, br m), 2.58–2.62 (1H, m), 3.35 (3H, s), 3.49–3.59 (2H, m), 3.64 (3H, s), 3.78 (1H, br), 4.00 (1H, br), 4.60 (2H, s), 5.07 (2H, s), 7.28–7.36 (5H, m); ^{13}C NMR (125 MHz) δ 13.98 (q), 22.64 (t), 22.72 (t), 24.40 (t), 26.37 (t), 26.94 (t), 28.12 (t), 29.71 (t), 32.58 (t), 37.50 (d), 38.68 (t), 49.02 (d), 51.40 (q), 54.99 (q), 66.56 (t), 67.33 (t), 67.37 (t), 96.22 (t), 127.78 (d), 127.83 (d), 127.92 (d), 128.30 (d), 136.73 (s), 156.40 (s), 172.21 (s); MS: 449 (M^+); HRMS: Calcd for $C_{25}H_{39}NO_6$ 449.2775; Found 449.2759; $[\alpha]_D^{26}$ −15.5° (*c* 4.27, $CHCl_3$).

4.1.8. (2*R*,3*S*,6*S*)-(+)-6-Allyl-3-butyl-2-(3-methoxymethoxypropyl)piperidine-1-carboxylic acid benzyl ester (12). To a stirred solution of **11** (83 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added a solution of DIBAL (0.93 M in hexane, 0.2 mL, 0.18 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 30 min. The reaction was quenched with MeOH (0.3 mL) and with satd. potassium sodium tartrate solution (aq). The aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred suspension of $CH_3P^+Ph_3I^-$ (374 mg, 0.92 mmol) in THF (2 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 0.52 mL, 0.83 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the above aldehyde in THF (2 mL) at 0 °C, and the orange suspension was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (10 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (15 g, hexane/acetone=80:1–30:1) to give **12** (44 mg, 57%) as a colorless oil.

IR (neat) 3070, 2930, 2869, 1699, 1110, 1042 cm^{-1}; ^1H NMR (500 MHz) δ 0.87 (3H, t-like, J=6.8 Hz), 1.18–1.82 (15H, br m), 2.39 (1H, br), 2.78 (1H, br), 3.36 (3H, s), 3.44–3.55 (3H, br m), 3.73 (1H, br), 4.60 (2H, s), 5.00–5.15 (4H, m), 5.73–5.81 (1H, m), 7.28–7.39 (5H, m); ^{13}C NMR (125 MHz) δ 14.03 (q), 22.80 (t), 24.44 (t), 26.74 (t), 28.49 (t), 29.62 (t), 33.04 (t), 37.51 (t), 37.94 (d), 53.16 (d), 55.04 (q), 58.40 (d), 66.56 (t), 67.48 (t), 96.27 (t), 116.40 (t), 127.79 (d), 127.86 (d), 128.36 (d), 136.24 (d), 136.92 (s), 156.80 (s); MS: 417 (M^+); HRMS: Calcd for $C_{25}H_{39}NO_4$ 417.2877; Found 417.2883; $[\alpha]_D^{26}$ +2.9° (*c* 2.24, $CHCl_3$).

4.1.9. (5*R*,8*S*,9*R*)-(+)-8-Butyl-5-propyloctahydroindolizine (1). To a solution of **12** (135 mg, 0.32 mmol) in EtOAc (15 mL) was added 10% Pd–C (100 mg), and the

resulting suspension was hydrogenated under a hydrogen atmosphere at 4 atm for 40 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the oil above in MeOH (6 mL) was added conc. HCl (aq) (4 drops), and the reaction mixture was refluxed for 1 h. After cooling, the solvent was evaporated and the residue was washed with Et_2O. To the hydrochloride salt was added NH_3 (aq), and the aqueous mixture was extracted with $CHCl_3$ (5 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colorless oil, which was used directly in the next step. Carbon tetrachloride (150 mg, 0.45 mmol) and Ph_3P (127 mg, 0.49 mmol) were added to a solution of the above oil in CH_2Cl_2 (4 mL) at 0 °C, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture was added Et_3N (0.72 mL, 5.18 mmol) at 0 °C, and the resulting suspension was stirred for 30 min. The volatiles were evaporated, and the residue was extracted with *n*-pentane (10 mL×4). The organic extracts were combined and evaporated to give a pale orange solid, which was chromatographed on silica gel (10 g, hexane/acetone/Et_3N=50:1:5 drops-20:1:5 drops) to give **1** (48 mg, 67%) as a pale yellow oil.

IR (neat) 2928, 2865, 2803, 1657, 1460, 1376, 1259, 1219, 1170, 1142, 1101, 905, 754 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J=6.8 Hz), 0.92 (3H, t, J=6.8 Hz), 1.01–1.67 (14H, br m), 1.56–1.70 (3H, m), 1.72–1.82 (1H, m), 1.87–1.94 (1H, m), 2.07–2.11 (1H, m), 2.63 (1H, q, J=8.5 Hz), 2.80 (1H, td, J=8.6, 2.9 Hz), 2.95–2.99 (1H, m); ^{13}C NMR (125 MHz) δ 14.06 (q), 14.40 (q), 20.65 (t), 20.94 (t), 23.00 (t), 24.28 (t), 24.83 (t), 27.88 (t), 28.88 (t), 29.68 (t), 33.06 (t), 42.45 (d), 48.92 (t), 54.94 (d), 60.29 (d); MS: 223 (M^+); HRMS: Calcd for $C_{15}H_{29}N$ 223.2299; Found 223.2290; $[\alpha]_D^{26}$ +31.0° (*c* 2.14, $CHCl_3$).

4.1.10. (*R*)-(+)-Propionic acid 2-hydroxymethylhexyl ester (15). To a stirred solution of **14** (3 g, 22 mmol) in MeCN (300 mL) were added vinyl propanoate (4.55 g, 45 mmol) and lipase PCL (Amano PS) (1.5 g), and the resulting suspension was stirred at room temperature for 20 h. The lipase catalyst was removed by filtration, and the volatiles were evaporated to give a colorless oil, which was chromatographed on silica gel (60 g, hexane/EtOAc=3:1) to give **15** (3.72 g, 90%) as a colorless oil. The enantiomeric excess was determined to be 95% ee by the GC analysis using a cyclodextrin-β-236M-19 chiral column.

IR (neat) 3449, 2931, 2868, 1736, 1193 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=6.6 Hz), 1.13 (3H, t, J=7.6 Hz), 1.26–1.34 (6H, br), 1.76–1.81 (1H, m), 2.21–2.27 (1H, m), 2.33 (2H, q, J=7.6 Hz), 3.44–3.61 (2H, m), 4.07 (1H, dd, J=11, 6.6 Hz), 4.19 (1H, dd, J=11, 4.7 Hz); ^{13}C NMR (125 MHz) δ 9.24 (q), 14.00 (q), 22.90 (t), 27.56 (t), 27.64 (t), 29.17 (t), 40.52 (d), 62.71 (t), 64.51 (t), 174.87 (s); MS: 188 (M^+); HRMS: Calcd for $C_{10}H_{20}O_3$ 188.1411; Found 188.1432; $[\alpha]_D^{26}$ +10.6° (*c* 1.96, $CHCl_3$).

4.1.11. (*S*)-(+)-Propionic acid 2-iodomethylhexyl ester. To a stirred solution of **15** (188 mg, 1 mmol) in CH_2Cl_2 (5 mL) were added MsCl (0.12 mL, 1.5 mmol) and pyridine (0.15 mL, 1.8 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated and the residue was chromatographed on Silica gel (10 g, hexane/acetone=12:1–8:1) to give the mesylate (265 mg, 99%) as a colorless oil.

IR (neat) 2938, 2867, 1738, 1355, 1178 cm^{-1}; ^1H NMR (500 MHz) δ 0.89 (3H, t, J=7.2 Hz), 1.13 (3H, t, J=7.7 Hz), 1.30–1.40 (6H, br m), 2.04–2.09 (1H, m), 2.34 (2H, q, J=7.7 Hz), 3.01 (3H, s), 4.03 (1H, dd, J=11.1, 6.8 Hz), 4.13 (1H, dd, J=11.1, 4.7 Hz), 4.16–4.23 (2H, m); ^{13}C NMR (125 MHz) δ 8.97 (q), 13.77 (q), 22.54 (t), 27.15 (t), 27.35 (t), 28.63 (t), 37.09 (q), 37.61 (d), 63.00 (t), 69.16 (t), 174.19 (s); MS: 266 (M^+); HRMS: Calcd for $C_{11}H_{22}O_5S$ 266.1187; Found 266.1199; $[\alpha]_D^{26}$ +3.9° (*c* 4.74, $CHCl_3$).

To a stirred solution of the mesylate obtained above (265 mg, 1 mmol) in acetone (10 mL) was added NaI (1.5 g, 9.96 mmol), and the resulting solution was stirred at room temperature for 14 h and at reflux for 2 h. After cooling, the reaction mixture was diluted with Et_2O. The ethereal layer was washed with 10% $Na_2S_2O_3$ in satd. $NaHCO_3$ (aq), dried and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=100:1–80:1) to give the iodide (280 mg, 94%) as a colorless oil.

IR (neat) 2956, 2931, 2863, 1740 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7.2 Hz), 1.12 (3H, t, J=7.4 Hz), 1.26–1.35 (6H, br), 1.52–1.58 (1H, m), 2.30 (2H, q, J=7.4 Hz), 3.23 (1H, dd, J=9.9, 5.2 Hz), 3.29 (1H, dd, J=9.9, 6.6 Hz), 3.89 (1H, dd, J=11, 7.1 Hz), 4.08 (1H, dd, J=11, 4.6 Hz); ^{13}C NMR (125 MHz) δ 9.18 (q), 11.10 (t), 13.95 (q), 22.62 (t), 27.52 (t), 28.61 (t), 30.97 (t), 38.49 (d), 66.44 (t), 173.90 (s); MS: 298 (M^+); HRMS: Calcd for $C_{10}H_{19}IO_2$ 298.0430; Found 298.0442; $[\alpha]_D^{26}$ +5.3° (*c* 2.00, $CHCl_3$).

4.1.12. (*S*)-(+)-2-Methylhexan-1-ol (16). To a stirred solution of the iodide (280 mg, 0.94 mmol) in Et_2O (20 mL) was added $LiAlH_4$ (380 mg, 10 mmol), and the resulting suspension was refluxed for 16 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with Et_2O (10 mL×4). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=15:1–10:1) to give **16** (75 mg, 69%) as a colorless oil.

IR (neat) 3445, 2935, 2862 cm^{-1}; ^1H NMR (500 MHz) δ 0.89–0.92 (6H, m), 1.06–1.13 (1H, m), 1.20–1.43 (5H, m), 1.57–1.64 (1H, m), 1.91 (1H, br), 3.39–3.42 (1H, m), 3.48–3.81 (1H, m); ^{13}C NMR (125 MHz) δ 14.04 (q), 16.52 (q), 22.93 (t), 29.15 (t), 32.79 (t), 35.66 (d), 68.28 (t); $[\alpha]_D^{26}$ −10.5° (*c* 2.01, $CHCl_3$), lit.[8] $[\alpha]_D^{26}$ +11° (*c* 2.5, $CHCl_3$).

4.1.13. (*S*)-(+)-2-(2-Butylbut-3-enyloxy)tetrahydropyran (17). To a stirred solution of **15** (1.814 g, 9.65 mmol) in CH_2Cl_2 (20 mL) were added DHP (1.32 mL, 14.5 mmol) and PPTS (485 mg, 1.93 mmol), and the reaction mixture was stirred at room temperature for 6 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (20 mL×3). The organic layer and

extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the above oil in MeOH (12 mL) was added K_2CO_3 (803 mg, 5.82 mmol), and the resulting suspension was stirred at room temperature for 19 h. The reaction mixture was diluted with H_2O, and the aqueous mixture was extracts with CH_2Cl_2 (15 mL×6). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of $(COCl)_2$ (1.25 mL, 14.33 mmol) in CH_2Cl_2 (15 mL) was added DMSO (2.05 mL, 28.89 mmol) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of the alcohol obtained above in CH_2Cl_2 (3 mL×2) at −78 °C, and the reaction mixture was stirred for 30 min. Triethylamine (6 mL, 43.37 mmol) was added to the reaction mixture at −78 °C, and the reaction was warmed to 0 °C for 1 h. The reaction mixture was diluted with H_2O and Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred suspension of $CH_3P^+Ph_3I^-$ (15.7 g, 38.8 mmol) in THF (35 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 22.9 mL, 36.6 mmol) at 0 °C, and the resulting orange suspension was stirred at 0 °C for 30 min. To the suspension was added a solution of the aldehyde obtained above in THF (10 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 22 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with Et_2O (20 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=100:1–80:1) to give **17** (1.63 g, 80%) as a colorless oil.

IR (neat) 3075, 2934, 2866, 1642, 1127, 1071, 1032 cm^{-1}; ^1H NMR (500 MHz) δ 0.88 (3H, t, J=7.3 Hz), 1.20–1.33 (5H, m), 1.44–1.61 (5H, m), 1.66–1.72 (1H, m), 1.78–1.85 (1H, m), 2.26–2.33 (1H, m), 3.28–3.32 (1H, m), 3.47–3.52 (1H, m), 3.65 (1H, dd, J=9.4, 6.8 Hz), 3.83–3.88 (1H, m), 4.56–4.59 (1H, m), 5.02–5.07 (2H, m), 5.62–5.70 (1H, m); ^{13}C NMR (125 MHz) δ 13.98 (q), 19.37 (t), 19.43 (t), 22.71 (t), 25.44 (t), 29.12 (t), 29.14 (t), 30.55 (t), 30.90 (t), 43.83 (d), 44.04 (d), 61.96 (t), 62.03 (t), 70.86 (t), 70.95 (t), 98.57 (d), 98.77 (d), 115.20 (t), 115.27 (t), 140.29 (d), 140.44 (d); MS: 212 (M^+); HRMS: Calcd for $C_{13}H_{24}O_2$ 212.1775; Found 212.1784; $[\alpha]_D^{26}$ +8.8° (*c* 16.20, $CHCl_3$).

4.1.14. 3-(Tetrahydropyran-2-yloxymethyl)heptane-1,2-diol (18). To a stirred solution of **17** (1.63 g, 7.69 mmol) in *t*-BuOH (30 mL) and H_2O (30 mL) was added AD-mix with $(DHQD)_2PYR$ (14 g) at 0 °C, and the resulting suspension was stirred at 0 °C for 17 h. The reaction was quenched with Na_2SO_3 (10 g), and the reaction mixture was extracted with EtOAc (30 mL×5). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (40 g, hexane/acetone=10:1–4:1) to give **18** (1.58 g, 84%) a colorless oil consisting of a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.91 (3H, t-like, J=6.8 Hz), 1.27–1.49 (5H, m), 1.55–1.63 (4H, m), 1.72–1.86 (4H, m), 2.56–2.63 (1H, m), 3.40–3.98 (8H, br m), 4.58–4.62 (1H, m).

4.1.15. 2-Azido-1-(*tert*-butyldiphenylsilanyloxy)-3-(tetrahydropyran-2-yloxymethyl)heptane (19). To a stirred solution of **18** (700 mg, 2.85 mmol) in CH_2Cl_2 (5 mL) were added Et_3N (0.51 mL, 3.7 mmol), DMAP (69 mg, 0.57 mmol), and TBDPSCl (0.82 mL, 3.13 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 45 h. The volatiles were evaporated and the residue was chromatographed on silica gel (30 g, hexane/acetone=50:1–30:1) to give the silyl ether (1.37 g, 99%) as a colorless oil consisting of a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.91 (3H, t-like, J=6 Hz), 1.09 (9H, s), 1.22–1.83 (14H, br m), 3.01–3.04 (1H, m), 3.38–3.56 (2H, m), 3.70–3.94 (4H, m), 4.51–4.53 (1H, m), 7.38–7.47 (6H, m), 7.70–7.76 (4H, m).

To a stirred solution of the silyl ether obtained above (1.37 g, 2.83 mmol) in CH_2Cl_2 (5 mL) were added MsCl (0.24 mL, 3.11 mmol) and Et_3N (0.59 mL, 4.25 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2). The organic layer and extracts were combined, dried, and evaporated to give the mesylate, which was used directly in the next step. To a stirred solution of the mesylate obtained above in DMF (5 mL) was added NaN_3 (1.84 g, 28.31 mmol), and the resulting suspension was heated at 80 °C for 15 h. After cooling, the insoluble material was removed by filtration, and the solvent was evaporated to give a pale yellow oil, which was chromatographed on silica gel (25 g, hexane/acetone=50:1–40:1) to give **19** (1.05 g, 73%) as a colorless oil containing a diastereomeric mixture.

^1H NMR (500 MHz) δ 0.87–0.91 (3H, m), 1.10 (9H, s), 1.10–1.75 (13H, br m), 3.22–3.29 (1H, m), 3.46–3.56 (1H, m), 3.64–3.84 (5H, m), 4.48–4.52 (1H, m), 7.40–7.48 (6H, m), 7.71–7.74 (4H, m).

4.1.16. 5-Azido-6-(*tert*-butyldiphenylsilanyloxy)-4-butyl-2-hexenoic acid ethyl ester (20). To a stirred solution of **19** (1.05 g, 2.06 mmol) in EtOH (5 mL) was added PPTS (104 mg, 0.41 mmol), and the reaction mixture was stirred at 60 °C for 2 h. After cooling, the reaction was quenched with satd. $NaHCO_3$ (aq), and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of $(COCl)_2$ (0.27 mL, 3.09 mmol) in CH_2Cl_2 (6 mL) was added DMSO (0.44 mL, 6.19 mmol) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of the oil obtained above in CH_2Cl_2 (2 mL) at −78 °C, and the resulting mixture was stirred at −78 °C for 30 min. Triethylamine (1.3 mL) was added to the reaction mixture, and the reaction was warmed to 0 °C for 1 h. The reaction mixture was then diluted with H_2O and Et_2O, and the organic layer was separated. The aqueous layer was extracted with Et_2O (20 mL×2). The organic layer and extracts were combined, dried, and evaporated to give a pale

yellow oil, which was used directly in the next step. To a stirred suspension of NaH (60%, 99 mg, 2.48 mmol) in THF (5 mL) was added (EtO) $_2$P(O)CH_2CO_2Et (0.5 mL, 2.48 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the aldehyde obtained above in THF (4 mL) at 0 °C, and then the reaction mixture was stirred at room temperature for 2 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (15 mL×4). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (25 g, hexane/acetone=100:1–50:1) to give **20** (890 mg, 88%) as a colorless oil as a 9:1 mixture of diastereomers.

^{1}H NMR (500 MHz) δ 0.89 (3H, t-like, J=7.2 Hz), 1.10 (9H, s), 1.11–1.38 9H, m, including at δ 1.32, 3H, t, J=7.3 Hz), 2.36–2.42 (1H, m), 3.34–3.38 (1H, m), 3.50–3.67 (1H, m), 3.68–3.80 (1H, m), 4.20 (2H, q, J=7.3 Hz), 5.81 (1H, d, J=15.4 Hz), 6.63 (1H, dd, J=15.4, 9.4 Hz), 7.40–7.48 (6H, m), 7.68–7.72 (4H, m).

4.1.17. (5*R*,6*S*)-(+)-5-Butyl-6-(*tert*-butyldiphenylsilanyloxymethyl)piperidin-2-one (13). To a solution of **20** (1.77 g, 3.59 mmol) in EtOAc (60 mL) was added 10% Pd–C (400 mg), and the resulting suspension was hydrogenated with 4 atm of hydrogen for 48 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil, which was chromatographed on silica gel (30 g, hexane/acetone=12:1–7:1) to give **13** (852 mg, 56%) as a colorless oil.

IR (neat) 3206, 3070, 2931, 2860, 1666 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.84 (3H, t, J=7.3 Hz), 1.07 (9H, s), 1.08–1.27 (7H, m), 1.68 (2H, q-like, J=6.4 Hz), 2.33–2.39 (2H, m), 3.53–3.67 (3H, br m), 6.27 (1H, br), 7.39–7.48 (6H, m), 7.66–7.67 (4H, m); ^{13}C NMR (125 MHz) δ 13.82 (q), 19.00 (s), 22.54 (t), 23.50 (t), 26.69 (q), 28.05 (t), 29.11 (t), 29.56 (t), 33.97 (d), 56.76 (d), 64.34 (t), 127.74 (d), 127.75 (d), 129.80 (d), 129.83 (d), 132.68 (s), 132.73 (s), 135.40 (d), 135.42 (d), 171.88 (s); MS: 423 (M^+); HRMS: Calcd for $C_{26}H_{37}NO_2Si$ 423.2591; Found 423.2597; $[\alpha]_D^{26}$ +25.4° (*c* 1.04, $CHCl_3$).

4.1.18. (2*S*,3*R*)-(−)-3-Butyl-2-(*tert*-butyldiphenylsilanyloxymethyl)-6-trifluoromethane-sulfonyloxy-3,4-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester (21). To a stirred solution of **13** (1.06 g, 2.50 mmol) in THF (7 mL) was added a solution of *n*-BuLi (1.6 M in hexane, 1.72 mL, 2.75 mmol) at −78 °C, and the reaction mixture stirred at −78 °C for 30 min. To the reaction mixture was added $ClCO_2Me$ (0.22 mL, 2.75 mmol), and the solution was warmed to 0 °C for 1 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the aqueous mixture was extracted with CH_2Cl_2 (20 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=30:1–10:1) to give the methyl urethane (1.17 g, 98%) as a colorless oil.

IR (neat) 1743, 1641, 3017, 2954, 2932, 2860, 1773, 1719, 1284 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.89 (3H, t, J=6.9 Hz), 1.04 (9H, s), 1.25–1.37 (6H, m), 1.81–1.87 (1H, m), 1.95–1.98 (1H, m), 2.01–2.08 (1H, m), 2.54–2.61 (1H, m), 2.64–2.66 (1H, m), 3.76 (1H, dd, J=11.1, 2.9 Hz), 3.82 (3H, s), 3.86 (1H, dd, J=11.1, 3.9 Hz), 4.28 (1H, br), 7.39–7.48 (6H, m), 7.64–7.71 (4H, m); ^{13}C NMR (125 MHz) δ 13.84 (q), 18.85 (s), 22.61 (t), 24.79 (t), 26.61 (q), 29.33 (t), 32.33 (t), 34.31 (t), 37.16 (d), 53.66 (q), 59.42 (d), 61.50 (t), 127.64 (d), 127.67 (d), 129.73 (d), 132.16 (s), 132.73 (s), 135.53 (d), 135.64 (d), 154.99 (s), 172.03 (s); MS: 424 (M^+−57); HRMS: Calcd for $C_{24}H_{30}NO_4Si$ 424.1942; Found 424.1961; $[\alpha]_D^{26}$ −27.4° (*c* 3.02, $CHCl_3$).

To a stirred solution of the methyl urethane obtained above (633 mg, 1.32 mmol) in THF (2 mL) was added a solution of LiHMDS, prepared from hexamethyldisilazane (0.33 mL, 1.6 mmol) and *n*-BuLi (1.6 M in hexane, 1 mL, 1.6 mmol) in THF (2 mL) at 0 °C for 30 min, at −78 °C, and the reaction mixture was stirred at the same temperature for 30 min. To the resulting mixture was added a solution of 2-[*N*,*N*-bis(trifluoromethanesulfonyl)amino]-5-chloropyridine (Comins' reagent, 640 mg, 1.6 mmol) in THF (2 mL) at −78 °C, and the reaction temperature was warmed to −40 °C for 30 min. The reaction was quenched with satd. NH_4Cl (aq), and the organic layer was separated. The aqueous layer was extracted with Et_2O (10 mL×3), and the organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (30 g, hexane/acetone=50:1–40:1) to give **21** (772 mg, 96%) as a colorless oil.

IR (neat) 3069, 2956, 2932, 2860, 1733, 1424, 1328, 1272, 1215, 1114 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (3H, t, J=6.9 Hz), 1.13 (9H, s), 1.15–1.36 (6H, br m), 1.68–1.75 (1H, m), 1.89 (1H, br), 2.31–2.37 (1H, m), 3.68 (1H, d-like, J=8.9 Hz), 3.85 (1H, t-like, J=6.8 Hz), 3.90 (3H, s), 4.70 (1H, br), 5.29 (1H, t, J=3.4 Hz), 7.45–7.51 (6H, m), 7.74–7.84 (4H, m); ^{13}C NMR (125 MHz) δ 13.67 (q), 18.89 (s), 22.42 (t), 26.41 (q), 26.59 (t), 29.22 (t), 31.97 (t), 35.64 (d), 53.27 (q), 58.26 (t), 59.87 (d), 105.64 (d), 117.01 (s), 119.55 (s), 127.56 (d), 127.59 (d), 129.56 (d), 129.67 (d), 133.14 (s), 133.17 (s), 135.45 (d), 135.59 (d), 138.13 (s), 153.89 (s); MS: 613 (M^+); HRMS: Calcd for $C_{29}H_{38}NO_6F_3SSi$ 613.2139; Found 613.2118; $[\alpha]_D^{26}$ −30.5° (*c* 8.45, $CHCl_3$).

4.1.19. (2*S*,3*R*)-(−)-6-Allyl-3-butyl-2-(*tert*-butyldiphenylsilanyloxymethyl)-3,4-dihydro-2*H*-pyridine-1-carboxylic acid methyl ester (22). To a stirred solution of **21** (1.18 g, 1.92 mmol) in THF (20 mL) were added allyltributyltin (1.2 mL, 3.8 mmol), $Pd(PPh_3)_4$ (222 mg, 0.19 mmol), and LiCl (480 mg, 11.32 mmol), and the resulting mixture was heated at 70 °C for 4 h. After cooling, the reaction mixture was diluted with Et_2O. The insoluble materials were removed by filtration, and the filtrate was evaporated to give a pale brown oil, which was chromatographed on silica gel (30 g, hexane/acetone=100:1) to give **22** (900 mg, 92%) as a pale yellow oil.

IR (neat) 3070, 2954, 2928, 2858, 1709, 1660, 1111 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87 (3H, t, J=6.8 Hz), 1.09 (9H, s), 1.12–1.50 (6H, m), 1.51–1.56 (1H, m), 1.82–1.91 (1H, m), 2.11–2.16 (1H, m), 3.13–3.17 (1H, m), 3.56 (1H, br), 3.60–3.63 (1H, m), 3.73 (1H, t-like, J=9.4 Hz), 3.78 (3H, s), 4.58 (1H, br), 5.00–5.08 (2H, br), 5.13 (1H, t-like, J=17 Hz), 5.85–5.94 (1H, m), 7.42–7.49 (6H, m), 7.71–7.78 (4H, m);

^{13}C NMR (125 MHz) δ 13.98 (q), 19.16 (s), 22.70 (t), 26.65 (q), 27.73 (t), 29.29 (t), 33.02 (t), 36.02 (d), 39.43 (t), 52.44 (q), 57.60 (d), 58.78 (t), 112.11 (d), 115.70 (t), 127.43 (d), 129.37 (d), 129.47 (d), 133.40 (s), 133.56 (s), 135.36 (d), 135.51 (d), 136.22 (d), 154.78 (s); MS: 505 (M^+); HRMS: Calcd for $C_{31}H_{43}NO_3Si$ 505.3010; Found 505.3025; $[\alpha]_D^{26}$ −62.6° (*c* 2.91, $CHCl_3$).

4.1.20. (2*S*,3*R*,6*S*)-(−)-6-Allyl-3-butyl-2-hydroxymethylpiperidine-1-carboxylic acid methyl ester (23). To a stirred solution of **22** (700 mg, 1.39 mmol) in CH_2Cl_2 (15 mL) were added $NaBH_3CN$ (95%, 460 mg, 6.95 mmol) at −78 °C, and then TFA (1.07 mL, 13.9 mmol) at −78 °C, and the resulting suspension was stirred at −78 to −45 °C for 3 h. The reaction was quenched with satd. $NaHCO_3$ (aq), and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (15 mL×5). The organic layer and extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (20 g, hexane/acetone=30:1–10:1) to give **23** (242 mg, 65%) as a colorless oil.

IR (neat) 3447, 3074, 1678 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.91 (3H, t-like, J=6.8 Hz), 1.21–1.41 (7H, br m), 1.73–1.89 (3H, m), 1.93–1.97 (1H, br), 2.18–2.24 (1H, m), 2.50–2.55 (1H, m), 3.18 (1H, br), 3.69–3.73 (1H, m), 3.74 (3H, s), 3.80–3.88 (2H, m), 4.06–4.09 (1H, m), 5.05–5.11 (2H, m), 5.71–5.78 (1H, m); ^{13}C NMR (125 MHz) δ 14.11 (q), 21.49 (t), 22.25 (t), 22.85 (t), 29.50 (t), 32.73 (t), 34.69 (d), 38.87 (t), 51.79 (d), 52.76 (q), 57.71 (d), 64.27 (t), 116.93 (t), 135.39 (d), 158.27 (s); MS: 269 (M^+); HRMS: Calcd for $C_{15}H_{27}NO_3$ 269.1989; Found 269.1999; $[\alpha]_D^{26}$ −25.6° (*c* 1.72, $CHCl_3$).

4.1.21. (5*S*,8*R*,9*S*)-(−)-5-Allyl-8-butylhexahydrooxazolo[3,4-*a*]pyridin-3-one (24). To a stirred solution of **23** (54 mg, 0.2 mmol) in THF (2 mL) was added NaH (60%, 8.8 mg, 0.22 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 10% AcOH (aq), and the aqueous mixture was extracted with CH_2Cl_2 (5 mL×3). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on silica gel (10 g, hexane/acetone=30:1–10:1) to give **24** (42 mg, 89%) as a colorless oil.

IR (neat) 3075, 2933, 2866, 1746 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.90 (3H, t-like, J=6.8 Hz), 1.15–1.17 (1H, m), 1.20–1.40 (6H, br m), 1.62–1.81 (4H, m), 2.25–2.30 (1H, m), 2.40–2.45 (1H, m), 3.93–3.96 (1H, m), 3.98–4.01 (1H, m), 4.14–4.19 (1H, m), 4.23–4.27 (1H, m), 5.05–5.10 (2H, m), 5.71–5.80 (1H, m); ^{13}C NMR (125 MHz) δ 13.96 (q), 20.38 (t), 21.07 (t), 22.69 (t), 22.87 (t), 29.31 (t), 34.43 (d), 34.99 (t), 48.41 (d), 53.95 (d), 64.34 (t), 117.38 (t), 134.57 (d), 157.20 (s); MS: 237 (M^+); HRMS: Calcd for $C_{14}H_{23}NO_2$ 237.1728; Found 237.1724; $[\alpha]_D^{26}$ −45.9° (*c* 2.58, $CHCl_3$).

4.1.22. (2*S*,3*R*,6*S*)-6-Allyl-3-butyl-2-(2-ethoxycarbonylvinyl)piperidine-1-carboxylic acid methyl ester (25). To a stirred solution of $(COCl)_2$ (0.12 mL, 1.41 mmol) in CH_2Cl_2 (3 mL) was added DMSO (0.2 mL) at −78 °C, and the reaction mixture was stirred for 5 min. To the reaction mixture was added a solution of **23** (253 mg, 0.94 mmol) in CH_2Cl_2 (2 mL), at −78 °C, and the reaction was stirred for 30 min. Triethylamine (0.59 mL) was added at −78 °C, and the reaction was warmed to 0 °C for 1 h. The reaction was quenched with H_2O, and the mixture was extracted with Et_2O (15 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred suspension of NaH (60%, 45 mg, 1.13 mmol) in THF (4 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.23 mL, 1.13 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of the aldehyde obtained above in THF (2 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 10 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×4). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on Silica gel (10 g, hexane/acetone=50:1) to give **25** (276 mg, 87%) as a colorless oil.consisting of a 4:1 mixture of *E*- and *Z*-isomers.

4.1.23. (2*R*,3*R*,6*R*)-(−)-3-Butyl-2-(3-hydroxypropyl)-6-propylpiperidine-1-carboxylic acid methyl ester (26). To a stirred solution of **25** (270 mg, 0.8 mmol) in EtOAc (20 mL) was added 10%Pd–C (250 mg), and the resulting suspension was hydrogenated at 1 atm for 20 h. The catalyst was removed by filtration, and the filtrate evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the ester obtained above in THF (10 mL) was added a solution of Super-Hydride (1 M in THF, 1.8 mL, 1.8 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 1 h. The reaction was quenched with H_2O, and the aqueous mixture was extracted with CH_2Cl_2 (10 mL×5). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was chromatographed on Silica gel (15 g, hexane/acetone=30:1–8:1) to give **26** (229 mg, 96%) as a colorless oil.

IR (neat) 3447, 2931, 2865, 11689 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87–0.93 (6H, m), 1.15–1.35 (9H, br m), 1.44–1.81 (10H, br m), 2.48 (1H, br), 3.52 (1H, br), 3.67 (3H, s), 3.62–3.71 (2H, br), 4.02 (1H, br); ^{13}C NMR (125 MHz) δ 14.14 (q), 20.58 (t), 22.91 (t), 23.14 (t), 25.10 (t), 25.92 (t), 29.40 (t), 33.23 (t), 36.60 (t), 37.20 (d), 52.07 (q), 52.44 (d), 55.17 (d), 62.50 (t), 156.81 (s); MS: 299 (M^+); HRMS: Calcd for $C_{17}H_{33}NO_3$ 299.2459; Found 299.2434; $[\alpha]_D^{26}$ −28.2° (*c* 2.33, $CHCl_3$).

4.1.24. (2*R*,3*R*,6*R*)-(−)-3-Butyl-2-(3-methoxymethoxypropyl)-6-propylpiperidine-1-carboxylic acid methyl ester (27). To a stirred solution of **26** (55 mg, 0.18 mmol) in CH_2Cl_2 (2 mL) were added MOMCl (0.084 mL, 1.10 mmol) and Hünig base (0.26 mL, 1.47 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 28 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (10 g, hexane/acetone=30:1–20:1) to give **27** (59 mg, 94%) as a colorless oil.

IR (neat) 2930, 2867, 1699 cm^{-1}; ^{1}H NMR (500 MHz) δ 0.87–0.92 (6H, m), 1.15–1.38 (9H, br m), 1.46–1.83 (10H, br m), 3.35 (3H, s), 3.39 (1H, br), 3.52 (2H, br), 3.65 (3H, s), 4.03 (1H, br), 4.61 (2H, s); ^{13}C NMR (125 MHz) δ 14.11 (q), 14.16 (q), 20.63 (t), 22.90 (t), 24.01 (t), 25.08 (t), 26.03

(t), 26.81 (t), 29.37 (t), 33.02 (t), 36.54 (t), 37.64 (d), 51.87 (q), 52.68 (d), 55.04 (q), 55.79 (d), 67.70 (t), 96.25 (t), 156.68 (s); MS: 343 (M^+); HRMS: Calcd for $C_{19}H_{37}NO_4$ 343.2721; Found 343.2749; $[\alpha]_D^{26}$ −23.1° (*c* 2.86, $CHCl_3$).

4.1.25. (2*S*,3*R*,6*S*)-(−)-6-Allyl-3-butyl-2-hydroxymethylpiperidine-1-carboxylic acid *tert*-butyl ester (28). 2 M Potassium hydroxide in *i*-PrOH (25 mL) was added to **23** (429 mg, 1.59 mmol), and the resulting solution was heated at 120 °C in a sealed tube for 48 h. After cooling, the solvent was evaporated, and the residue was dissolved in H_2O. The aqueous mixture was saturated with K_2CO_3, and extracted with $CHCl_3$ (10 mL×10). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a pale yellow oil, which was used directly in the next step.

To a stirred solution of the oil obtained above in dioxane (20 mL) and H_2O (10 mL) were added NaOH (270 mg, 6.75 mmol) at 0 °C, and then Boc_2O (1.1 g, 5.04 mmol) at the same temperature. The reaction mixture was stirred at room temperature for 12 h, then it was extracted with CH_2Cl_2 (15 mL×5), and the organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=40:1–30:1) to give **28** (350 mg, 70%) as a colorless oil.

IR (neat) 3446, 3074, 2931, 2867, 1665, 1173 cm^{-1}; ^1H NMR (500 MHz) δ 0.92 (3H, t-like, J=6.9 Hz), 1.18–1.23 (1H, m), 1.27–1.39 (6H, m), 1.50 (9H, s), 1.74–1.84 (3H, m), 1.92–1.97 (1H, m), 2.16–2.22 (1H, m), 2.49–2.53 (1H, m), 3.45 (1H, br), 3.62–3.67 (1H, m), 3.78–3.86 (2H, m), 4.08–4.11 (1H, m), 5.05–5.11 (2H, m), 5.73–5.81 (1H, m); ^{13}C NMR (125 MHz) δ 14.11 (q), 21.28 (t), 21.97 (t), 22.88 (t), 28.54 (q), 29.53 (t), 33.36 (t), 34.59 (d), 39.29 (t), 51.86 (d), 57.08 (d), 64.69 (t), 80.24 (s), 116.75 (t), 135.68 (d), 157.45 (s); MS: 311 (M^+); HRMS: Calcd for $C_{18}H_{33}NO_3$ 311.2459; Found 311.2463; $[\alpha]_D^{26}$ −35.4° (*c* 1.52, $CHCl_3$).

4.1.26. (2*S*,3*R*,6*S*)-6-Allyl-3-butyl-2-(2-ethoxycarbonylvinyl)piperidine-1-carboxylic acid *tert*-butyl ester (29). To a stirred solution of $(COCl)_2$ (0.055 mL, 0.63 mmol) in CH_2Cl_2 (2 mL) was added DMSO (0.089 mL, 1.25 mmol) at −78 °C, and the reaction mixture was stirred at −78 °C for 5 min. To the reaction mixture was added a solution of **18** (130 mg, 0.42 mmol) in CH_2Cl_2 (2 mL), and the resulting mixture was stirred at −78 °C for 30 min. Triethylamine was added to the reaction mixture, and the reaction mixture was warmed to 0 °C for 1 h. The reaction was quenched with H_2O and Et_2O was added. The organic layer was separated, and the aqueous layer was extracted with Et_2O (10 mL×2). The organic layer and extracts were combined, dried, and evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred suspension of NaH (60%, 22 mg, 0.54 mmol) in THF (5 mL) was added $(EtO)_2P(O)CH_2CO_2Et$ (0.11 mL, 0.54 mmol) at 0 °C, and the reaction mixture was stirred at 0 °C for 30 min. To the reaction mixture was added a solution of the aldehyde obtained above in THF (2 mL) at 0 °C, and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with H_2O, and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The organic extracts were combined, dried, and evaporated to give a pale yellow oil, which was chromatographed on silica gel (20 g, hexane/acetone=80:1–70:1) to give **29** (150 mg, 95%) as a colorless oil consisting of a 4:1 mixture of *E*- and *Z*-isomers.

4.1.27. (5*R*,8*R*,9*R*)-(−)-8-Butyl-5-propylhexahydroindolizin-3-one (30). To a stirred solution of **29** (150 mg, 0.40 mmol) in EtOAc (10 mL) was added 10% Pd–C (100 mg), and the resulting suspension hydrogenated at 1 atm for 20 h. The catalyst was removed by filtration, and the filtrate was evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the ester obtained above in EtOH (3 mL) and H_2O (1 mL) was added $LiOH\cdot H_2O$ (33 mg, 0.79 mmol), and the reaction mixture was heated at 60 °C for 2 h. After cooling, the solvent was evaporated, and the residue was extracted with EtOAc (5 mL×10). The organic extracts were combined, dried, and evaporated to give a colorless oil, which was used directly in the next step. To a stirred solution of the carboxylic acid obtained above in CH_2Cl_2 (2 mL) was added TFA (0.18 mL, 2.37 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 5 h. The volatiles were evaporated to give a pale yellow oil, which was used directly in the next step. To a stirred solution of the amine obtained above in DMF (2 mL) were added Et_3N (0.16 mL, 1.19 mmol) and DEPC (0.09 mL, 0.59 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The volatiles were evaporated, and the residue was chromatographed on silica gel (15 g, hexane/acetone=30:1–10:1) to give **30** (86 mg, 90%) as a pale yellow oil.

IR (neat) 2933, 2867, 1682 cm^{-1}; ^1H NMR (500 MHz) δ 0.83–0.90 (6H, m), 1.10–1.42 (10H, br m), 1.55–1.67 (5H, m), 1.72–1.83 (1H, m), 1.94–1.99 (1H, m), 2.22–2.34 (2H, m), 3.76–3.81 (1H, m), 4.12–4.19 (1H, br); ^{13}C NMR (125 MHz) δ 14.10 (q), 14.19 (q), 19.71 (t), 20.44 (t), 21.46 (t), 22.25 (t), 22.98 (t), 23.09 (t), 29.58 (t), 30.68 (t), 32.59 (t), 37.25 (d), 47.49 (d), 56.61 (d), 173.48 (s); MS: 237 (M^+); HRMS: Calcd for $C_{15}H_{27}NO$ 237.2091; Found 237.2076; $[\alpha]_D^{26}$ −38.4° (*c* 3.96, $CHCl_3$).

4.1.28. (5*R*,8*R*,9*R*)-(−)-8-Butyl-5-propyloctahydroindolizine (2). To a stirred solution of **30** (79 mg, 0.33 mmol) in THF (10 mL) was added $LiAlH_4$ (126 mg, 3.33 mmol), and the resulting suspension was refluxed for 15 h. After cooling, the reaction was quenched with 10% NaOH (aq), and the aqueous mixture was extracted with Et_2O (10 mL×5). The organic extracts were combined, dried over K_2CO_3, and evaporated to give a colorless oil, which was chromatographed on Silica gel (15 g, hexane/acetone/Et_3N=450:15:10 drops) to give **2** (60 mg, 81%) as a colorless oil.

IR (neat) 2954, 2927, 2868, 2796, 1461, 1375, 1268, 1187, 1059, 899 cm^{-1}; ^1H NMR (500 MHz) δ 0.88–0.93 (6H, m), 1.12–1.31 (10H, br m), 1.35–1.47 (1H, m), 1.48–1.66 (5H, br m), 1.78–1.84 (2H, m), 1.94 (1H, br), 2.11–2.15 (1H, m), 2.66–2.72 (1H, m), 3.00–3.05 (1H, m), 3.15–3.19 (1H, m); ^{13}C NMR (125 MHz) δ 14.19 (q), 14.63 (q), 19.40 (t), 20.95 (t), 21.44 (t), 23.01 (t), 25.29 (t), 29.48 (t), 31.29 (t), 33.35 (t), 36.78 (d), 37.00 (t), 50.43 (t), 54.19 (d), 64.17 (d) (s);

MS: 223 (M^+); HRMS: Calcd for $C_{15}H_{29}N$ 223.2299; Found 223.2292; $[\alpha]_D^{26}$ −29.0° (*c* 2.99, $CHCl_3$).

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Bioactive steroidal glycosides from the marine sponge *Erylus lendenfeldi*

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Abstract—Bioassay-guided fractionation of the methanol extract of *Erylus lendenfeldi* using engineered strains of budding yeast (*Saccharomyces cerevisiae*) has resulted in the isolation of the known compound eryloside A (**1**) and two new compounds, erylosides K (**2**) and L (**3**). The structures were established based mainly on 1D and 2D NMR data. The absolute stereochemistry of eryloside A, which had never been fully characterized, was determined using the modified Mosher's method. The absolute stereochemistry of eryloside K was determined by comparison with tetrahydroeryloside A. Compounds **1**–**3** exhibited selective cytotoxicity against a yeast strain (*Δrad50*) deficient in double strand break (DSB) repair.

1. Introduction

The modern approach to finding new anticancer drugs relies on the discovery of compounds that target the subtle molecular differences between malignant and healthy human cells.[1] The recent integration of genetics and drug discovery has resulted in the engineering of a wide array of molecular alterations in model organisms that can be used to screen for selectively bioactive small molecules. In particular, budding yeast (*Saccharomyces cerevisiae*) have proven to be an excellent model for discovering novel anticancer agents.[2] In an effort to rapidly identify bioactive marine natural products that target cancer-related pathways, we began screening our collection using an assay[3] to identify extracts that were selectively cytotoxic to budding yeast strains with defined alterations in cell-cycle checkpoint and DNA-damage repair genes. The methanol extract from the Red Sea sponge *Erylus lendenfeldi* Sollas,[4] 1888 (Demospongiae, Astrophorida, Geodiidae) exhibited selective cytotoxicity against a *Δrad50* mutant (yMP11406) deficient in DSB repair. Herein, we describe the structure and bioactivity of three steroidal glycosides, erylosides A, K, and L, which were isolated from this extract.

Keywords: Cell-based assay; Double strand break repair; Steroidal glycoside; Modified Mosher's method; Catalytic hydrogenation.
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2. Results and discussion

2.1. Isolation and structural elucidation

The marine sponge *Erylus lendenfeldi* was collected in February, 2000 in the Red Sea just north of Hurghada. The methanol extract exhibited selective activity against a *Δrad50* strain of *S. cerevisiae*. Bioassay-guided fractionation led to the isolation of the known steroidal glycoside, eryloside A (**1**, 720 mg, 0.4% dry weight), along with two new steroidal glycosides: eryloside K (**2**, 145 mg, 0.08% dry weight), and eryloside L (**3**, 90 mg, 0.05% dry weight). The molecular formula of eryloside A (**1**) was determined to be $C_{40}H_{66}O_{12}$ by high resolution MALDI-MS (*m/z* 761.4472 ($[M+Na]^+$). The spectral properties of **1** (Table 1) were identical with the reported values for eryloside A.[5] Thus, **1** is a 3β-*O*-{β-D-galactopyranosyl-(1→2)-β-D-galactopyranosyl}-23β-hydroxy-4α-methyl-5α-cholesta-8,14-diene.

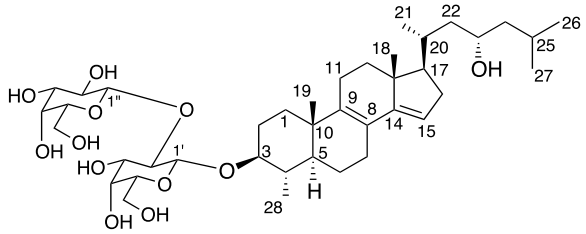

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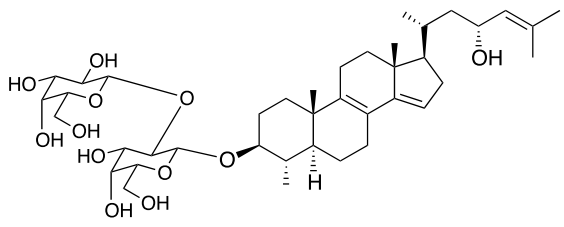
Table 1. ^{13}C and ^{1}H NMR data for compounds **1** and **3** (CD_3OD)

Position	^{13}C NMR, ppm		^{1}H NMR, ppm; mult. (*J*, Hz)	
	1	**3**	**1**	**3**
1	36.6	36.2	1.24 m	1.25 m
			1.87 m	1.89 m
2	31.0	30.5	1.61 m	1.62 m
			2.13 m	2.13 m
3	87.9	87.4	3.16 dt (10.6, 5.2)	3.17 dt (10.6, 5.1)
4	39.1	38.7	1.51 dd (11.4, 10.6)	1.51 dd (11.0, 10.8)
5	49.1	48.7	1.07 ddd (12.2, 11.4, 2.4)	1.08 ddd (12.0, 10.8, 2.4)
6	21.9	21.5	1.30 m	1.31 m
			1.85 m	1.88 m
7	28.1	27.6	2.13 m	2.13 m
			2.25 m	2.25 m
8	124.1	123.6		
9	141.6	141.5		
10	38.0	37.6		
11	22.9	22.5	2.21 m	2.23 m
12	38.5	38.0	1.37 m	1.38 m
			2.05 m	2.02 m
13	46.3	46.2		
14	152.1	152.2		
15	118.2	117.4	5.34 s	5.34 s
16	37.1	36.7	2.07 m	2.07 m
			2.34 m	2.30 m
17	59.4	58.1	1.48 m	1.55 m
18	16.3	15.8	0.84 s	0.86 s
19	19.9	19.4	1.02 s	1.04 s
20	31.9	31.7	1.94 m	2.22 m
21	19.5	20.2	0.97 d (6.6)	0.94 d (5.6)
22	45.6	50.9	1.01 m	2.21 m
			1.47 m	2.49 m
23	67.5	213.3	3.75 m	
24	49.3	53.0	1.15 m	2.32 m
			1.37 m	2.29 m
25	25.9	25.3	1.75 m	2.08 m
26	23.9	22.5	0.90 d (6.4)	0.90 d (6.4)
27	22.7	22.6	0.92 d (6.2)	0.91 d (6.4)
28	16.0	15.6	1.08 d (6.4)	1.10 d (6.4)
Galactose at C-3				
1′	104.8	104.4	4.43 d (8.0)	4.45 d (7.6)
2′	80.7	80.2	3.79 m	3.83 m
3′	75.3	74.8	3.67 m	3.67 m
4′	70.1	69.8	3.85 m	3.86 m
5′	76.2	75.9	3.49 m	3.50 m
6′	62.3	62.2	3.71	3.71 m
Galactose at C-2′				
1″	105.9	105.4	4.57 d (7.4)	4.57 d (7.6)
2″	73.2	72.1	3.62 m	3.64 m
3″	74.8	74.4	3.50 m	3.51 m
4″	70.1	69.8	3.85 m	3.82 m
5″	77.0	76.6	3.52 m	3.54 m
6″	62.2	62.3	3.70 m	3.72 m



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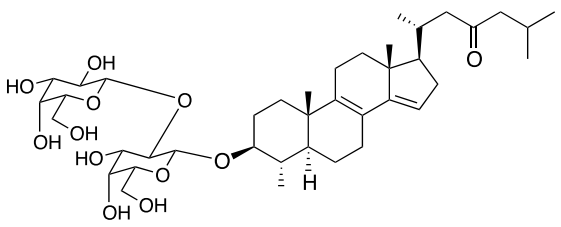
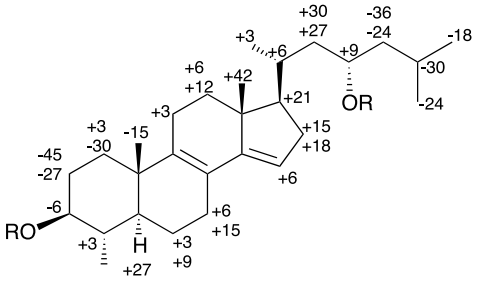


3

The absolute configuration of eryloside A, which had never been fully characterized, was determined using the modified Mosher's method.[6] Compound **1** was hydrolyzed with HCl to afford the aglycon (**4**), which was converted to the (*R*)- and (*S*)-MTPA diesters. Interpretation of $\Delta\delta$ values (Fig. 1) allowed the absolute configuration of C-3 and C-23 to be assigned as 3*S* and 23*S*, respectively. This is in agreement with other sponge-derived steroidal glycosides



4: R=H
5a: R=(R)-MTPA
5b: R=(S)-MTPA

Figure 1. Distribution of $\Delta\delta$ values (Hz) for the MTPA esters of **4**.

for which the absolute configurations have been determined,[7,8] as well as common steroids such as cholesterol and ergosterol.[6]

Eryloside K (**2**) had the molecular formula of $C_{40}H_{64}O_{12}$, which was determined by high resolution MALDI-MS (*m/z* 759.4320; $[M+Na]^+$) and ^{13}C NMR. Careful analysis of the ^{13}C NMR and multiplicity-edited HSQC spectra showed that **2** contained six methyl, 10 methylene, 18 methine, and six quaternary carbons (Table 2). Chemical shifts indicated that two of the methylene and 10 of the methine carbons were associated with two sugar units, and that the remaining 28 carbons belonged to the steroid. Four quaternary and two methine carbons were associated with three double bonds (δ 124.1, 141.6, 152.1, 117.8, 130.2, 133.3), while two of the remaining steroid methines were oxygenated (δ 87.4, 66.3). A major portion of the tetracyclic backbone was assembled through interpretations of HMBC correlations from two methyl singlets (δ 0.86, 1.04), a methyl doublet (δ 1.10) and an olefinic methine (δ 5.34) to ring junction carbons (Me-18 to C-14; Me-19 to C-5, C-9; Me-28 to C-5; H-15 to C-8, C-13). Additional HMBC correlations from the methyl signals established all carbons two and three bonds removed from the methyls. Analysis of the COSY and TOCSY data allowed for assignment of the C-1/C-2/C-3/C-4/C-28/C-5/C-6/C-7, C-11/C-12, and C-15/C-16/C-17 spin systems.

The UV spectrum for **2** suggested the presence of a chromophore due to a conjugated diene system (λ_{max} 249). Whereas one double bond (δ 130.2, 133.3) was shown by COSY and HMBC experiments to be on the side-chain of the steroid, the remaining diene appeared to be within the tetracyclic ring system. Since three of the four olefinic carbons were quaternary, only two locations for a conjugated system were possible: $\Delta^{8,14}$ and $\Delta^{9(11),8(14)}$. Comparison with ^{13}C NMR values for 5α-cholesta-8,14-dien-3β-ol[9] and 3β-hydroxy-5α-cholesta-8(14),9(11)-dien-15-one[10] allowed us to eliminate $\Delta^{9(11),8(14)}$ and establish the 8,14 diene system as correct.

HMBC correlations from H-17 (δ 1.46) to C-20 (δ 31.6) established attachment of the side-chain at C-17. An HMBC correlation from Me-21 (δ 1.02) to C-22 (δ 45.0), along with COSY correlations between H_2-22 (δ 1.00, 1.66), H-23 (δ 4.42) and H-24 (δ 5.17), firmly established the configuration of the side chain, including the C-23 allylic alcohol and the C-24/C25 alkene. The side-chain methyl doublets at δ 1.70 and 1.67 were assigned to the vinyl methyl groups at C-26 and C-27 respectively, on the basis of HMBC correlations to the fully substituted olefinic carbon at C-25 (δ 133.3) and the olefinic methine at C-24 (δ 130.2).

The identity and arrangement of the glycon moiety was established by a combination of 1D and 2D NMR experiments. The ^{13}C NMR shifts of the anomeric methine carbons (δ 104.5, 105.9) suggested that both sugars were connected through β-glycosidic linkages.[11] An HMBC correlation between H-3α (δ 3.16) and C-1$'$ (δ 104.5) established the location of the glycosidic linkage at C-3, and a correlation from H-2$'$ to C-1$''$ defined the linkage between the two sugar units. This latter finding was supported by an observed NOE between H-2$'$ (δ 3.81) and H-1$''$ (δ 4.58). Comparison of the COSY data and proton *J*-values with the literature[5] established both sugars as β-galactopyranoside units.

The relative stereochemistry of the steroid was assigned on the basis of a ROESY experiment (Fig. 2) and ^1H–^1H coupling constants. Observed 1,3-diaxial NOE correlations between Me-19, H-2β (δ 1.62), H-4β (δ 1.51), and H-6β (δ 1.86) established the chair conformation and the *trans*-ring fusion of the A and B rings, as well as the axial orientation of Me-19 and the 10*S** stereochemistry for C-10. The 4α-methyl configuration was determined by a large diaxial coupling ($J=10.7$) between H-3α (δ 3.16) and H-4β (δ 1.51). Since the H-5 ^1H NMR signal was obscured by the Me-28 doublet (δ 1.10), 1D-TOCSY experiment was used to determine the 11.2-Hz diaxial coupling constant between H-4β and H-5 (δ 1.07). This established the α position for H-5, as well as the 4*S** and 5*S** configurations at C-4 and C-5. It was not possible to distinguish the H_2-11 methylene signals (δ 2.21) by ^1H NMR, making it difficult to determine the orientation of Me-18. However, the axial orientation of Me-18 was assignable based on ROESY correlations from Me-18 to both Me-21 (δ 1.02) and H-20 (δ 1.87). In addition, a long-range COSY correlation between Me-18 and H-12α suggested that both groups were axial. Finally, the β-orientation for the side-chain could be assigned based on an NOE between H-12α (δ 1.36) and H-17 (δ 1.46). The relative stereochemistries at C-13 and C-17 were thus established as 13*R** and 17*R**. The overall structure of eryloside K was assigned as 3β-*O*-{β-D-galactopyranosyl-(1$\rightarrow$2)-β-D-galactopyranosyl}-23β-hydroxy-4α-methyl-5α-cholesta-8,14,24-triene.

Eryloside L (**3**) had a molecular formula of $C_{40}H_{64}O_{12}$, which was determined by high-resolution MALDI-MS (*m/z* 759.4283; $C_{40}H_{64}O_{12}$ Na) and ^{13}C NMR. The spectral data of **3** were very similar to those of **1** and **2**. Careful examination of the ^1H and ^{13}C NMR data (Table 1) revealed that both the disaccharide chain and the tetracyclic backbone were conserved in **3**. The significant change was the disappearance of the side-chain olefinic group and the appearance of a strongly deshielded ^{13}C signal (δ 213.3). This, combined with an IR band at 1705 cm^{-1} and a downfield alpha methylene signal (δ 2.32), suggested that **3** contained a side-chain ketone. HMBC correlations from the carbonyl carbon to H_2-22 and H_2-24 established the location

Table 2. ^{13}C, ^{1}H, and HMBC NMR data for compound **2** (CD_3OD)

Position	^{13}C NMR, ppm		^{1}H NMR, ppm; mult. (J, Hz)	HMBC
1	36.3	CH_2	1.28 m	C-10, C-19
		CH_2	1.87 m	C-10, C-19
2	30.6	CH_2	1.62 m	
		CH_2	2.14 m	
3	87.4	CH	3.16 dt (10.7, 5.1)	C-4, C-28, C-1′
4	38.8	CH	1.51 dd (10.8, 11.2)	C-3, C-5, C-28
5	48.7	CH	1.07 ddd (12.2, 11.4, 2.4)	
6	21.6	CH_2	1.30 m	C-5, C-7
		CH_2	1.86 m	C-7, C-8
7	27.7	CH_2	2.12 m	C-5, C-8, C-9
		CH_2	2.25 m	C-8, C-9
8	124.1	C		
9	141.6	C		
10	37.8	C		
11	22.6	CH_2	2.21 m	C-13
12	38.2	CH_2	1.36 m	C-11, C-13, C-17, C-18
		CH_2	2.06 m	C-11, C-13, C-18
13	46.3	C		
14	152.1	C		
15	117.8	CH	5.34 s	C-8, C-13, C-16, C-17
16	36.7	CH_2	2.11 m	C-14, C-15, C-17, C-20
		CH_2	2.36 m	C-13, C-14, C-15, C-17
17	59.0	CH	1.46 m	C-12, C-13, C-16, C-18, C-20
18	15.9	CH_3	0.86 s	C-12, C-13, C-14, C-17
19	19.2	CH_3	1.04 s	C-1, C-5, C-9, C-10
20	31.6	CH	1.87 m	
21	19.2	CH_3	1.02 d (6.8)	C-17, C-20, C-22
22	45.0	CH_2	1.00 m	
		CH_2	1.66 m	C-23
23	66.3	CH	4.42 m	
24	130.2	CH	5.17 dt (8.4, 1.2)	C-22, C-26, C-27
25	133.3	C		
26	25.6	CH_3	1.70 d (1.2)	C-24, C-25, C-27
27	17.8	CH_3	1.67 d (1.2)	C-26
28	15.7	CH_3	1.10 d (6.4)	C-3, C-4, C-5
Galactose at C-3				
1′	104.5	CH	4.45 d (8.0)	C-3, C-2′, C-3′, C-5′, C-1″
2′	80.2	CH	3.81 m	C-1′, C-1″
3′	74.9	CH	3.65 m	C-2′
4′	69.8	CH	3.85 m	C-2′
5′	76.1	CH	3.50 m	C-1′, C-3′, C-4′, C-6′
6′	62.2	CH_2	3.71 m	C-4′
Galactose at C-2′				
1″	105.5	CH	4.58 d (7.6)	C-2′, C-2″, C-3″
2″	72.8	CH	3.62 m	C-1″, C-3″
3″	74.5	CH	3.49 m	C-1″
4″	69.8	CH	3.85 m	C-2″, C-3″, C-6″
5″	76.8	CH	3.53 m	C-2″, C-4″, C-6″
6″	62.3	CH_2	3.72 m	C-4″, C-5″

of the ketone at C-23. Thus, **3** has been assigned as a 3β-*O*-{β-D-galactopyranosyl-(1→2)-β-D-galactopyranosyl}-4α-methyl-5α-cholesta-8,14-dien-23-one.

To establish the absolute configuration for eryloside K, we attempted to obtain the aglycon of **2** via acid hydrolysis. Not surprisingly, the allylic alcohol readily dehydrated upon exposure to HCl or milder acids. To circumvent this problem, we decided to reduce the side-chain alkene in **2** and compare the properties of the resulting product to the product of **1** when exposed to the same conditions. Rhodium was chosen as the catalyst since it is known to minimize hydrogenolysis of allylic alcohols.[12] Hydrogenation of both **1** and **2** in the presence of 5% rhodium catalyst yielded compound **6** (Fig. 3), in which the C-24/25 alkene (**2**) and the C-14/15 alkene (**1** and **2**) were reduced, while the more highly substituted C-8/9 alkene remained intact. The resulting products exhibited identical ^{1}H NMR spectra, HPLC retention times, and optical rotations (see Section 3). Compound **2** must therefore have the same overall configuration as **1**.[13] Eryloside L also has the same absolute stereochemistry as **1** and **2** based on similarities in optical rotation and biogenetic reasoning.

2.2. Biological activity

Glycosylated marine natural products tend to exhibit potent and/or selective bioactivity.[14] The erylosides, a series of unusual steroidal glycosides isolated from sponges of the genus *Erylus*, have been reported with anticancer, antifungal, and anticoagulative activity.[5,15–18] Erylosides A, K,

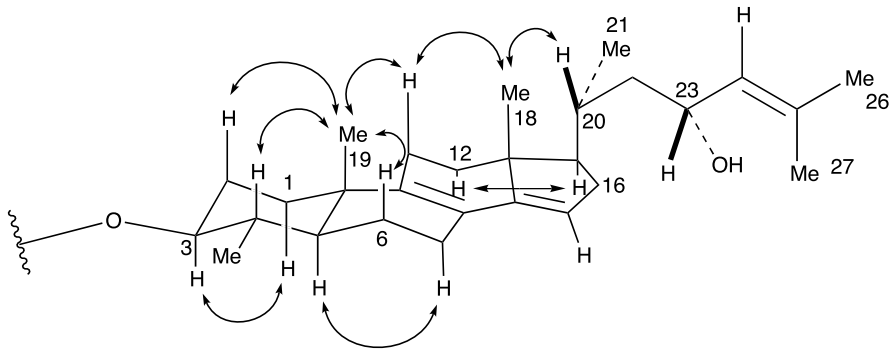


Figure 2. NOE correlations for the steroidal portion of **2**.

and L all exhibited selective cytotoxicity against a Δ*rad50* budding yeast strain (Table 3). RAD50 is needed for repair of DNA double-strand breaks by recombination and by KU-mediated end-joining (reviewed in Ref. 19). Similar studies[3,20] have suggested that selective cytotoxicity against DSB repair mutants may be an indicator of topoisomerase poisons. Topoisomerase inhibitors such as camptothecin and idarubicin exhibit marked selectivity against DSB repair mutants.[1] Topo I and topo II poisons can be distinguished by increased potency against yeast strains overexpressing TOP1 and TOP2 respectively, as compared to a wild-type yeast strain. Based on this, compounds **1**–**3** do not appear to be topoisomerase poisons (Table 3). In addition, compounds **1**–**3** failed to stabilize the TOP1

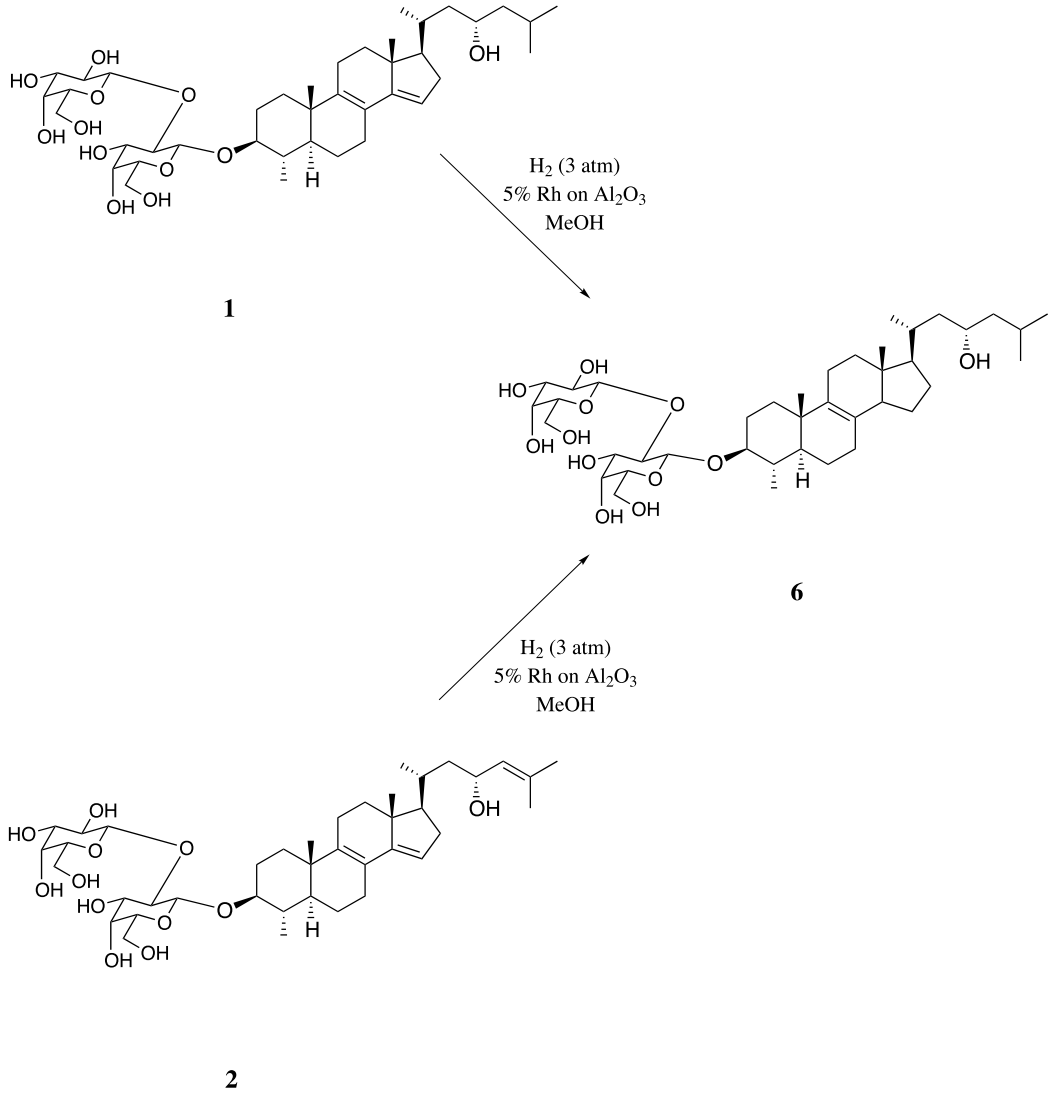


Figure 3. Catalytic hydrogenation of **1** and **2**.

Table 3. Activity[a] of erylosides and some reference topoisomerase poisons against different yeast strains[b]

Compound	Yeast strains			
	Parent	*Δrad50*	TOP1oe	TOP2oe
Eryloside A (**1**)	3.5	0.8	5.7	10.8
Eryloside K (**2**)	6.1	2.0	7.5	12.2
Eryloside L (**3**)	11.4	3.4	10.9	9.5
Aglygon (**4**)	>50	>50	NT[c]	NT
Camptothecin[d]	3.8	0.1	0.4	1.5
Idarubicin[d]	3.5	0.2	3.5	0.2

[a] IC_{50} (μM).
[b] Log-phase culture of *S. cerevisiae* strains (135 μL, OD_{600} of 0.5) treated with serial dilution of drug or DMSO (15 μL) for 18 h and optical density monitored.
[c] Indicates not tested.
[d] See Ref. 12.

cleavable complex or cause TOP2 cleavage when screened for DNA strand break activity[21] at a dose of 500 μM (data not shown). Thus their target remains unknown.

The aglycon (**4**) did not exhibit significant activity against any of the yeast strains (Table 3), suggesting that glycosylation of these molecules is integral to their bioactivity. Although the sugars themselves seem to have little or no therapeutic action, their presence strongly affects the physical, chemical, and biological properties of molecules to which they are attached, presumably due to modifications in their binding properties.[22] In addition, modifications in the side chain between **1**, **2**, and **3** corresponded to noticeable differences in both the potency and selectivity of the erylosides (Table 3). Interestingly, a similar class of steroidal glycosides were reported to have selective cytotoxicity against DSB repair yeast mutants,[23] suggesting a common mechanism of action for this class of compounds.

3. Experimental

3.1. General methods

Optical rotations were measured on a Rudolf Autopol III polarimeter at 598 nm. IR spectra were recorded on a Perkin–Elmer 1600 FT-IR spectrophotometer. UV spectra were obtained using a Perkin–Elmer Lambda Bio-20 spectrophotometer. ^{1}H, COSY, HMBC, HSQC, 1D-NOESY, 1D-TOCSY, and ROESY NMR spectra were measured on a Varian Inova 300 MHz spectrometer. ^{13}C and DEPT spectra were measured on a Varian Gemini 400 MHz spectrometer. ESIMS spectra were recorded using a Finnigan LCQ mass spectrometer. High-resolution MALDI-MS data were obtained on a PE Biosystems DE-STR MALDI TOF system at the U.C. Riverside Regional Facility. All solvents were distilled prior to use.

3.2. Extraction and purification

The sponge *Erylus lendenfeldi* was collected by SCUBA in February, 2000 in the Red Sea just north of Hurghada. The crude methanol extract exhibited selective cytotoxicity against a *Δrad50* yeast strain, and was thus selected for further study. A portion of the freeze-dried sponge (180 g) was extracted three times in methanol to give 1 L of crude extract. Roughly half of the methanol was removed in vacuo, and the remaining extract was partitioned on HP20 (Supelco Diaion®) using an increasing concentration of acetone in water.[24] The 50% aqueous acetone fraction (200 mg) exhibited the most potent and selective activity against Δ*rad50* mutants and was thus purified using reversed-phase HPLC (Dynamax C8 semi-prep, 75% MeOH, 3 mL/min) to give eryloside A (**1**, 720 mg, 0.4% dry weight), eryloside K (**2**, 145 mg, 0.08% dry weight), and eryloside L (**3**, 90 mg, 0.05% dry weight).

3.2.1. Eryloside A (1). White powder; $[\alpha]_D$ +6° (*c* 1.11, MeOH); mp: 168–172 °C; UV (MeOH) λ_{max} (log ε) 250 (4.24); IR ν_{max} (MeOH) 3360, 2930, 1060 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) see Table 1; ^{13}C NMR (100 MHz, CD_3OD) see Table 1; HRMALDI-MS *m/z* 761.4472 ([M+Na]$^+$ calcd for $C_{40}H_{66}O_{12}Na$, 761.45543).

3.2.2. Eryloside K (2). White powder; $[\alpha]_D$ +10° (*c* 0.12, MeOH); mp: 208–212 °C; UV (MeOH) λ_{max} (log ε) 249 (4.31); IR ν_{max} (MeOH) 3400, 2925, 1380, 1060 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) see Table 2; ^{13}C NMR (100 MHz, CD_3OD) see Table 2; HRMALDI-MS *m/z* 759.4320 ([M+Na]$^+$ calcd for $C_{40}H_{64}O_{12}Na$, 759.4290).

3.2.3. Eryloside L (3). White powder; $[\alpha]_D$ +10° (*c* 0.34, MeOH); mp: 200–204 °C; UV (MeOH) λ_{max} (log ε) 250 (4.33); IR ν_{max} (MeOH) 3375, 2930, 1705, 1370, 1060 cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) see Table 1; ^{13}C NMR (100 MHz, CD_3OD) see Table 1; HRMALDI-MS *m/z* 759.4283 ([M+Na]$^+$ calcd for $C_{40}H_{64}O_{12}Na$, 759.4290).

3.2.4. Acid hydrolysis of eryloside A (1). A portion of **1** (90 mg) was dissolved in 9 mL of a 1:1:48 mixture of HCl:benzene:EtOH and stirred at 65 °C. After 3 h, the mixture was neutralized with $NaCO_3$. The filtered slurry was dried down in vacuo, and the purified aglycon (**4**) was obtained in roughly quantitative yield by silica gel chromatography eluting with ethyl acetate.

Compound **4**. ^{1}H NMR (CD_3OD) 0.84 (3H, s, H-18), 0.91 (3H, d, H-26), 0.91 (3H, d, H-27), 0.97 (3H, d, H-21), 0.98 (3H, d, H-28), 1.01 (3H, s, H-19), 1.01 (1H, m, H-22a), 1.06 (1H, m, H-5), 1.15 (1H, m, H-24a), 1.27 (1H, m, H-1a), 1.32 (1H, m, H-6a), 1.34 (1H, m, H-4), 1.38 (1H, m, H-24b), 1.38 (1H, m, H-12a), 1.47 (1H, m, H-17), 1.51 (1H, m, H-22b), 1.54 (1H, m, H-2a), 1.76 (1H, m, H-25), 1.84 (1H, m, H-2b), 1.86 (1H, m, H-6b), 1.90 (1H, m, H-1b), 1.94 (1H, m, H-20), 2.06 (1H, m, H-12b), 2.10 (1H, m, H-16a), 2.14 (1H, m, H-7a), 2.22 (2H, m, H-11), 2.25 (1H, m, H-7b), 2.32 (1H, m,

H-16b), 3.02 (1H, m, H-3), 3.75 (1H, m, H-23), 5.33 (1H, s, H-15); ESIMS *m/z* 415 $(M+H)^+$.

3.2.5. MTPA esterification of 4. To a solution of 14.5 mg of **4** in 250 μL dry DCM and 28 μL pyridine was added 200 μL of (*S*)-MTPACl. The mixture was stirred over an ice bath for 4 h. After the consumption of the starting material was confirmed by TLC, the solution was twice washed with 5% aq $NaHCO_3$. The organic phase was dried under N_2 and chromatographed on silica gel (95:5 $CHCl_3$/MeOH) to give 5.2 mg of **5a**. Using the same procedure, 200 μL of (*R*)-MTPACl and 14.5 mg of **4** were reacted to obtain 3.8 mg of **5b**.

Compound **5a**. ^{1}H NMR (CD_3OD) 0.64 (3H, s, H-18), 0.92 (3H, d, H-26), 0.96 (3H, d, H-27), 0.90 (3H, d, H-21), 0.98 (3H, s, H-19), 1.22 (1H, m, H-1a), 1.14 (1H, m, H-5), 1.23 (1H, m, H-6a), 1.34 (3H, d, H-28), 1.38 (1H, m, H-12a), 1.43 (1H, m, H-24a), 1.43 (1H, m, H-20), 1.57 (1H, m, H-25), 1.60 (1H, m, H-17), 1.62 (1H, m, H-22a), 1.65 (1H, m, H-24b), 1.69 (1H, m, H-2a), 1.72 (1H, m, H-6b), 1.72 (1H, m, H-22b), 1.97 (1H, m, H-1b), 2.02 (1H, m, H-12b), 2.04 (1H, m, H-4), 2.05 (1H, m, H-16a), 2.09 (1H, m, H-2b), 2.20 (2H, m, H-11), 2.20 (1H, m, H-7a), 2.38 (1H, m, H-16b), 2.55 (1H, m, H-7b), 4.6 (1H, m, H-3), 5.34 (1H, m, H-23), 5.53 (1H, s, H-15).

Compound **5b**: ^{1}H NMR (CD_3OD) 0.78 (3H, s, H-18), 0.86 (3H, d, H-26), 0.88 (3H, d, H-27), 0.91 (3H, d, H-21), 0.93 (3H, s, H-19), 1.23 (1H, m, H-1a), 1.23 (1H, m, H-5), 1.24 (1H, m, H-6a), 1.31 (1H, m, H-24a), 1.37 (3H, d, H-28), 1.40 (1H, m, H-12a), 1.45 (1H, m, H-20), 1.47 (1H, m, H-25), 1.54 (1H, m, H-2a), 1.57 (1H, m, H-24b), 1.67 (1H, m, H-17), 1.72 (1H, m, H-22a), 1.75 (1H, m, H-6b), 1.81 (1H, m, H-22b), 1.87 (1H, m, H-1b), 2.00 (1H, m, H-2b), 2.05 (1H, m, H-4), 2.06 (1H, m, H-12b), 2.10 (1H, m, H-16a), 2.21 (2H, m, H-11), 2.22 (1H, m, H-7a), 2.44 (1H, m, H-16b), 2.60 (1H, m, H-7b), 4.58 (1H, m, H-3), 5.37 (1H, m, H-23), 5.55 (1H, s, H-15).

3.2.6. Catalytic hydrogenation product (6). Compounds **1** and **2** (10 mg) were each dissolved in 10 mL of MeOH. Hydrogenation was effected under H_2 gas (~3 atm) in the presence of 5% rhodium on Al_2O_3. The reaction was complete after 50 min as indicated by TLC. The filtered slurry was dried to give the identical product (**6**) in both cases. Products from hydrogenation reactions using **1** and **2** had identical masses (ESIMS, *m/z* 764 [M+Na]) corresponding to the reduction of one double bond in **1**, and two double bonds in **2**. The products from **1** and **2** had similar optical rotation values of $[\alpha]_D$ +12.4° (*c* 0.20, MeOH) and $[\alpha]_D$ +12.3° (*c* 0.21, MeOH) respectively, the same ^{1}H NMR spectra (data not shown), and identical HPLC retention times on C8 (Zorbax XDB; 67% MeOH; detected at 254 nm; t_R=20.7 min) and C18 (Phenomenex Luna; 46% CH_3CN; detected at 254 nm; t_R=12.6 min).

3.3. Yeast strains

All budding yeast strains were obtained from the Molecular Pharmacology Program at the Fred Hutchinson Cancer Research Center in Seattle, WA. Six strains were used, each with drug-sensitizing mutations that increased membrane porosity (Δ*erg6*)[25] and hindered drug efflux (Δ*pdr1* and Δ*pdr3*).[26] In addition, two of the strains contained a mutation in a double-strand break repair gene (yMP11406; *Δrad50*)[19] and a DNA damage checkpoint gene (yMP10605; *mec2-1/rad53*)[27] respectively. Three other strains contained double mutations in a postreplication repair gene (yMP10425; *Δrad18*)[28] and a mismatch repair gene (SP50248; *Δmlh1*)[29], a nucleotide excision repair gene (yMP10691; *Δrad14*) (review in Ref. 30) and overexpression of the G_1 cylcin CLN2 (*CLN2oe*),[31] and a 5′ to 3′ helicase gene (SP50265; *Δsgs1*)[32] and an alkylguanine transferase gene (yMP10612; *Δmgt1*).[33] The parent strain (yMP10381) was used as a control.

3.4. Yeast assay

Exponentially growing yeast in enriched liquid media were diluted to OD_{600}=0.07, and 135 μL of cells along with 15 μL of extract in DMSO was dispensed into each well of flat-bottomed 96-well microtiter plates. The assay was conducted in two stages. In stage 1, extracts (50 μg/mL) that produced a 70% or greater inhibition of growth in any or all strains advanced to stage 2. In stage 2, extracts were tested at 50, 25, 12.5, 6.3, 3.1, and 1.6 μg/mL. Extracts that produced a two-fold or greater difference in sensitivity between the most sensitive strain and less sensitive strains were studied further. Plates were incubated for 18 h at 30 °C, and the optical density (600 nm) of the cultures was determined using a Bio-Tek Instruments EL_x808 microplate reader to assess relative growth. DMSO and cycloheximide were used as negative and positive controls, respectively.

Acknowledgements

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Synthesis and transformations of alkyl *N*-(1-cyclohex-3-enyl)carbamates prepared from cyclohex-3-ene carboxylic acid via Curtius rearrangement

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Abstract—The Curtius rearrangement of cyclohex-3-ene carboxylic acid using diphenylphosphoryl azide in the presence of triethylamime and ethanol, *t*-butanol or benzyl alcohol has been described. As a result the synthesis of ethyl, *t*-butyl or benzyl *N*-(1-cyclohex-3-enyl)carbamates has been achieved in one pot, in good chemical yield. A series of transformations of benzyl *N*-(1-cyclohex-3-enyl)carbamate, such as iodination and epoxidation, as well as opening of the corresponding ring epoxide, have been carried out leading to some useful oxygenated cyclohexylamimo building blocks.

1. Introduction

exo-2-Substituted 7-azabicyclo[2.2.1] derivatives (**A**) (Chart 1) are useful synthetic intermediates[1] for the synthesis of a number of natural products.[2] Consequently, a series of methodologies have been reported for the preparation of this type of molecules.[3] In this context, and in connection with a current project in progress in our laboratory, in this paper we report our initial results on this subject, that have ended in a new synthetic protocol for the synthesis of *N*-(1-cyclohex-3-enyl)carbamates (**B**, R= Et, *t*-Bu, Bn, Chart 1) from cyclohex-3-ene carboxylic acid (**1**) via Curtius rearrangement;[4] in addition, we have carried out some additional transformations on these substrates affording differently substituted cyclohexylamino derivatives of potential synthetic interest.

In our retrosynthetic analysis, compounds of type **A** should be possibly obtained after double bond activation (halogenation, epoxidation, etc.) and heterocyclization reaction on alkyl *N*-(1-cyclohex-3-enyl)carbamates (**B**, Chart 1). In fact, carbamates (**B**) have been proposed as key intermediates for the synthesis of the natural products, such as clausenamide,[5] and the related 4-(*N*-methyl-*N* trifluoroacetylamino)cyclohexene,[6] has been transformed into epibatidine.[7]

Carbamates **B** have been prepared by using different

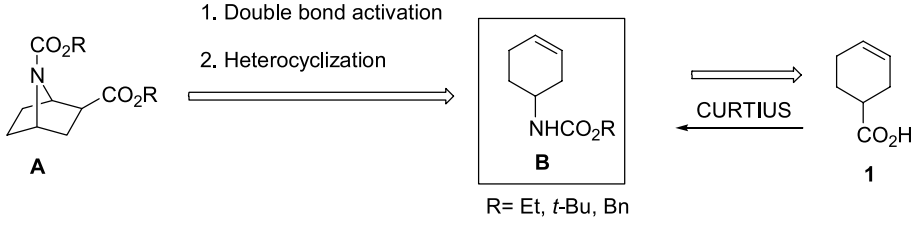

Chart 1.

Keywords: Cyclohex-3-ene carboxylic acid; Curtius rearrangement; Diphenylphosphoryl azide; Alkyl *N*-(1-cyclohex-3-enyl)carbamates; Epoxides; Ring-opening.
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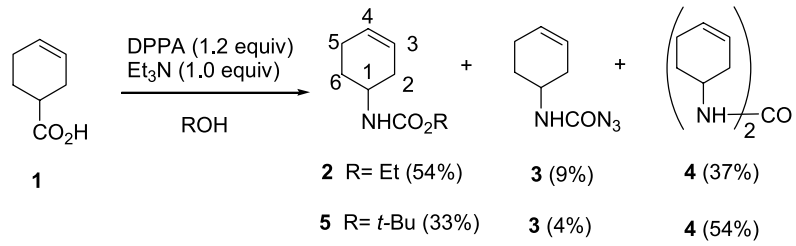
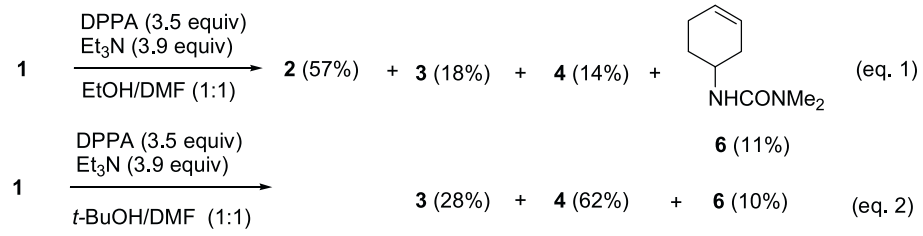


Scheme 1.



Scheme 2.

synthetic methodologies. For instance, carbamates of type **B** (R=Et) (Chart 1) have been synthesized by photolysis of cyclohexene in the presence of ethyl azidoformate,[8a] by reaction of *trans*-1,2-dichlorohexane with ethyl azidoformiate followed by reduction with zinc in ethanol[8b] or by standard Curtius rearrangement on the acyl azide, obtained from cyclohex-3-ene carboxylic acid via the acid chloride, followed by reaction with sodium azide, in the presence of ethanol.[8c] For carbamates of type **B** (R=*t*-Bu) (Chart 1), by ring closing metathesis (RCM) reaction of 1-allyl-4-pentenylamines[9a] and by palladium catalyzed reaction of the allyl ester of cyclohex-3-ene carboxylic acid with diphenylphosphoryl azide [$(PhO)_2P(O)N_3$, DPPA] in the presence of sodium azide and *t*-BuOH.[9b] Finally, for carbamates of type **B** (R=Bn) (Chart 1), by RCM as above[9a] and also by rearrangement of the adduct obtained in the hetero Diels–Alder reaction of 1,3-cyclohexadiene and *N*-sulfinyl,benzyl carbamate.[10] Very surprisingly, to the best of our knowledge, Curtius rearrangement of cyclohex-3-ene carboxylic acid (**1**) in the original conditions as reported by Yamada et al.[11] with DPPA, in the presence of triethylamine and the corresponding alcohol, only has been reported once in literature patent[10c,d] for the synthesis of benzyl *N*-(1-cyclohex-3-enyl)carbamate (Chart 1). This fact, coupled to the simplicity of this method, prompted us to investigate the general feasibility of this approach.

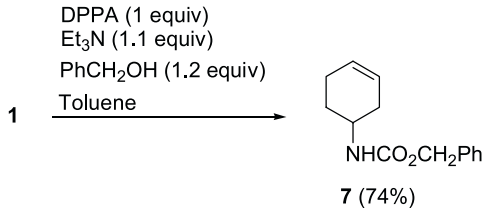
2. Results and discussion

Under the standard conditions [DPPA (1.2 equiv), Et_3N (1.0 equiv)],[11] compound **1** afforded carbamates **2**[8] (54%) and **5**[9] (33%) (Scheme 1), using ethanol or *t*-butanol as solvent, respectively. In these reactions, in addition to compounds **2** and **5**, amounts of other secondary compounds, such as the carbamoyl azide (**3**) or the urea (**4**) were detected and isolated (Scheme 1). These are commonly formed by-products in this reaction, and the mechanism involved in these processes has been discussed extensively.[11]

Next, several experiments were carried out in order to improve these results.

In fact, when toluene was used as solvent in the presence of ethanol (1.2 equiv), carbamate **2** and carbamoyl azide **3** were isolated in 51 and 32% yields, respectively, while only traces of urea **4** could be detected. When Curtius reaction shown in Scheme 1 was conducted in the presence of an excess of DPPA (3.5 equiv) and triethylamine (3.9 equiv) in a mixture of ethanol/DMF (1:1, in volume), the reaction was more complex, giving carbamate **2** in 57% yield accompanied by compounds **3** (18%) and **4** (14%), as well as urea **6** (11%) (Scheme 2, Eq. 1). Interestingly, in these conditions, but using *t*-butanol as co-solvent no carbamate **5** was detected, but products **3**, **4** and **6** were isolated in 28, 62, 10% yields, respectively (Scheme 2, Eq. 2). The good yield in the formation of carbamoylazide **4** in these experimental conditions is worth of mention, as these are particularly useful synthetic intermediates.[12]

Finally, and to our delight, when we applied the experimental conditions shown in Scheme 1, but using benzylic alcohol (1.0 equiv) and toluene as solvent, we obtained *N*-benzyl carbamate **7**[10] in 74% yield (Scheme 3) in a very clean reaction, that we have scaled up without loss of chemical yield.



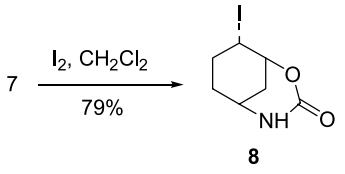
Scheme 3.

All new (**3**, **4**, **6**) or known compounds (**2**, **5**, **7**) gave analytical data and showed spectroscopic data (see Section 3) in good agreement with their structures or with the

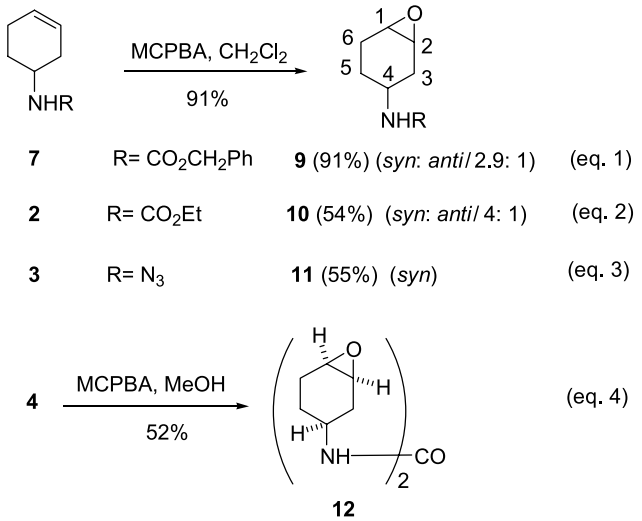
reported data in literature.[8–10] Particularly, in the ^{1}H NMR spectra of these compounds a new and very diagnostic signal for H1 appears in the range δ 4.02–3.78 as a multiplet. This signal correlates with C1, observed in the range 46.3–45.7 ppm, in the HMQC experiment. The carbamates, carbamoyl azides and ureas also showed the typical bans in the IR spectra for the carbonyl [(1696–1689 (st, NCO_2R), 1703 (st, CON_3), 1618 (NHCONH) cm^{-1}] and the azido (2135 cm^{-1}) moieties.

Being this protocol and this compound, the best in terms of simplicity and chemical yields (Scheme 3), *N*-benzyl carbamate **7** has been selected to carry out several experiments in order to functionalize the alkene moiety, looking for more advanced, functionalized, preferentially halogenated or oxygenated intermediates, according to our synthetic plan (see Chart 1).

With this idea in mind, first, we tested the iodination of the double bond in order to prepare suitable activated precursors for the subsequent aza-heterocyclization reaction (Chart 1). As shown in Scheme 4, the reaction of compound **7** with iodine in methylene chloride gave the bicyclic carbamate **8**, a compound that has been previously obtained in the reaction of carbamate **5** (Scheme 1) with iodine in the presence of potassium carbonate in ethyl ether.[9a] The reported data for the analogous bromide derivative[9a] were in good agreement with those observed for compound **8**. This result was interesting, but was not optimal for our purposes, and accordingly, we reasoned that the epoxidation of the double bond should provide possibly more useful precursors.



Scheme 4.



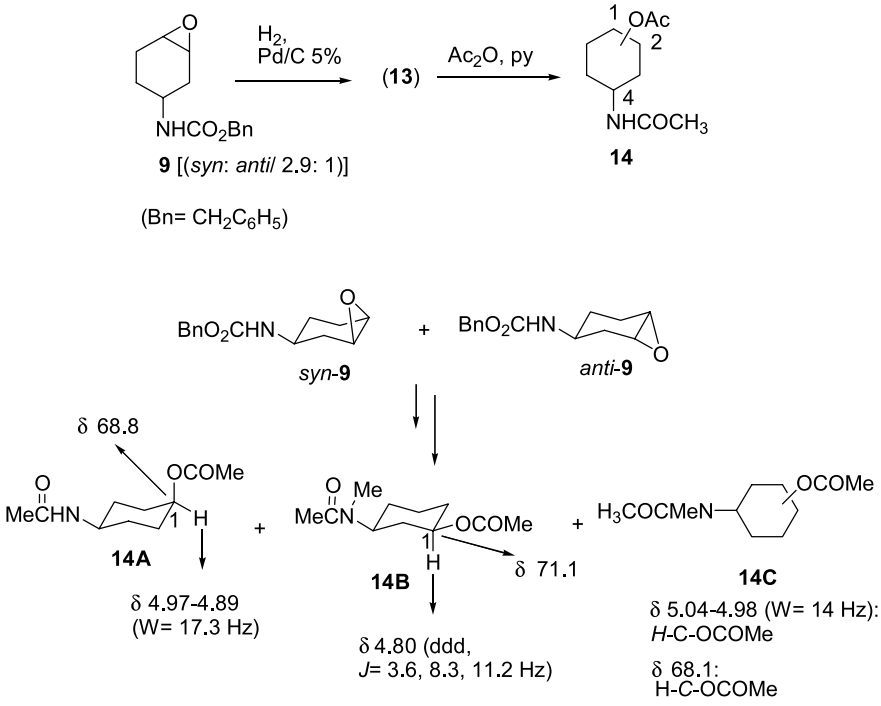
Scheme 5.

The epoxidation of carbamate **7** with MCPBA in methylene chloride gave epoxide **9** (Scheme 5, Eq. 1) as an inseparable mixture of *syn*/*anti* isomers in a 2.9:1 ratio (determined by GLC–MS analysis) in 91% yield. This result prompted us to investigate the epoxidation reaction on the ethyl carbamate **2**, and the analogous carbamoyl azide **3** and urea **4**. Under the same experimental conditions (see Section 3), compound **2** gave epoxide **10** as a mixture of the *syn* and *anti* isomers in lower yield 54%, but in a slightly better diastereoselection (4:1) (Scheme 5, Eq. 2). Similarly, compounds **3** and **4** afforded the expected compounds **11** (Scheme 5, Eq. 3) and **12** (Scheme 5, Eq. 4) have been isolated in 55 and 52% yields, respectively, as almost diastereomerically pure samples.

From the structural and analytical point of view, these compounds showed excellent data. In the ^{1}H NMR spectra, in particular, the signals for the vinylic protons have been substituted by new signals, as singlets or multiplets, for protons H1 and H2 in the range 3.20–3.13 ppm, corresponding to the epoxide protons. Compounds **11** and **12**, as well as the major isomers in compounds **9** and **10**, have been tentatively assigned as the *syn* isomers, based on the well established stereochemical trend observed during the epoxidation of related 1-aminocyclohene derivatives, and also by detailed comparison of their similar spectroscopic data with those observed for the epoxide of (*N*-benzyl,*N*-trifluoroacetyl)aminocyclohex-3-ene.[6]

With a high yielding and simple access to epoxides **9**–**12**, next we decided to investigate the opening of the epoxide ring on these cyclohexylamino containing substrates, a reaction that to the best of our knowledge has not been previously investigated. Conversely, the analogous ring opening of 1,2-epoxides on *cis* and *trans*-1,2-oxides of 4-(benzyloxy)cyclohexene, 4-[(benzyloxy)methyl]cyclohexene and related compounds[13,14] has been extensively investigated, and proved useful for the synthesis of the cyclohexyl moiety of several target molecules of interest.[15] According to the *trans*-diaxial ring opening reaction (Fürst–Plattner rule[16]) the *cis*-1,2-oxide of 4-[(benzyloxy)methyl]-cyclohexene, for instance, gives exclusively, nucleophilic *trans*-attack at C-2,[15] a result that is suitable for our initial purposes leading to the synthesis of precursors for 7-azabicyclo[2.2.1]heptane derivatives (Chart 1). For the exploratory experiments we have selected the inseparable mixture (2.9:1) of epoxides *syn*/*anti*-**9**, and the hydrogenation reaction as we speculated that after the hydrogenolysis of the benzyloxycarbonyl group the resulting free amino group would spontaneously cyclize to give the desired intermediates.

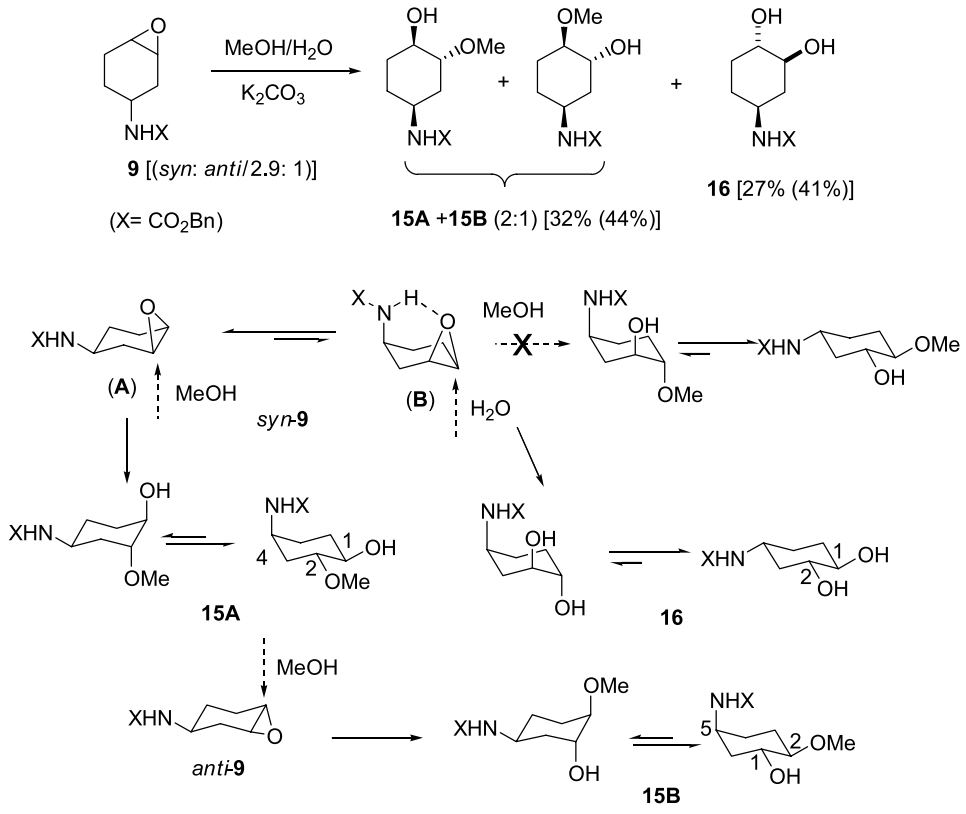
The hydrogenation (H_2, Pd/C 5%, 1 atm, rt) of epoxide **9** [(*syn*/*anti* 2.9:1)] gave a crude (**13**) that, after acetylation and chromatography, provided a mixture of products, whose spectroscopic and chromatographic analysis showed that it was formed by three compounds (**14A**–**C**) in 70, 22.5 and 7.5% ratio, respectively (Scheme 6). The coupled MS/GLC analysis gave the corresponding mass spectrum for each component. Accordingly, we could assign 199 as the molecular picks for **14A**, and for **14B/C**, 213, each one. The ^{1}H NMR analysis of the whole mixture showed no *N*-benzyl and epoxide protons, appearing broad singlets for



Scheme 6.

N*H*COCH$_3$ at 5.62–5.25 ppm, multiplets and singlets for H–C–OCOCH$_3$ in the range 5.05–4.50 ppm, and 2.04/1.97 and 2.03/1.95 ppm, respectively; a broad multiplet between 4.00–3.78 ppm for *H*CNHCOR and, finally, we could observe a series of three singlets (intensity) at 2.87 (31.6) and 2.84 (19.9) ppm that correlated in the HMQC experiment with signals at 30.2 and 27.0 ppm, respectively, in the ^{13}C NMR spectrum. Coherent with these data, in this experiment we could also locate signals for carbonyl (not a carbamate) function at 170.3/169.1 and 170.0/168.9 ppm, as well as 23.5/21.3 and 23.4/21.2 ppm, which clearly suggest the presence of an acetate and/or acetamide functional moieties. To sum up, it is clear that the hydrogenation of epoxides **9** has resulted in the reduction of the epoxide with simultaneous hydrogenolysis of the *N*-benzyl carbamate to yield a mixture of 3 or 4-(*cis*/*trans*)-aminocyclohexanols (**13**);[17] after acetylation major (*cis*/*trans*)-3 (or 4)-acetamidocyclohexyl acetate (**14A**) should have resulted (M^+ 199, $C_{10}H_{17}NO_3$), while the two minor derivatives with molecular picks equal to 213 are presumably *N*-methyl *cis* or *trans*-3(or 4)-acetamidocyclohexyl acetates (**14B/C**, $C_{11}H_{19}NO_3$). Looking more carefully into the ^{13}C NMR, DEPT and HMQC spectra for the major isomer (**14A**) we observed signals for H–*C*–OCOCH$_3$ (68.8 ppm), H–*C*–NHCOCH$_3$ (46.8 ppm) and for two methylene groups, as intense signals, at 28.4 and 27.5 ppm, a fact that suggests a very symmetric compound, only possible in *cis*-4-acetamidocyclohexyl acetate (Scheme 6), obtained by reduction of the major epoxide *syn*-**9**; this is also in agreement with the bandwidth (W=17.3 Hz)[13] observed for H1 (4.97–4.89 ppm) in the ^{1}H NMR spectrum. As in the DEPT experiment we also detected six significant (at 38.1, 32.2, 31.1, 29.6, 24.2, 21.2 ppm) and three minor (at 35.7, 29.7, 25.3 ppm) signals for the carbons of methylene groups, we have hypothesized that the second product (22.5%) in the mixture (**14B**) is the *N*-methyl known *cis*-3-acetamidocyclohexyl acetate.[18,19] In agreement with this, the proton at C1 joint to the acetoxy moiety appears at 4.80 ppm (as a ddd) with vicinal coupling constants for two axial and one equatorial protons (Scheme 6). Regarding the third compound (**14C**) (7.5%) the spectroscopic data shown in Scheme 6 agree for the *cis*-4-(*N*-methyl 9acetamidocyclohexyl acetate, but we cannot rule out an alternative *trans*-3-(*N*-methyl)acetamidocyclohexyl acetate structure. In summary, we conclude that the hydrogenation of the mixture **9** (*syn*/*anti*: 2.9/1) gave mixtures of 3- and 4-substituted aminocyclohexyl derivatives.

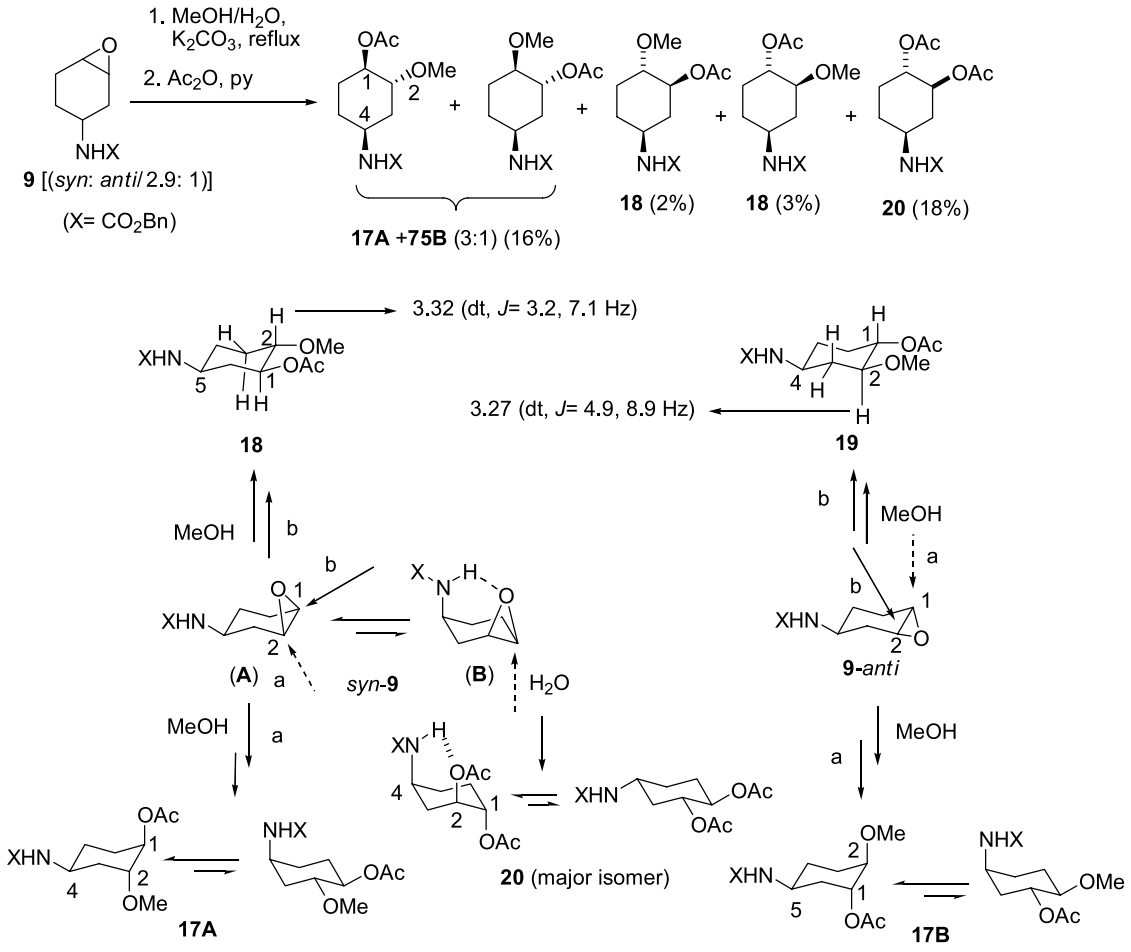
This unexpected result prompted us to investigate the potassium carbonate/MeOH/H$_2$O intramolecular epoxide ring opening, a process that has been applied by Fletcher et al. on *trans*-1,2-epoxide-(*N*-benzyl,*N*-trifluoroacetyl)-aminocyclohexane for the synthesis of intermediates on route to epibatidine.[6b] After 6 days at rt (see Section 3) we isolated recovered pure *syn*-**9** staring material, and two sets of products. The first set consisted of an inseparable mixture of compounds **15A/B** in a 2:1 ratio, isolated in 32% yield; the second set was formed by product **16** isolated in 27% yield (Scheme 7). The full analysis of the mixture **15A/B** clearly showed us this was a mixture of *trans*-2-methoxy-1-cyclohexanols obtained by intermolecular ring opening by the methanol at the *syn*/*anti*-**9** epoxides, respectively. In fact, the stereospecific *anti* addition appears to be the rule for the ring opening addition of oxiranes with nucleophiles.[14] Major product (**15A**) should be the result of the diaxial attack, in accordance with the Fürst–Plattner rule,[16] of methanol at C2 on *syn*-**9** epoxide. Assuming that in related *trans* 4-(or 5)(benzyloxy)-2-methoxy-1-cyclohexanol derivatives,[13a] δ *H*–C–OCH$_3$ $\gg$ δ *H*–C–OH, and that conformer *syn*(**A**)-**9** is more stable than conformer *syn*(**B**)-**9**,[13] the shapes for H1 (δ 3.22–3.16, W=24.5 Hz) and H2 (δ 3.63–3.54, W=28.5 Hz) suggest that in compound **15A** two



Scheme 7.

conformers are in equilibrium, favoring the conformer with the carbamate in pseudoaxial orientation (Scheme 7), giving values for the bandwidth promedium between W_{Heq}= 15.0 Hz, and W_{Hax}=37.5 Hz.[13a] Analogously, compound **15B** should be the result of the diaxial attack of methanol at C 1 on *anti*-**9** epoxide, as shown by the observed shapes for H1 (δ 3.76–3.68, W=24.5 Hz) and H2 (δ 3.10–3.04, W= 26.7 Hz). Precisely, and based on these data, we have ruled out the nucleophilic attack of methanol on possible chelated species,[13] by the potassium counterion or by a simple O–H bond, on the less stable conformer of *syn*(**B**)-**9**, that would yield *t*-5-(*N*-benzyloxycarbonylamino)-*t*-2-methoxy-*r*-1-cyclohexanol with the three substituents in pseudoequatorial orientation, showing protons with higher bandwidths (Scheme 7). Product **16** was isolated as a diastereomerically pure compound, whose analytical and spectroscopic data are in good agreement with a *trans*-1,2-diol derivative, possibly obtained after epoxide ring opening by water on the chelated conformer of isomer *syn*(**B**)-**9** by an hydrogen bond (Scheme 7). In fact, in the ^{1}H NMR spectrum we could locate H1, H2 and H4 with bandwidth in the high range of around 37 Hz, what means that **16** is a compound in a highly preferred conformation with these protons in axial orientation.

To sum up, in this reaction no intramolecular epoxide ring opening was observed, the only isolated products came from the intermolecular epoxide ring opening by the solvents used; in addition, the reaction was incomplete. Thus, we decided to force the reaction conditions (refluxing for 20 h) and the crude was acetylated. After work-up and chromatography we have isolated and characterized compounds **17A/B** (a mixture of isomers in a 3:1 ratio in 16% overall yield from **9**), **18** (2%), **19** (3%) and **20** (18%, as a mixture of isomers in a 2/1 ratio) (Scheme 8). After inspection of the spectroscopic data for compounds **17A/B** we conclude that these compounds are the corresponding acetylated derivatives of the mixture of alcohols **15A/B** (Scheme 7), but in this case the equilibrium of conformers must be significantly shifted to the conformers with the acetoxy and the methoxy groups in axial orientation, as it was deduced from the values for the bandwidth for H1 and H2, in the range of 11–12 Hz. This fact could be a result of the absence of the stabilizing hydrogen bonds present in the pair **15A/B**, and the unfavorable *gauche* interaction between the acetoxy and the methoxy groups, absent in the conformer with these groups in axial orientation that places also the sterically demanding *N*-benzyl carbamate group in a more favorable equatorial orientation. Accordingly, and as expected a mixture of compounds **15A/B** after acetylation afforded a mixture of acetated identical to compounds **17A/B**. To sum up, these products should be the result of the initial attack of methanol on the major conformer *syn*(**A**)-**9** at carbon C2, or in conformer *anti*-**9** at carbon C1, respectively, following a preferred *trans*-diaxial orientation. Conversely, minor compounds **18** and **19** are possibly the result of methanol attack on the major conformer *syn*(**A**)-**9** at carbon C1, and on conformer *anti*-**9** at carbon C2 (Scheme 8); the chemical shift and coupling constants for the protons bonded to the C–OMe are in very agreement with this hypothesis (see Scheme 8). Finally, product **20** was isolated a as a mixture of two isomers, but the spectroscopic data only allowed us to assign the structure shown in Scheme 8 for the major isomer; in fact, in the ^{1}H NMR spectrum we observed signals for H1 and H2 corresponding for two protons joint to carbons substituted with acetoxy groups and bandwidth

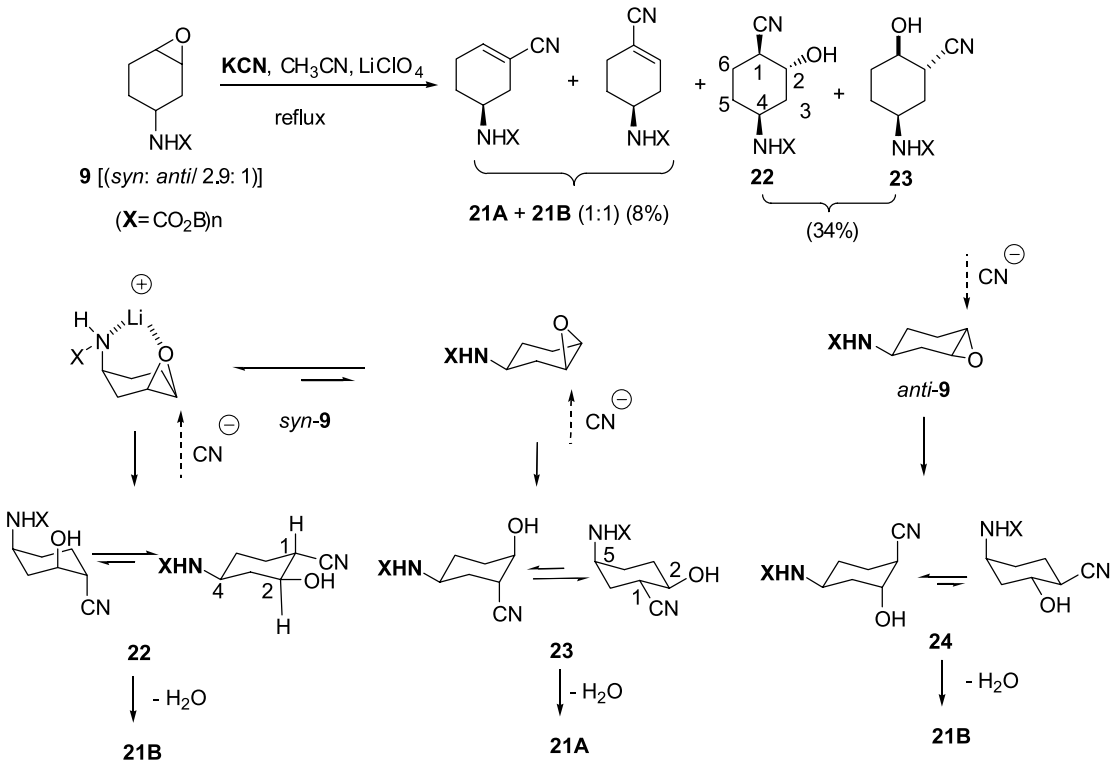


Scheme 8.

around 13–18 Hz, what means that these protons are oriented in equatorial, the acetoxy groups being axial, a strong hydrogen bond between the NH on the carbamate and the oxygen at the acetoxy at C2 stabilizing this conformer, minimizing also the unfavorable gauche-interaction between the acetoxy groups in the other conformer in equilibrium. This product should be the result of the attack of water to the *syn*(**B**)-**9** conformer in a *trans*-diaxial orientation. In fact, and as expected, the acetylation of compound **16** (Scheme 7) gave a compound similar to the major product **20**, confirming this structural assignment. In summary, the epoxide ring opening with methanol/water in the presence of potassium carbonate of compound **9** resulted in exclusive intermolecular reactions, following preferential attack in diaxial orientation in chelated or non-chelated intermediates.

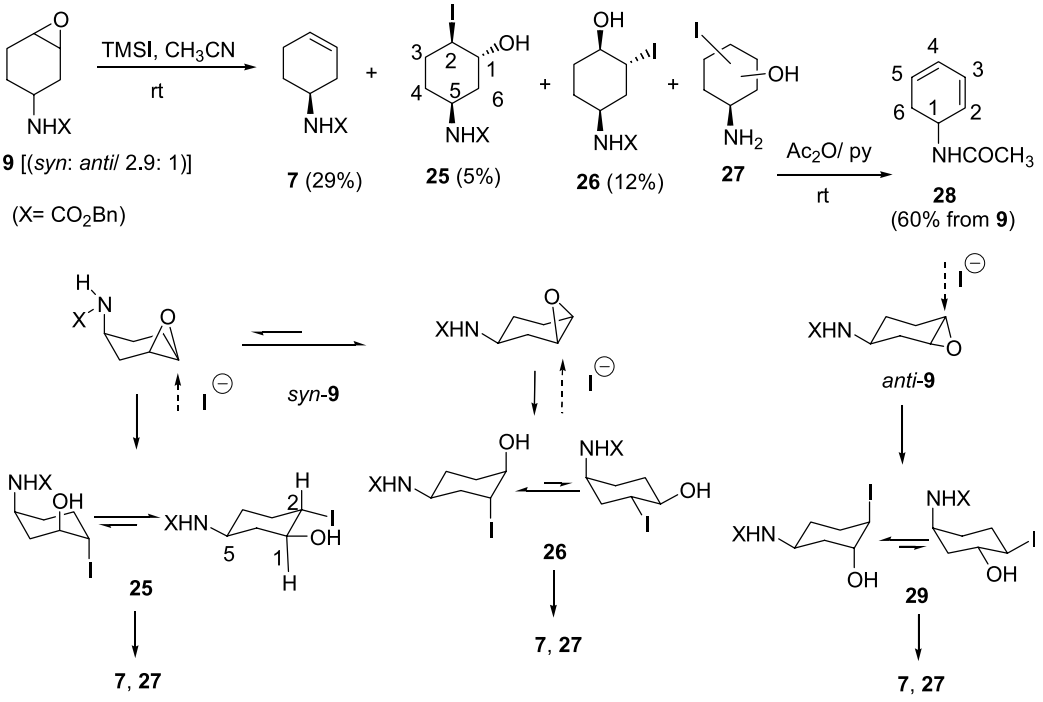
In view of this, and pursuing with our initial project, then we considered the direct incorporation of a carbon fragment by nucleophilic attack to epoxide. In consequence, in the next experiments we investigated similar reaction using potassium cyanide in acetonitrile in the presence of lithium perchlorate, a reaction system which is presumed to favor, depending on the concentration, lithium-chelated participating reactive species.[13] Under these conditions (see Section 3), and starting from the mixture *syn*/*anti*-**9** we have isolated minor amounts of an inseparable mixture (1:1) of α,β-unsaturated nitriles **21**, in poor yield (8%), and the β-hydroxynitrile derivatives **22** and **23** in 34% overall yield (Scheme 9).

The structure of compounds **21A/B** has been easily established by their analytical data, as well as by simple inspection of the IR spectrum (band at 2210 cm^{-1} for a α,β-unsaturated nitrile). In the ^{1}H NMR we observed vinylic protons at 6.62 and 6.54 ppm spectrum, consistent with the signals at 144.4/142.1 ppm, at 118.8/118.7 and 112.4/110.3 ppm in the ^{13}C NMR spectrum for the carbons in a H–C=C(CN) functional moiety. Regarding the other products, and according to the spectroscopic and analytical data, major compound **22** is a β-hydroxynitrile resulting from the attack on epoxide *syn*-**9** following the diaxial orientation in a chelated intermediate (Scheme 9) as we could deduce by analysis of the coupling constants for H1 (2.42 ppm, ddd, $J=8.8$, 11.1, 3.9 Hz) and H2 (3.86 ppm, br t, $J=8.7$ Hz). These assignments were confirmed in the ^{1}H-^{13}C HMQC and in the ^{1}H–^{1}H COSY experiments, as the multiplet at 3.70–3.60 ppm, corresponding to a proton bonded to a carbon a 47.3 ppm (C4) was coupled exclusively to the multiplets at 1.43–1.23 ppm, corresponding for H3 and 2 H5; accordingly, the proton (3.86 ppm, H2) bonded to the carbon (69.1 ppm, C2), bearing the hydroxyl group was coupled with the signals for H–C(CN) (2.42 ppm) and with the signals at ppm (H3) at 2.32 and at 1.43–1.23 ppm (H3′). The structure of the minor β-hydroxynitrile is **23** (Scheme 9), resulting after diaxial



Scheme 9.

attack on the minor conformer 'non-chelated' of major *syn*-**9**. In agreement with this, in the ^{1}H NMR spectrum of compound **23** we could locate H1 (2.76–2.62) as a multiplet with a high (W=39 Hz) bandwidth. This also possible on the major conformer of possible compound **24**, obtained by *trans*-diaxial attack on the minor *anti*-**9** isomer (Scheme 9), but we have excluded this possibility after careful inspection of the ^{1}H–^{1}H COSY and the HMQC experiments, which clearly showed us that H5 was coupled with one of the protons (H6) coupled to H1, only possible in product **23**. Obviously, we cannot rule out the possible formation of compound **24**, but we suggest that this product, not observed, if formed, gives the α,β-unsaturated nitrile **21B**, after dehydration. In addition, the formation of compounds **21A/B** are the result of cyanide mediated H–C–CN abstraction followed by elimination of the β-hydroxy



Scheme 10.

group with the final result of loss of water on compounds **22** and **23**, respectively (Scheme 9).

Next we turned our attention to the reaction of epoxide **9** with trimethylsilyl iodide[20] in order to achieve selective hydrogenolysis of the carbamate looking for a free amino derivative in which we could induce possibly intramolecular ring opening of the epoxide. Under the usual conditions[20] we observed a very complex reaction mixture, but after careful chromatography we were able to isolated carbamate **7** (29%), identical to an authentic sample previously prepared by us (see above), iodohydrins **25** (5%), **26** (12%), and a more polar product (**27**), which showed no benzyl carbamate functional moiety in the ^{1}H NMR spectrum. The acetylation of this product as usual afforded acetamide **28** (Scheme 10) in 60% overall yield from epoxide **9**. The structure of the less polar, minor iodohydrin **25**, has been assigned by detailed spectroscopic analysis; in fact, we could analyze the proton joint at the carbon bearing the iodide atom at 3.84 ppm as a ddd, with vicinal coupling constants (4.2, 9.6, 11.7 Hz) in agreement with a proton in C1 in axial orientation, while in the major, diastereomerically pure, iodohydrin **26**, the same proton appeared as a multiplet with $W=22.2$ Hz, coherent with a iodide atom located at C2 in a product showing a mixture of chair conformers (Scheme 10). For the same reasons, and as shown in Scheme 10, we cannot discard the structure **29** for this product, arising by *trans*-diaxial attack on the minor *anti*-**9** isomer; unfortunately, in this case the protons bonded to the carbon bearing the *N*-benzyl carbamate and the hydroxyl group overlap at 3.76–3.66 ppm, and the final assignment is difficult; however, we think that the second, major iodohydrin should be most probably **26**, coming from the major isomer *syn*-**9** in a 'non-chelated' intermediate.[13] In addition, in this reaction we have isolated a more polar product (**27**), without the benzyl group, that after acetylation, afforded acetamide **28** (Scheme 10). In fact, in the ^{1}H NMR of compound **28** we have observed signals for four vinylic protons in the range 6.47–5.43 ppm that correspond to the signals at 125.0, 124.1, 122.1 and 108.7 ppm in the ^{13}C NMR spectrum according to the HMQC experiment; in addition, only an acetyl group has been located H1 (5.56–5.50 ppm, multiplet) and two protons at high field corresponding to 2 H6, as a broad singlet at 2.49 ppm. These data fit perfectly in the 1-acetamido-2,4-cyclohexadienyl structure for **28**. In overall, the formation of product **7** is possibly the result of the reaction of TMSI on iodohydrins **25** and/or **26**. The formation of product **27** is the result of the *N*-benzyl deprotection on the iodohydrins **25** and/or **26**; finally, it is expected that the basic medium compound **27** suffers large dehydration, elimination of HI, followed by acetylation, to give **28**.

In summary, the Curtius rearrangement on cyclohex-3-ene carboxylic acid is a simple and efficient method for the synthesis of alkyl *N*-(1-cyclohex-3-enyl)carbamates, that compares very favorably with other methodologies in terms of simplicity and chemical yields. Some useful synthetic transformations on the *N*-benzylcarbamate **7** have been also reported, including the iodination and epoxidation reactions. Finally, on the mixture of *syn*/*anti*-**9** epoxides, we have investigated the ring opening reaction with different reactive systems, such as hydrogen, methanol/water, potassium cyanide and ITMS, processes that have afforded diverse functionalized cyclohexylamino derivatives with moderate selectivities and acceptable chemical yields.

3. Experimental

3.1. General methods

Reactions were monitored by TLC using precoated silica gel aluminum plates containing a fluorescent indicator (Merck, 5539). Anhydrous Na_2SO_4 was used to dry organic solutions during work-ups and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using silica gel 60 (230–400 mesh, Merck). ^{1}H spectra were recorded with a Varian VXR-300S spectrometer and ^{13}C NMR spectra were recorded with a Bruker WP-200-SY. Values with (*) can be interchanged.

General method for the Curtius rearrangement. (A) A solution of cyclohex-3-ene carboxylic acid (**1**), DPPA (1.2 equiv) and triethylamine (1.0 equiv) in the corresponding dry alcohol (ethanol or *t*-butanol) (0.16 M) were refluxed until complete reaction (TLC analysis). The reaction mixture was cooled, the solvent was removed, the residue was dissolved in methylene chloride; then, the organic phase was washed with 5% aqueous solution of citric acid, water, aqueous saturated solution of sodium bicarbonate, and brine. The organic phase was dried with (Na_2SO_4), filtered, evaporated and the crude submitted to chromatography to give the corresponding products. (B) *With toluene as solvent*. As above, a solution of cyclohex-3-ene carboxylic acid (**1**), DPPA (1.2 equiv) and triethylamine (1.1 equiv) in dry toluene (0.13 M) was stirred at rt for 30 min, and were warmed at 60 °C for 30 min; then, the alcohol (1.2 equiv) and the reaction was warmed at 60 °C complete reaction (TLC analysis). (C) *With DMF as co-solvent*. As above, a solution of cyclohex-3-ene carboxylic acid (**1**), DPPA (3.5 equiv) and triethylamine (3.9 equiv) in a mixture of the corresponding dry alcohol (ethanol or *t*-butanol) and dry DMF (1:1 in volume) (0.13 M) were warmed at 80 °C, until complete reaction (TLC analysis).

General method for the epoxidation. To a solution of the substrate in dry methylene chloride (0.11 M), under argon and stirring, cooled in a water-ice bath, MCPBA (1.5 equiv) was slowly added. Then, the mixture was warmed at rt overnight. The precipitated solid was filtered, washed with cold methylene chloride, and the organic phase was washed with a 10% aqueous solution of sodium thiosulfite, 10% aqueous solution of sodium bicarbonate, brine, and the dried. After filtration, the solvent was evaporated, and the residue purified by chromatography.

General method for acetylations. The product to be acetylated was reacted with a mixture of Ac_2O/pyridine (1/1, in volume) at rt for the time stated in each case. When the reaction was complete, the solvents were removed using toluene, and the crude was submitted to chromatography.

3.1.1. Curtius rearrangement of cyclohex-3-ene carboxylic acid (1) with ethanol. (a) Following General

method for the Curtius rearrangement, a solution of cyclohex-3-ene carboxylic acid (**1**) (0.19 mL, 1.58 mmol), DPPA (0.41 mL, 1.90 mmol, 1.2 equiv) and triethylamine (0.24 mL, 1.74 mmol, 1.0 equiv) in dry ethanol (10 mL, 0.16 M) were refluxed 14 h. After work-up and chromatography (hexane/EtOAc, 5% to AcOEt) ethyl carbamate **2** (145.6 mg, 54%), carbamoylazide **3** (23.5 mg, 9%) and urea **4** (64 mg, 37%) were isolated.

(b) Following General method for the Curtius rearrangement with toluene as solvent a solution of cyclohex-3-ene carboxylic acid (**1**) (0.19 mL, 1.58 mmol), DPPA (0.41 mL, 1.90 mmol, 1.2 equiv) and triethylamine (0.24 mL, 1.74 mmol, 1.0 equiv) in dry ethanol (10 mL) were refluxed 16 h. After work-up and chromatography (hexane/EtOAc, 10% to AcOEt) ethyl carbamate **2**[8] (137.2 mg, 51%) and carbamoylazide **3** (83.3 mg, 32%) were isolated.

(c) Following General method for the Curtius rearrangement with DMF as co-solvent, a solution of cyclohex-3-ene carboxylic acid (**1**) (0.19 mL, 1.58 mmol), DPPA (1.12 mL, 5.55 mmol, 3.5 equiv) and triethylamine (0.85 mL, 6.14 mmol, 3.9 equiv) in a mixture of dry ethanol/DMF (6 mL/6 mL, 0.13 M) were warmed at 80 °C for 13 h. After work-up and chromatography (hexane/EtOAc, 10% to AcOEt) ethyl carbamate **2**[8] (152 mg, 57%), carbamoylazide **3** (47 mg, 18%), and ureas **4** (24 mg, 14%) and **6** (30 mg, 11%) were isolated. *Compound* **2**[8]: oil; IR (film) ν 3325, 2920, 1693 (st, $NCO_2CH_2CH_3$), 1533, 1306, 1236, 1052 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.64 (dm, J= 10.2 Hz, 1H, H4), 5.63 (dm, J=10.2 Hz, 1H, H3), 4.74 (br s, 1H, N*H*$CO_2CH_2CH_3$), 4.07 (q, J=6.8 Hz, 2H, $NHCO_2$-C*H*$_2CH_3$), 3.79 (m, 1H, H1), 2.35 (d, J=16.7 Hz, 1H, H2), 2.09 (br s, 2H, 2H5), 1.89–1.79 (m, 2H, H6, H2′), 1.58–1.46 (m, 1H, H6′), 1.20 (t, 3H, $NHCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.9 (NH*C*$O_2CH_2CH_3$), 126.8 (C4), 124.2 (C3), 60.4 ($NHCO_2$*C*H_2CH_3), 45.9 (C1), 31.9 (C2), 28.2 (C6), 23.4 (C5), 14.5 ($NHCO_2CH_2$*C*H_3); MS (CI): *m*/*z* 170 $[M+1]^+$, 192 $[M+Na]^+$, 339 $[2M+1]^+$, 361 $[2M+Na]^+$. Anal. Calcd $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.67; H, 8.74; N, 8.42. *Compound* **3**: mp 69–71 °C; IR (KBr) ν 3430, 2135 (st, CO*N*$_3$), 1703 (st, *C*ON_3), 1675, 1544, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.69 (dm, J=10.1 Hz, 1H, H4), 5.60 (dm, J=10.1 Hz, 1H, H3), 5.08 (br s, 1H, N*H*CON_3), 3.96 (m, 1H, H1), 2.40 (d, J=17.3 Hz, 1H, H2), 2.13 (br s, 2H, 2H5), 1.94–1.85 (m, 2H, H6, H2′), 1.67 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 ($NHCON_3$), 127.0 (C4), 123.8 (C3), 46.3 (C1), 31.4 (C2), 27.7 (C6), 23.1 (C5); MS (CI): *m*/*z* 167 $[M+1]^+$, 189 $[M+Na]^+$. Anal. Calcd $C_7H_{10}N_4O$: C, 50.59; H, 6.07; N, 33.71. Found: C, 50.42; H, 6.11; N, 33.56. *Compound* **4**: mp 222–225 °C; IR (KBr) ν 3427, 3322, 2937, 1618 (st, NHCONH), 1575, 1300 cm^{-1}; ^1H NMR (DMSO-d_6, 300 MHz) δ 5.73 (d, J=6.8 Hz, 2H, N*H*CON*H*), 5.63–5.54 (m, 2×2H, H4, H3), 3.60 (m, 2×1H, H1), 2.19 (d, J= 16.8 Hz, 2×1H, H2), 2.03 (br s, 2×2H, H5), 1.78–1.70 (m, 2×2H, H6, H2′), 1.41–1.29 (m, 2×1H, H6′); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 156.9 (NHCONH), 126.6 (C4), 125.1 (C3), 44.1 (C1), 32.0 (C2), 28.6 (C6), 23.6 (C5); MS (CI): *m*/*z* 221.2 $[M+1]^+$, 243.0 $[M+Na]^+$, 441.4 $[2M+Na]^+$. Anal. Calcd $C_{13}H_{20}N_2O$: C, 70.87; H, 9.15; N, 12.72. Found: C, 70.68; H, 9.04; N, 12.65. *Compound* **6**: mp 119–121 °C; IR (KBr) ν 3427, 3324, 2915, 1628 [st, $NHCON(CH_3)_2$], 1534 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.68–5.57 (m, 2H, H4, H3), 4.33 [br s, 1H, N*H*$CON(CH_3)_2$], 4.02–3.91 (m, 1H, H1), 2.87 [s, 6H, $NHCON(CH_3)_2$], 2.39 (d, J=17.2 Hz, 1H, H2), 2.11 (s, 2H, H5), 1.92–1.81 (m, 2H, H6, H2′), 1.55–1.49 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 158.0 [NH*C*$ON(CH_3)_2$], 127.1 (C4), 124.9 (C3), 45.7 (C1), 36.2 [$NHCON(CH_3)_2$], 32.6 (C2), 28.9 (C6), 23.8 (C5); MS (CI): *m*/*z* 169 $[M+1]^+$, 191 $[M+Na]^+$, 337 $[2M+1]^+$, 359 $[2M+Na]^+$. Anal. Calcd $C_9H_{16}N_2O$: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.41; H, 9.63; N, 16.42.

3.1.2. Curtius rearrangement of cyclohex-3-ene carboxylic acid (1) with *t*-butanol. (a) Following General method for the Curtius rearrangement, a solution of cyclohex-3-ene carboxylic acid (**1**) (0.19 mL, 1.58 mmol), DPPA (0.34 mL, 1.58 mmol, 1.2 equiv) and triethylamine (0.22 mL, 1.58 mmol, 1.0 equiv) in dry *t*-butanol (10 mL, 0.16 M) were refluxed 48 h. After work-up and chromatography (hexane/EtOAc, 5% to AcOEt) *t*-butyl carbamate **5**[9] (104 mg, 33%), carbamoylazide **3** (9.3 mg, 4%) and urea **4** (94 mg, 54%) were isolated. *Compound* **5**[9]: mp 52–55 °C; IR (film) ν 3427, 3316, 3021, 2929, 1696 [st, $NHCO_2$-$C(CH_3)_3$], 1677, 1531, 1364, 1048 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.70–5.56 (m, 2H, H4, H3), 4.54 [br s, 1H, N*H*$CO_2C(CH_3)_3$], 3.78 (m, 1H, H1), 2.38 (d, J=17.0 Hz, 1H, H2), 2.12 (br s, 2H, 2H5), 1.90–1.83 (m, 2H, H6, H2′), 1.57–1.50 (m, 1H, H6′), 1.45 [s, 9H, $NHCO_2C(CH_3)_3$]; ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4 [NH*C*$O_2C(CH_3)_3$], 127.0 (C4), 124.6 (C3), 79.1 [$NHCO_2$*C*$(CH_3)_3$], 45.7 (C1), 32.1 (C2), 28.5 [2 C, C6, $NHCO_2C$(*C*$H_3)_3$, C6], 23.7 (C5); MS (CI): *m*/*z* 142.1 $[M-55]^+$, 198.2 $[M+1]^+$, 220.2 $[M+Na]^+$, 417.5 $[2M+23]^+$. Anal. Calcd $C_{11}H_{19}NO_2$: C, 66.97; H, 9.71; N, 7.10. Found: C, 66.81; H, 9.82; N, 7.23.

(b) Following General method for the Curtius rearrangement with DMF as co-solvent, a solution of cyclohex-3-ene carboxylic acid (**1**) (0.19 mL, 1.58 mmol), DPPA (1.12 mL, 5.55 mmol, 3.5 equiv) and triethylamine (0.85 mL, 6.14 mmol, 3.9 equiv) in a mixture of dry ethanol/DMF (6 mL/6 mL, 0.13 M) were warmed at 80 °C for 13 h. After work-up and chromatography (hexane/EtOAc, 10% to AcOEt) carbamoylazide **3** (73 mg, 28%), and ureas **4** (108 mg, 62%) and **6** (27 mg, 10%) were isolated.

3.1.3. Curtius rearrangement of cyclohex-3-ene carboxylic acid (1) with benzyl alcohol. Following General method for the Curtius rearrangement in toluene as solvent, a solution of cyclohex-3-ene carboxylic acid (**1**) (2 g, 16.17 mmol), DPPA (4.1 mL, 19.40 mmol, 1.2 equiv), triethylamine (2.48 mL, 17.79 mmol, 1.0 equiv) in dry toluene (10 mL, 0.16 M) were stirred 30 min at rt, and at reflux for 30 min more. Then, benzyl alcohol (2.0 mL, 19.40 mmol) was added and the mixture was refluxed 13 h. After work-up and chromatography (hexane/EtOAc, 5%) ethyl carbamate **7**[10] (3.0 g, 74%) was isolated. *Compound* **7**: mp 64–67 °C; IR (KBr) ν 3427, 3322, 2937, 1689 (st, $NCO_2CH_2C_6H_5$), 1575, 1300 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.29 (m, 5H, $HNCO_2CH_2C_6H_5$), 5.67 (dm, J=10.0 Hz, 1H, H4), 5.58 (dm, J=10.0 Hz, 1H, H3), 5.09 (s, 2H, $NCO_2CH_2C_6H_5$), 4.80 (br s, 1H, *H*NCO_2CH_2-C_6H_5), 3.87 (m, 1H, H1), 2.39 (d, J=17.1 Hz, 1H, H2), 2.12 (br s, 2H, 2H5), 1.93–1.85 (m, 2H, H6, H2′), 1.63–1.51 (m,

1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7 ($HNCO_2CH_2C_6H_5$), 136.5, 128.4, 128.1, 128.0 ($HNCO_2CH_2C_6H_5$), 126.9 (C4), 124.2 (C3), 66.6 ($HNCO_2CH_2C_6H_5$), 46.1 (C1), 31.8 (C2), 28.1 (C6), 23.3 (C5); MS (CI): *m/z* 232 $[M+1]^+$, 254 $[M+Na]^+$. Anal. Calcd $C_{14}H_{17}NO_2$: C, 72.70; H, 7.41; N, 6.06. Found: C, 72.55; H, 7.35; N, 6.22.

3.1.4. Iodination of carbamate 7. To a solution of compound **7** (79.7 mg, 0.34 mmol) in dry methylene chloride (6 mL), under argon and at rt, I_2 (131.2 mg, 0.517 mmol) was added. After 88 h, a 5% aqueous solution of $Na_2S_2O_3$ was added, and the mixture was extracted with more CH_2Cl_2. The organic phase was washed with brine dried, filtered and evaporated to give a crude, that was submitted to chromatography eluting with hexane/AcOEt mixtures, to give compound **8** (72.3 mg, 79%): amorphous solid; IR (KBr) ν 3427, 3234, 3108, 2947, 1732 (st, NCO_2), 1696, 1417, 1272, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.49 (br s, 1H, $HNCO_2$), 4.68 (s, 1H, HCOC=O), 4.62 (s, 1H, HCI), 3.62 (br s, 1H, $HCNHCO_2$), 2.67 (d, J=13.6 Hz, 1H), 2.29–2.16 (m, 1H), 2.01–1.92 (m, 3H), 1.75–1.67 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.8 (NCO_2), 76.6 (HCOC=O), 44.9 ($HCNHCO_2$), 27.8, 27.4, 26.2, 24.8. MS (CI): *m/z* 140.1 $[M-I]^+$, 267.9 $[M+1]^+$, 289.9 $[M+Na]^+$, 556.8 $[2M+Na]^+$. Anal. Calcd $C_7H_{10}INO_2$: C, 31.48; H, 3.77; N, 5.24. Found: C, 31.64; H, 3.52; N, 5.01.

3.1.5. Epoxidation of carbamate 7. Following the General method for the epoxidation, carbamate **7** (500 mg, 2.16 mmol), in CH_2Cl_2 (10 mL), was treated with MCPBA (729.7 mg, 3.24 mmol) for 2 h at rt. After work-up and chromatography (hexane/EtOAc, 50%) epoxide **9** (486 mg, 91%) was isolated as a mixture of *syn*/*anti* isomers in 2.9:1 ratio (GLC analysis): mp 63–68 °C; IR (KBr) ν 3313, 1686 (st, $NCO_2CH_2C_6H_5$), 1545 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36–7.30 (m, 5H, $HNCO_2CH_2C_6H_5$), 5.12 (br s, 1H, $HNCO_2CH_2C_6H_5$), 5.07 (s, 2H, $NCO_2CH_2C_6H_5$), 3.72 (m, 1H, H4), 3.17 (br s, H1, H2, *syn*), 3.13 (m, H1, H2, *anti*), 2.36 (dd, J=14.9, 5.1 Hz, H3 *anti*), 2.22 (ddd, J=15.4, 5.6, 2.6 Hz, H3 *syn*), 2.14 (t, J=6.4 Hz, 1H, H6 *anti*), 2.09 (t, J=6.6 Hz, 1H, H6 *syn*), 2.04–1.90 (m, H6′ *syn*, *anti*), 1.84 (dd, J=15.4, 6.9 Hz, H3′ *syn*), 1.78–1.62 (m, H3′ *anti*), 1.55–1.42 (m, 2H, 2H5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4 ($HNCO_2CH_2C_6H_5$), 136.5, 128.4, 128.0, 127.9 ($HNCO_2CH_2C_6H_5$), 126.9 (C4), 124.2 (C3), 66.4 ($HNCO_2CH_2C_6H_5$), 52.0, 50.9 (C1, C2, *anti*), 51.6, 51.5 (C1, C2, *syn*), 44.7 (C4), 30.4 (C3), 24.6 (C6)*, 21.8 (C5)*; MS (CI): *m/z* 248.1 $[M+1]^+$, 270.0 $[M+Na]^+$, 517.3 $[2M+Na]^+$. Anal. Calcd $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.15; H, 7.05; N, 5.45.

3.1.6. Epoxidation of carbamate 2. Following the General method for the epoxidation, carbamate **2** (93.3 mg, 0.55 mmol), in CH_2Cl_2 (5 mL), was treated with MCPBA (185.3 mg, 0.82 mmol) for 19 h at rt. After work-up and chromatography (hexane/EtOAc, 50%) epoxide **10** (55.1 mg, 54%) was isolated as a mixture of *syn*/*anti* isomers in 4:1 ratio (GLC analysis): oil; IR (film) ν 3316, 3054, 2934, 1682 ($HNCO_2CH_2CH_3$), 1544, 1341, 1279, 1049 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) (major *syn* isomer) δ 5.01 (br s, 1H, $HNCO_2CH_2CH_3$), 4.04 (q, J=7.1 Hz, 2H, $HNCO_2CH_2CH_3$), 3.65 (m, 1H, H4), 3.14 (s, 2H, H1, H2), 2.19 (ddd, J=15.3, 5.9, 3.2 Hz, 1H, H3), 2.08 (m, 1H, H6), 1.92 (m, 1H, H6′), 1.82 (dd, 1H, J=7.2, 15.3 Hz, 1H, H3′), 1.45 (m, 2H, 2H5), 1.18, (t, 3H, $HNCO_2CH_2CH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) (major *syn* isomer) δ 155.8 ($HNCO_2CH_2CH_3$), 60.5 ($HNCO_2CH_2CH_3$), 51.7, 51.6 (2 C, C1, C2) 44.6 (C4), 30.5 (C3), 24.7 (C6)*, 21.9 (C5)*, 14.5 ($HNCO_2CH_2CH_3$); MS (CI): *m/z* 186 $[M+1]^+$, 208 $[M+Na]^+$. Anal. Calcd $C_9H_{15}NO_3$: C, 58.36; H, 8.16; N, 7.56. Found: C, 58.47; H, 8.01; N, 7.42.

3.1.7. Epoxidation of carbamoyl azide 3. Following the General method for the epoxidation, carbamoyl azide **3** (213.6 mg, 1.28 mmol), in CH_2Cl_2 (6 mL), was treated with MCPBA (432.1 mg, 1.93 mmol) for 5 h at rt. After work-up and chromatography (hexane/EtOAc, 50%) epoxide **11** (134.4 mg, 55%) was isolated as an almost diastereomerically pure *syn* isomer: mp 108–111 °C; IR (KBr) ν 3442, 3308, 3057, 2992, 2142 (st, CON_3), 1676 (st, CON_3), 1553, 1313, 1284, 1243 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.93 (br s, 1H, $NHCON_3$), 3.81 (m, 1H, H4), 3.20–3.15 (m, 2H, H1, H2), 2.39 (dd, J=14.8, 4.6 Hz, 1H, H3), 2.03 (m, 2H, 2H6), 1.82–1.60 (m, 1H, H3′), 1.39–1.20 (m, 2H, 2H5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.4 ($NHCON_3$), 127.0 (C4), 51.5, 51.4 (C1, C2), 44.7 (C4), 29.8 (C3), 24.1 (C5), 21.3 (C6); MS (CI): *m/z* 140.1 $[M-N_3]^+$, 183.1 $[M+1]^+$, 205.1 $[M+Na]^+$. Anal. Calcd $C_7H_{10}N_4O_2$: C, 46.15; H, 5.53; N, 30.75. Found: C, 46.32; H, 5.70; N, 30.66.

3.1.8. Epoxidation of urea 4. Following the General method for the epoxidation, urea **3** (90.9 mg, 0.41 mmol), in MeOH (7 mL), was treated with MCPBA (277.4 mg, 1.24 mmol) for 2 h at rt. After work-up and chromatography (hexane/EtOAc, 50%) epoxide **12** (54 mg, 52%) was isolated as an almost diastereomerically pure *syn* isomer: mp °C; IR (KBr) ν 3325, 3000, 2934, 1622 (st, NHCONH), 1574, 1429, 1306, 1084 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.60 (br s, 2H, $NHCONH$), 3.79 (m, 2×1H, H4), 3.18 (m, 2×1H, H1, H2), 2.20 (ddd, J=15.3, 6.6, 3.0 Hz, 2×1H, H3), 2.08 (dt, J=15.6, 6.8 Hz, 2H, H6), 1.94 (m, 2×1H, H6′), 1.82 (dd, J=15.3, 6.6 Hz, 2×1H, H3′), 1.52–1.43 (m, 2×2H, H5); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5 (NHCONH), 51.9 (2 C, C1, C2), 43.6 (C4), 30.9 (C3), 25.0 (C5)*, 21.9 (C6)*; MS (CI): *m/z* 253.1 $[M+1]^+$, 275.0 $[M+Na]^+$, 505.0 $[2M+1]^+$, 527.0 $[2M+Na]^+$. Anal. Calcd $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.63; H, 7.85; N, 11.22.

3.1.9. Hydrogenation of epoxide 9. A solution of compound **9** (251 mg, 1.01 mmol) in methanol (10 mL) was hydrogenated at atmospheric pressure in the presence of a catalytic amount of Pd/C 5% for 4 h 30 min at rt. The catalyst was filtered over Celite-545, washed with methanol, the solvent was evaporated, and the residue was submitted to chromatography (hexane/AcOEt, 25%) to give un separable mixture of compound **13** (122.5 mg), that was submitted to standard acetylation (pyridine/Ac_2O: 1 mL/1 mL) at rt for 40 h. After work-up and chromatography (hexane/AcOEt, 10%) afforded an inseparable mixture of compounds **14** (15.9 mg). The analysis on GLC showed that this mixture was formed by three compounds: (**14A**) rt=22.39 min; 70%; MS (EI): *m/z* 199 (M^+), 139, 97, 80, 60, 43 (100); (**14B**) rt=24.72 min; 22.5%; MS (EI) *m/z* 213 (M^+), 153, 138, 112, 96, 80, 74, 70, 57, 43 (100); (**14C**) rt=25.25 min; 7.5; MS (EI): *m/z* 213 (M^+),153, 138, 128, 112,

74, 70, 57, 43 (100): oil; IR (film) ν 3291, 3065, 2942, 1734, 1649, 1547, 1247 cm^{-1}; ^1H and ^{13}C NMR (see text).

3.1.10. Reaction of epoxide 9 with MeOH/H_2O in the presence of K_2CO_3. (A) A solution of epoxide **9** (104.1 mg, 0.404 mmol) in methanol (2 mL) a solution of K_2CO_3 (143.7 mg, 1.04 mmol) in water (0.5 mL) was added. The reaction was stirred at rt for 160 h. Then, the solvent was removed and the residue taken in ethyl acetate, washed with brine, dried, filtered, and evaporated to give crude that was submitted to chromatography (hexane/EtOAc, 70% to AcOEt–MeOH, 10%) to give unreacted pure *syn*-**9** (27.2 mg), **15** [37.5 mg, 32% (44%), mixture of isomers in a 2:1 ratio], **16** [32.9 mg, 27% (41%)] and two fractions containing 8.3 mg and 6.4 mg, corresponding to isomers of **15** and **16**, respectively, whose structures could not be assigned. *Compound* **15**: oil; IR (film) ν 3326, 2933, 1695, 1533, 1455, 1234, 1090, 1043 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.34 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.11–5.09 (m, 2H, $NHCO_2CH_2C_6H_5$), 4.76 (br s, 1H, $NHCO_2CH_2C_6H_5$), 3.97 (br s, 1H), 3.76–3.68 (m, W=24.5 Hz, H2, minor isomer), 3.63–3.54 (m, W=28.5 Hz, H2, major isomer), 3.39 (s, 3H, OCH_3, minor isomer), 3.37 (s, 3H, OCH_3, major isomer), 3.22–3.16 (m, W=24.5 Hz, H1, major isomer), 3.10–3.04 (m, W=26.7 Hz, H1, minor isomer), 2.49 and 2.38 (2×br s, 1H), 2.15–1.89 (m, 2H), 1.73–1.40 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.5 ($NHCO_2CH_2C_6H_5$), 136.4, 128.5, 128.2 ($NHCO_2CH_2C_6H_5$), 82.3 (C1, minor isomer), 80.7 (C1, major isomer), 71.5 (C2, major isomer), 69.5 (C2, minor isomer), 66.1 ($NHCO_2CH_2C_6H_5$), 56.9 (OCH_3, major isomer), 56.8 (OCH_3, minor isomer), 46.2 (C4, major isomer), 45.9 (C5, minor isomer), 35.8, 31.9, 27.8, 27.6, 26.9 (CH_2); MS (CI): m/z 280.0 $[M+1]^+$, 302.1 $[M+23]^+$, 581.5 $[2M+23]^+$, 248.1 $[M-31]^+$, 236.2 $[M-43]^+$ 236.2. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.66; H, 7.81; N, 5.13. *Compound* **16**: amorphous solid; IR (KBr) ν 3326, 3036, 2930, 1693, 1533, 1454, 1233, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.29 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.08 (s, 2H, $NHCO_2CH_2C_6H_5$), 5.02 (br s, 1H, $NHCO_2CH_2C_6H_5$), 3.95–3.83 (m, W=38.1 Hz, 1H, H4), 3.60–3.47 (m, W=38.4 Hz,1H, H1)*, 3.44–3.31 (m W=36.9 Hz,1H, H2)*, 2.93–2.80 (br s, 2H, 2×OH), 2.08–1.26 (m, 6H, 2H3, 2H5, 2H6); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.7 ($NHCO_2CH_2C_6H_5$), 136.3, 128.5, 128.2 ($NHCO_2CH_2C_6H_5$), 73.6 (C1), 71.2 (C2), 66.7 ($NHCO_2CH_2C_6H_5$), 46.4 (C4), 36.3, 28.0, 27.3 (C3, C5, C6); MS (CI): m/z 266.0 $[M+1]^+$, 288.0 $[M+Na]^+$, 553.3 $[2M+Na]^+$, 158.1 $[M-107]^+$, 222.1 $[M-43]^+$, 248.1 $[M-17]$. Anal. Calcd for $C_{14}H_{19}NO_4$: C, 63.38; H, 7.22; N, 5.28. Found: C, 63.54; H, 7.03; N, 5.17.

(B) A solution of epoxide **9** (99.4 mg, 0.404 mmol) in methanol (2 mL) was treated with a solution of K_2CO_3 (145.1 mg, 1.05 mmol) in water (0.5 mL) at ~65 °C (bath temperature) for 20 h. After work-up as above, the crude was submitted to standard acetylation (Ac_2O/pyridine: 2 mL/2 mL) for 24 h at rt. After work-up and chromatography (hexane/EtOAc, 50%) compounds **17** (21.3 mg, 16% from **9**, as a mixture of isomers in 3:1 ratio), **18** (3.1 mg, 2% from **9**), **19** (4.6 mg, 3% from **9**) and **20** (26.5 mg, 18%, as a mixture of two isomers in 2:1 ratio) were isolated. *Compound* **17A/B**: oil; IR (film) ν 3335, 3057, 2940, 1723, 1531, 1455, 1371, 1240, 1151, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.25 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.28–5.04 (br s, $NHCO_2CH_2C_6H_5$, H1 minor isomer), 4.89–4.86 (m, W=11.7 Hz, H1 major isomer), 4.62 (br s, 1H, $NHCO_2CH_2C_6H_5$), 3.84 (br s, 1H), 3.42–3.39 (m, W=11.6 Hz, H2 major isomer), 3.37 (s, OMe, minor isomer), 3.36 (s, OMe, major isomer), 3.30–3.24 (m, W=12 Hz, H2 minor isomer), 2.04 (s, 3H, $OCOCH_3$), 2.00–1.39 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.0 ($OCOCH_3$), 155.4 ($NHCO_2CH_2C_6H_5$), 136.4, 128.5, 128.1 ($NHCO_2CH_2C_6H_5$), 76.2 (C1 major isomer), 75.0 (C1, minor isomer), 69.8 (C2, major isomer), 69.3 (C2, minor isomer), 66.5 ($NHCO_2CH_2C_6H_5$), 45.4 (C5, minor isomer), 45.1 (C4, major isomer), 32.5/32.2, 27.3/26.9, 24.5/24.1 (C3, C5, C6), 21.2 ($OCOCH_3$); MS (CI): m/z 322.3 $[M+1]^+$, 344.1 $[M+Na]^+$. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.73; H, 7.44; N, 4.18. *Compound* **18**: oil; IR (film) ν 3424, 3065, 2933, 1721, 1530, 1455, 1374, 1244, 1095, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.25 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.30–5.26 (m, 1H, H1), 5.09 (br s, 2H, $NHCO_2CH_2C_6H_5$), 4.82 (br s, 1H, $NHCO_2CH_2C_6H_5$), 3.73 (br s, H5), 3.39 (s, OMe), 3.32 (dt, J=3.2, 7.1 Hz, 1H, H2), 2.07 (s, 3H, $OCOCH_3$), 2.20–1.40 (m, 6H), 1.55–1.20 (m, 4H); MS (CI): m/z 322.3 $[M+1]^+$, 344.1 $[M+Na]^+$. *Compound* **19**: oil; IR (film) ν 3430, 3340, 2931, 1731, 1691, 1540, 1454, 1374, 1246, 1102, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.35–7.25 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.09 (br s, 2H, $NHCO_2CH_2C_6H_5$), 4.91–4.80 (br s, 2H, $NHCO_2CH_2C_6H_5$, H1), 3.81–3.75 (m, H4), 3.38 (s, OMe), 3.27 (dt, J=4.9 and 8.9 Hz, 1H, H2), 2.07 (s, 3H, $OCOCH_3$), 2.40–1.95 (m, 2H), 1.55–1.20 (m, 4H); MS (CI): m/z 322.3 $[M+1]^+$, 344.1 $[M+Na]^+$. *Compound* **20**: oil; IR (film) ν 3342, 3028, 2951, 1737, 1529, 1455, 1369, 1233, 1045 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.44–7.32 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.11 (s, 2H, $NHCO_2CH_2C_6H_5$), 5.04–4.97 (m, W=14.8 Hz, H1, major isomer)*, 4.88–4.81 (m, W=13.5 Hz, H2, major isomer)*, 4.70 (br s ancho, 1H, $NHCO_2CH_2C_6H_5$), 3.90 (br s, H4, major isomer), 3.68 (br s, minor isomer), 2.06 (s, 2×$OCOCH_3$, major isomer), 2.04 (s, 2×$OCOCH_3$, minor isomer), 2.00–1.50 (m, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 170.4 ($OCOCH_3$, minor isomer), 169.7 ($OCOCH_3$, major isomer), 155.5 ($NHCO_2CH_2C_6H_5$, major isomer), 154.8 ($NHCO_2CH_2C_6H_5$, minor isomer), 136.3, 128.5, 128.1 ($NHCO_2CH_2C_6H_5$), 72.7/71.3 (2 CH_2, minor isomer), 69.4 (2×C, C1, C2, major isomer), 66.7 ($NHCO_2CH_2C_6H_5$), 47.2 (CH, minor isomer), 45.4 (C4, major isomer), 36.2, 30.7, 26.8 (3 CH_2, minor isomer), 33.1, 27.2, 24.7 (C3, C5, C6), 21.0 (2×$OCOCH_3$, major isomer), 20.9 (2×$OCOCH_3$, minor isomer); MS (CI): m/z 350 $[M+1]^+$, 372 $[M+Na]^+$. Anal. Calcd for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64; N, 4.01. Found: C, 61.65; H, 6.73; N, 4.14.

3.1.11. Reaction of epoxide 9 with potassium cyanide. To a solution of epoxide **9** (123.3 mg, 0.5 mmol) in dry acetonitrile (1 mL), under argon and stirring, KCN (49 mg, 0.75 mmol) and $LiClO_4$ (79.8 mg, 0.75 mmol) were added. The mixture was warmed at 80 °C for 28 h, cooled and diluted with ethyl ether, washed with brine, dried, filtered and evaporated. The crude was submitted to chromatography (hexane/EtOAc, 5% to 40%) to give compounds **21** (10.2 mg, 8%, mixture of isomers in 1:1 ratio), **22** (13.8 mg), **22**+**23** (29.9 mg, 1/1 ratio) and **23** (3.5 mg) (total (**22**+**23**): 47.2 mg, 34%). *Compound* **21**

(two isomers in 1:1 ratio): oil; IR (film) ν 3334, 3028, 2925, 2210, 1694, 1525, 1259, 1230, 1049 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.30 (m, 5H, $NHCO_2CH_2C_6H_5$), 6.62/6.54 [s, s, H–C=C(CN)], 5.10 (s, 2H, $NHCO_2CH_2C_6H_5$), 4.72/3.88 (2×br s, 1H, $NHCO_2CH_2C_6H_5$), 2.62 (d, J= 4.89 Hz, 1H), 2.36–2.35 (br s, 2H), 2.14–1.95 (m, 2H), 1.68–1.56 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.6 ($NHCO_2CH_2C_6H_5$), 144.4/142.1 [H–C=C(CN)], 136.2, 128.6, 128.3, 128.2 ($NHCO_2CH_2C_6H_5$), 118.8/118.7 [2 C, H–C=C(CN)], 112.4/110.3 [2 C, H–C=C(CN)], 66.9 (2 C, $NHCO_2CH_2C_6H_5$), 45.0, 44.8 (H–C–$NHCO_2CH_2C_6H_5$), 32.9/32.4 (CH_2), 27.3/26.6 (CH_2), 25.3/24.3 (CH_2); MS (CI): m/z 257.0 $[M+1]^+$, 279.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.33; H, 618; N, 10.87. *Compound* **22**: oil; IR (film) ν 3338, 3028, 2950, 2243 (CN), 1695, 1532, 1453, 1317, 1258, 1224, 1069, 1044 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.31 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.09 (s, 2H, $NHCO_2CH_2C_6H_5$), 4.95 (br d, J=5.7 Hz, 1H, $NHCO_2CH_2C_6H_5$), 3.86 (br t, J= 8.8 Hz, 1H, CH–OH), 3.70–3.60 (m, W=30 Hz, 1H, CH-$NHCO_2CH_2C_6H_5$), 2.79 (br s, 1H, OH), 2.47–2.39 (ddd, J= 3.9, 8.8, 11.1 Hz, 1H, CH–CN), 2.32 (br d, J=12.3 Hz, 1H, H3), 2.20–2.10 (m, 1H, H6), 1.70–1.57 (m, 1H, H6′), 1.42–1.23 (m, 3H, H3′, 2H5); ^{13}C NMR ($CDCl_3$, 75 MHz)? δ 155.4 ($NHCO_2CH_2C_6H_5$), 136.2, 128.6, 128.2, 128.1 ($NHCO_2CH_2C_6H_5$), 120.5 (CN), 69.1 (CH–OH), 66.8 ($NHCO_2CH_2C_6H_5$), 47.3 (CH–$NHCO_2CH_2C_6H_5$), 39.4 (C3), 36.4 (CH–CN), 29.7 (C5), 24.5 (C6); MS (CI): m/z 275.0 $[M+1]^+$, 297.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.73; H, 6.82; N, 10.44. *Compound* **23**: oil; IR (film) ν 3338, 3028, 2932, 2243 (CN), 1694, 1532, 1454, 1324, 1253, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.29 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.03 (s, 2H, $NHCO_2CH_2C_6H_5$), 4.65 (br s), 3.87–3.75 (m, 2H, H2 –CH–OH–, H5 –HCNHCO$_2$CH$_2$C$_6$H$_5$–), 2.76–2.62 (m, W=39 Hz, 1H, H1 –H–C–CN–), 2.32 (br s, 1H, OH), 2.16 (br s, 1H, H4), 2.01–1.96 (m, 1H, H6), 1.93–1.86 (m, 1H, H4′), 1.75–1.67 (m, 2H, 2H3), 1.58 (m, 1H, H6′); ^{13}C NMR ($CDCl_3$, 75 MHz)? δ 155.2 ($NHCO_2CH_2C_6H_5$), 136.1, 128.7, 128.2, 128.1 ($NHCO_2CH_2C_6H_5$), 120.5 (CN), 68.3 (CH–OH), 66.9 ($NHCO_2CH_2C_6H_5$), 45.3 (CH–$NHCO_2CH_2C_6H_5$), 32.6 (CH–CN), 30.3 (C4), 28.1 (C6), 27.0 (C3); MS (CI): m/z 275.0 $[M+1]^+$, 297.0 $[M+Na]^+$. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61; N, 10.21. Found: C, 65.82; H, 6.53; N, 10.54.

3.1.12. Reaction of epoxide 9 with trimethylsilyl iodide. To a solution of epoxide **9** (142.8 mg, 0.58 mmol) in dry acetonitrile (2 mL), under argon, TMSI (0.1 mL, 0.69 mmol) was added and the reaction was stirred at rt for 44 h. Then, methanol was added, and the solvents were removed. The crude was submitted to chromatography (hexano/AcOEt, 30% to AcOEt) giving compounds **7** (39.9 mg, 29%), **25** (10.5 mg, 5%), **26** (26.4 mg, 12%), and more polar product (**27**), isolated a viscous oil, (60.5 mg) that was submitted to standard acetylation (0.5 mL pyridine/0.5 mL Ac_2O, rt, 15 h; chromatography: hexane/AcOEt, 50%) to give product **28** (48.5 mg, 60% from **9**). *Compound* **25**: 144–147 °C; IR (KBr) ν 3467, 2927, 1689, 1658, 1548, 1306, 1273, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.31 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.01 (s, 2H, $NHCO_2CH_2C_6H_5$), 4.70 (br s, 1H, $NHCO_2CH_2C_6H_5$), 3.84 (ddd, J=4.2, 9.6, 11.7 Hz, 1H, CH–I) 3.68 (dt, J=4.2, 9.9 Hz, CH–OH), 3.66–3.57 (m, 1H, CH–$NHCO_2CH_2C_6H_5$), 2.47–2.27 (m, 2H, H3, H6), 2.10–1.90 (m, 1H, H3′), 1.82–1.77 (m, 1H, H4), 1.56 (br s, 1H, OH), 1.26–1.06 (m, 2H, H6′, H4′); ^{13}C NMR ($CDCl_3$, 75 MHz)? δ 155.8 ($NHCO_2CH_2C_6H_5$), 136.7, 128.9, 128.6, 128.5 ($NHCO_2CH_2C_6H_5$), 74.6 (CH–OH), 67.2 ($NHCO_2CH_2C_6H_5$), 48.4 (CH–$NHCO_2CH_2C_6H_5$), 39.6 (2 C, C2, C6), 34.9 (C3), 34.4 (C4); MS (CI): m/z 359 $[M-16]^+$, 332.0 $[M-43]^+$, 248.3 $[M-126.9]^+$, 376.0 $[M+1]^+$, 398.0 $[M+Na]^+$, 773.0 $[2M+Na]^+$. Anal. Calcd for $C_{14}H_{18}INO_3$: C, 44.82; H, 4.84; N, 3.73. Found: C, 44.93; H, 4.77; N, 3.62. *Compound* **26**: oil; IR (film) ν 3326, 3032, 2939, 1694, 1532, 1454, 1231, 1071 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.39–7.31 (m, 5H, $NHCO_2CH_2C_6H_5$), 5.02 (s, 2H, $NHCO_2CH_2C_6H_5$), 4.83 (br d, J=6.6 Hz, 1H, $NHCO_2CH_2C_6H_5$), 4.16–4.09 (m, W=22.2 Hz, 1H, CH–I) 3.76–3.66 (m, 2H, CH–OH, CH–$NHCO_2CH_2C_6H_5$), 2.47–2.27 (m, 1H, H3), 2.28 (br s, 1H, OH), 2.19–2.13 (m, 1H, H3′), 2.11–2.00 (m, 1H, H6)*, 1.81–1.58 (m, 2H, 2H4)*, 1.53–1.45 (m, 1H, H6′)*; ^{13}C NMR ($CDCl_3$, 75 MHz)? δ 156.0 ($NHCO_2CH_2C_6H_5$), 136.2, 128.5, 128.2 ($NHCO_2CH_2C_6H_5$), 74.0 (CH–OH), 66.8 ($NHCO_2CH_2C_6H_5$), 47.8 (CH–$NHCO_2CH_2C_6H_5$), 40.6 (C6), 35.8 (C2), 28.2 (C3)*, 27.7 (C4)*; MS (CI): m/z 376.0 $[M+1]^+$, 398.0 $[M+Na]^+$, 773.0 $[2M+Na]^+$. Anal. Calcd for $C_{14}H_{18}INO_3$: C, 44.82; H, 4.84; N, 3.73. Found: C, 44.73; H, 4.91; N, 3.62. *Compound* **28**: amorphous solid; IR (KBr) ν 3436, 2920, 1634, 1394, 1342, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 6.98 (br s, 1H, $NHCOCH_3$), 6.47 (d, J=7.5 Hz, 1H, H5), 5.98 (dd, J=5.2, 9.3 Hz, 1H, H3), 5.79 (dd, J=9.9, 15.6 Hz, 1 1H, H2), 5.56–5.50 (m, 1H, H1), 5.43 (t, J= 6.6 Hz, 1H, H4), 2.49 (s, 2H, 2H6), 2.23 (s, 3H, $NHCOCH_3$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.1 ($NHCOCH_3$), 125.0 (C5), 124.1 (C2), 122.1 (C3), 108.7 (C4), 47.7 (C1), 38.7 (C6), 21.9 ($NHCOCH_3$); MS (CI): m/z 138.0 $[M+1]^+$, 160.0 $[M+Na]^+$. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.25; H, 8.21; N, 10.01.

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Synthesis of substituted pyrrolidines and piperidines from endocyclic enamine derivatives. Synthesis of (±)-laburnamine

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Abstract—Functionalization of the α- and β-positions of readily available endocyclic enamine derivatives provides a convenient method for the formation of substituted pyrrolidines and piperidines. α-Alkoxy-β-iodopyrrolidines are formed by the electrophilic addition of iodine to the endocyclic enamine double bond of an *N*-substituted 2-pyrroline, and nucleophillic attack by an alcohol on the intermediate iodonium ion. The resultant α-alkoxy-β-iodopyrrolidines can be used in radical cyclization reactions to give bicyclic hemiaminal compounds, which can be further elaborated using *N*-acyliminium chemistry to form α,β-*cis*-dialkylsubstituted pyrrolidines. A strategy for the incorporation of amino functionality at the β-position was also established by using iodoamination of the enamine double bond, followed by migration of the amine functionality through an aziridination/methanolysis protocol. An alternative method uses an azidomethoxylation protocol using ceric ammonium nitrate (CAN) in the presence of NaN_3 and methanol. Formation and trapping of the *N*-acyliminium ions derived from these substrates, afforded the 3-carbamate and 3-azido-2-substituted products with good diastereoselectivity, with the preferential formation of the *trans* and *cis* stereoisomers, respectively. Using the sequential iodoamination, aziridination in methanol and *N*-acyliminium transformation, *trans*-3-$NHCO_2Me$-2-allyl-pyrrolidine was prepared, which was used as the key precursor in a synthesis of the natural 1-amidopyrrolizidine alkaloid, (±)-laburnamine.

1. Introduction

The importance of substituted pyrrolidines and piperidines as biologically active compounds and their widespread occurrence in alkaloids, have led to the development of numerous synthetic methods for their preparation.[1] An example of these targets are 3-aminopyrrolidine and 3-aminopiperidines, which are useful building blocks for the construction of bioactive compounds.[2] As part of our ongoing interest in the functionalization of *N*-acylated cyclic enamines, we have developed synthetic methodologies for the functionalization of the α and β position of the pyrrolidine or piperidine ring.[3] In this paper, we will present these simple sequential strategies, starting with oxidation processes using electrophilic iodine or ceric ammonium nitrate (CAN). Further manipulation through radical cyclizations, aziridination/methanolysis and/or *N*-acyliminium chemistry provides ready access to a structurally diverse range of pyrrolidines and piperidines, including the 3-aminopyrrolidine and 3-aminopiperidine units.

2. Results and discussion

The electron-rich alkene bond of endocyclic *N*-acylenamides presents numerous synthetic opportunities. Perhaps the most versatile application of such derivatives would be the simultaneous addition of an electrophile (E) and a nucleophile (Nu) to the C=C bond, in what is formally a three-component coupling reaction (Fig. 1). This process results in the simultaneous functionalization of the

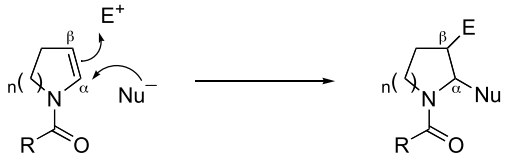

Figure 1. Three component coupling of an endocyclic enamide with an electrophile and a nucleophile.

Keywords: Enamines; Radical cyclizations; Aziridination; *N*-Acyliminium; 1-Amidopyrrolizidine; (±)-Laburnamine.
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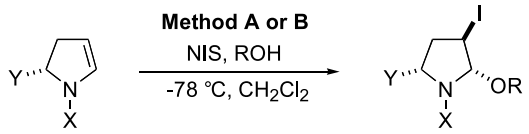
Table 1. Examples of iodoetherification of *N*-acyl-enamide precursors



1a: X = Cbz, Y = H
1b: X = acetyl, Y = H
1c: X= Boc, Y = COOMe

2

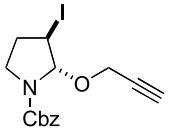
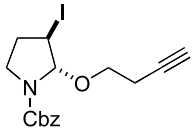
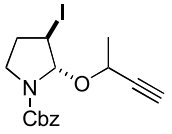
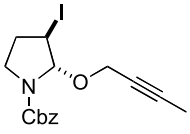
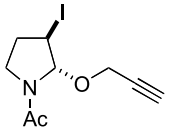
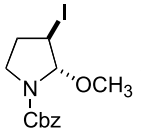
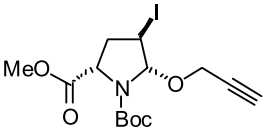
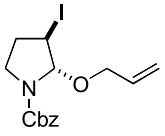
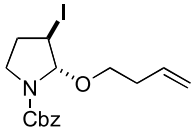
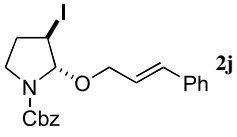
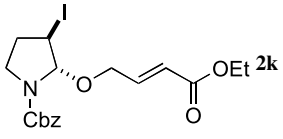
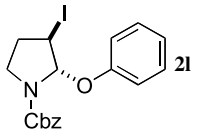
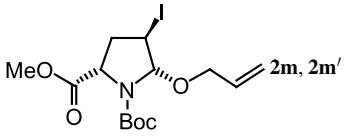
Entry	*N*-Acyl-2-pyrroline	Alcohol	Major product	Method[a]	Yield[b] (%)
1	**1a**	Propargyl alcohol	 **2a**	A	80
2	**1a**	3-Butyn-1-ol	 **2b**	A	75
3	**1a**	3-Butyn-2-ol	 **2c**	A	50[c]
4	**1a**	2-Butyn-1-ol	 **2d**	A	65
5	**1b**	Propargyl alcohol	 **2e**	A	83
6	**1a**	Methanol	 **2f**	A	92
7	**1c**	Propargyl alcohol	 **2g, 2g′**	A	57[c]
8	**1a**	Allyl alcohol	 **2h**	B	65
9	**1a**	3-Buten-1-ol	 **2i**	B	62
10	**1a**	Cinnamyl alcohol	 **2j**	B	74
11	**1a**	Ethyl-(2*E*)-hydroxy-2-butenoate	 **2k**	B	62

Table 1 (*continued*)

Entry	*N*-Acyl-2-pyrroline	Alcohol	Major product	Method[a]	Yield[b] (%)
12	**1a**	Phenol	 **2l**	B	57
13	**1c**	Allyl alcohol	 **2m**, **2m′**	B	88[d]

[a] Method A: **1** was added to a mixture of NIS and ROH in CH_2Cl_2. Method B: NIS was added to a mixture of **1** and ROH in CH_2Cl_2.
[b] Yield of purified product isolated by flash chromatography.
[c] Isolated as a mixture of two diastereomers, ratio not determined.
[d] The two diastereomers were separated by column chromatography, and isolated in a 57:43 ratio.

α- and β-positions of these substrates, with the electrophilic addition step to the more electron-rich β-position triggering the subsequent addition of the nucleophile at the electrophilic α-position.[4] This process would represent an excellent strategy for diversification of the central *N*-heterocyclic scaffold, assuming conditions can be found that prevent the direct competitive attack of the nucleophile with the electrophile. One way, in which this can be accomplished is to use an electrophile–nucleophile combination that are unreactive together. This situation occurs when the electrophile and nucleophile are both heteroatom based, since the direct reaction would result in the formation of a weak E–Nu bond. We have therefore focused upon this approach using heteroatom based electrophiles (e.g. $E^+ = I^+$) to trigger the addition. The addition products can be further elaborated. In this paper, we describe three such processes: (i) free radical cyclizations from the β-position, (ii) substituent rearrangement from the α to β-position, and (iii) nucleophilic attack at the α-position via N-acyliminium chemistry.

The synthetic potential of the *N*-acyl-enamide endocyclic double bond, was first explored by performing electrophilic iodine additions. Treatment of enamide substrates **1a**,[5] **1b**[5] and **1c**[6] with various alcohols in the presence of *N*-iodosuccinimide (NIS) afforded the *trans*-2-alkoxy-3-iodopyrrolidines **2** (Table 1). The high levels of *trans* diastereoselectivity arise because the intermediate iodonium ion undergoes *anti* nucleophilic attack at the α-position.[7] The transformations readily occur at −78 °C, even for less nucleophilic substrates (Table 1, entry 12), and no side reaction was observed between iodine and the unsaturated alcohols, because of the greater nucleophilicity of the enamine π-bond over the alkenol/alkynol π-bonds (Table 1, entries 8–11 and 13). Reaction of the chiral substrate **1c**, which contains an ester group at the 5-position of the pyrroline ring, resulted in poor facial selectivity for the electrophilic addition step, although the products again had a *trans*-relationship between the 3-iodo- and 2-alkoxy substituents (Table 1, entries 7 and 13).

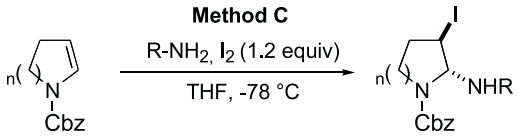
Iodine promoted addition of nitrogen nucleophiles[8,9] on substrates **1a** and **1d** is also possible. Attempts to use primary amines (allylamine and propargylamine), dialkylamines (*N*-methylallylamine and *N*-cyclohexylamine), arylamines (aniline, *N*-acetylaniline) and amides (acrylamide and trifluoracetamide) failed to give stable products.[10] However, the addition of carbamates as the nucleophilic component did give stable addition products, affording a *trans*/*cis* mixture of 3-iodo-2-carbamate substituted pyrrolidines **3a**–**3d** in good yields (Table 2). This transformation occurs at low temperature and uses I_2 instead of *N*-iodosuccinimide, to prevent competitive nucleophilic attack of succinimide on the electrophilic intermediate. Interestingly, in the case of the 6-membered substrate **1d**, only the Boc-carbamate yielded a stable addition product[11] (Table 2, entry 5).

Free-radical cyclization methods, particularly in a 5-*exo* or 6-*exo* manner, constitute one of the most powerful and versatile methods for the construction of cyclic systems and have found extensive application in the synthesis of carbocycles and heterocycles.[12] Radical cyclization reactions of *trans*-α-alkoxy-β-iodopyrrolidines **2** using a sodium cyanoborohydride-catalytic tributylstannane system, generated the bicyclic compounds **4** (Table 3).[7,13] The yields were moderate to high, except for the 6-*exo* ring closures where the direct reduction pathway was strongly competitive (Table 3, entries 2 and 8). The cyclizations were highly regiospecific with only the *cis*-fused 5-*exo* or 6-*exo* products being formed. Such selectivity is well known in radical cyclization reactions. In the 5-*exo* and 6-*exo* cyclization onto alkenes a new asymmetric center is formed (Table 3, entries 7 and 9–12), with the *endo*-isomer being preferentially formed.[14]

However, as the alkene substituent in **2** becomes bulkier, the steric interaction at the *endo* position becomes larger and the selectivity diminishes. For the 6-*exo*-trig ring closure and as expected for acyclic examples,[15] a lower selectivity in favor of the *trans* product was observed (Table 3, entry 8) resulting from the *exo* (1,6-*trans*) transition state.

The above results illustrate the utility of introducing β-I and α-N/O functionality on the C=C bond of endocyclic enamide derivatives. A further goal of our research was to establish whether the endocyclic enamides **1**, or the corresponding 3-iodo-2-carbamate derivatives **3**, could be functionalized to give compounds having β-amino functionality (i.e. 3-aminopyrrolidines/piperidines). Although comparable amino functionalization of glycals (cyclic enol ethers) has been intensively studied in the glycoconjugate

Table 2. Iodocarbamation of *N*-Cbz-enamide substrates



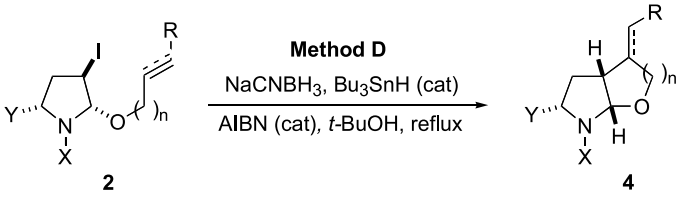
1a: n=1
1d: n=2

3

Entry	Substrate	Product	Yield (%)[a]	d.r.[b]
1	**1a** ($n=1$)	**3a** (R=Boc)	74	72:28
2	**1a** ($n=1$)	**3b** (R=Cbz)	71	77:23
3	**1a** ($n=1$)	**3c** (R=CO_2Me)	70	73:27
4	**1a** ($n=1$)	**3d**[c] (R=Ts)	32[c]	69:31
5	**1d** ($n=2$)	**3e** (R=Boc)	75	—

[a] Yield of pure product purified by flash chromatography.
[b] Determined by ^{1}H NMR.
[c] Partial decomposition was observed within a few days at 4 °C.

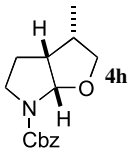
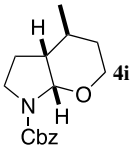
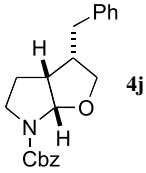
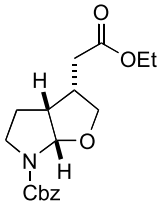
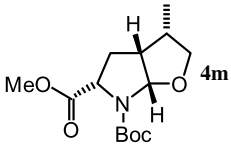
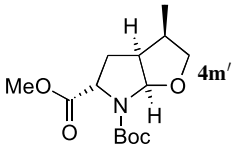
Table 3. Conversion of pyrrolidines **2** into bicyclic pyrrolidines **4**



2 **4**

Entry	Pyrrolidine	Bicyclic	Yield (%)[a]	*endo*/*exo*
1	**2a**	**4a**	71	—
2	**2b**	**4b**	46[b]	—
3	**2c**	**4c**	61	—
4	**2d**	**4d**	74[c]	—
5	**2e**	**4e**	75	—
6	**2g**	**4g**, **4g′**	61	—

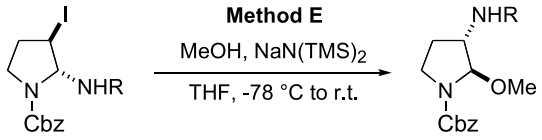
Table 3 (*continued*)

Entry	Pyrrolidine	Bicyclic	Yield (%)[a]	*endo*/*exo*
7	**2h**	 **4h**	92[d]	95:5
8	**2i**	 **4i**	30[d,e]	40:60
9	**2j**	 **4j**	66[d]	74:26
10	**2k**	 **4k**	82[d]	80:20
11	**2m**	 **4m**	96[d]	95:5
12	**2m′**	 **4m′**	76[d]	95:5

[a] Yield of purified product isolated by flash chromatography.
[b] The corresponding uncyclized reduced product was isolated in 37% yield.
[c] Isolated as a 1:1 mixture of *E*/*Z* isomers.
[d] The stereochemistry of the products were assigned by a combination of 1D NMR and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-d_2-tetrachloroethane.
[e] The corresponding uncyclized reduced products were also isolated in 26% yield.

chemistry, very few examples are known for N-heterocyclic equivalents.[16] The most straightforward pathway would involve a direct aminohydroxylation protocol on the endocyclic substrates **1**, but initial attempts to achieve such reactions have failed.[17] However, *cis*/*trans*-2-methoxy-3-*N*-(trifluoroacetyl)aminopyrrolidines have been prepared,[17] albeit in moderate yields, via a formal aziridination protocol using a manganese nitrido complex.[18]

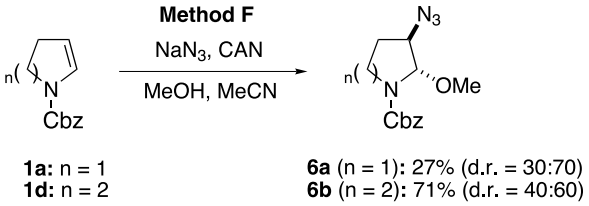
Table 4. Aziridination/methanolysis of **3**



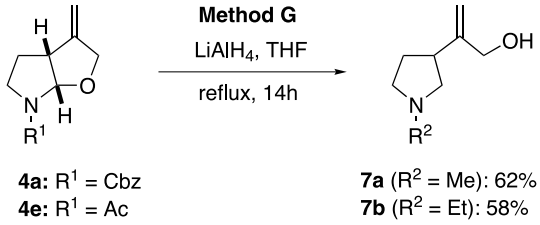
3 **5**

Entry	Substrate	Product	Yield (%)[a]	d.r.[b] (*trans*/*cis*)
1	**3a**	**5a** (R=Boc)	82	85:15
2	**3b**	**5b** (R=Cbz)	73	77:23
3	**3c**	**5c** (R=MeOCO)	85	78:22

[a] Yield of purified pure product isolated by flash chromatography.
[b] Determined by ^{1}H NMR.



Scheme 1. Azidomethoxylation with ceric ammonium nitrate (CAN).



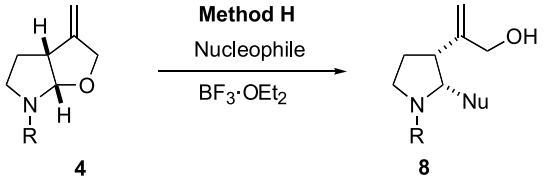
Scheme 2. $LiAlH_4$ Reduction of bicyclic hemiaminal derivatives **4**.

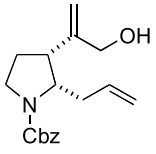
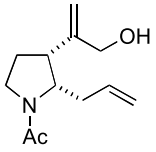
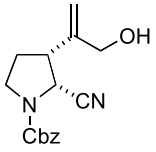
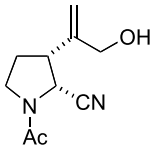
The adducts described above provide an alternative approach for the introduction of β-amino functionality. A migration/methanolysis protocol on **3** allows for the preparation of 3-amino-2-methoxy functionalized pyrrolidines and piperidines. Treatment of compounds **3a**–**3c** with $NaN(SiMe_3)_2$ in THF and methanol, results in cyclization to give an aziridine intermediate, which is then ring-opened in situ at low temperature by methanol, to afford inseparable diastereomeric mixtures of **5a**–**5c** (Table 4). The same transformation could also be achieved, but in lower yields (60% for **5a** and 59% for **5b**), using KOH (0.1 M)/MeOH at 35 °C for 5 h.[19]

Surprisingly the aziridination/methanolysis protocol was unsuccessful on the piperidine substrate **3e**. However, treatment of the enecarbamates **1a** or **1d** with CAN[20,21] in the presence of sodium azide and methanol afforded 3-azido-2-methoxypyrrolidines **6a** and piperidine **6b** respectively, as diastereomeric mixtures (Scheme 1). This azidomethoxylation protocol allows for the introduction of latent amino functionality, as an azido group, in the β position of both pyrrolidines and piperidines. Interestingly, this reaction occurred in much better yields using the piperidine substrate **1d** than with the pyrrolidine substrate **1a**.

Both the bicyclic compounds **4** and the 2-methoxy-3-substituted-pyrrolidines **2**, **5** and **6** constitute versatile intermediates by virtue of the hemiaminal functionality, which can undergo reaction with nucleophiles at the α-position. The simplest nucleophilic addition reaction is hydride addition, as exemplified by the use of lithium aluminium hydride.[22] For example, substrates **4a** and **4e**

Table 5. *N*-Acyliminium ion additions of bicyclic hemiaminal derivatives **4**



Entry	Substrate	Nucleophile	Major product[a]	Yield (%)[b]	d.r.[c] (*cis*/*trans*)
1	**4a** (R=Cbz)	$H_2C{=}CHCH_2SiMe_3$	 **8a**	89	76:24
2	**4e** (R=Ac)	$H_2C{=}CHCH_2SiMe_3$	 **8b**	58	63:37
3	**4a** (R=Cbz)	Me_3SiCN	 **8c**	76	67:33
4	**4e** (R=Ac)	Me_3SiCN	 **8d**	64	74:26

[a] The stereochemistry of the products were assigned by a combination of 1D and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-tetrachloroethane-d_2.
[b] Yield of purified pure product isolated by flash chromatography.
[c] Determined by ^1H NMR.

underwent reduction to *N*-alkyl-3-alkyl-substituted pyrrolidines in moderate yields (Scheme 2).

More importantly these compounds can be utilized as *N*-acyliminium ion precursors in C–C bond forming reactions[23] as exemplified by reactions with allyltrimethylsilane or cyanotrimethylsilane. Reaction of **4** with these nucleophiles in the presence of $BF_3 \cdot OEt_2$ gave compounds **8a**–**8d** in moderate diastereoselectivity. The major diastereomers were the *cis*-isomers,[24] as determined by 2D-NOESY experiments (Table 5) and, in the case of compound **8d**, further confirmed by an X-ray structure determination (Fig. 2).

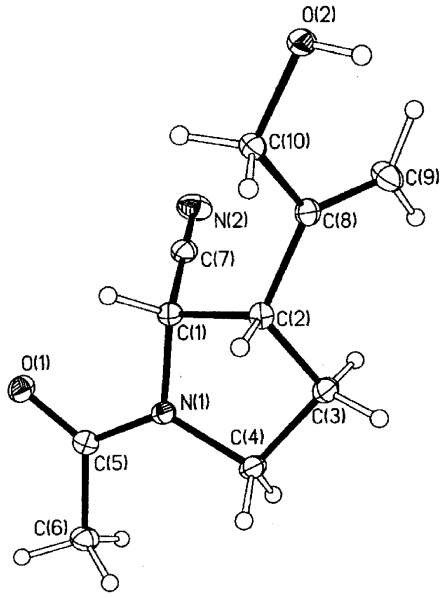


Figure 2. Representation of the X-ray structure of **8d**.

Further transformations of *N*-acyl-iminium intermediates derived from 3-carbamate and 3-azido substituted pyrrolidines **5** and piperidines **6** would be of special interest because they would allow for the preparation of potential precursors for natural and non-natural products synthesis.[25] Reaction of allyltrimethylsilane, cyanotrimethylsilane or *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane with pyrrolidines **5a**–**5c** under Lewis acidic conditions afforded the 3-carbamate-2-alkyl-substituted pyrrolidines **9a**–**9d** in moderate to good yields, and with moderate *trans* stereoselectivity (Table 6, entries 1–4). This observed *trans* selectivity can be rationalized by a neighboring group effect.[26] In contrast, similar attack of the 3-azido substrates **6a** and **6b** gave substituted products **9e** and **9f** with moderate yields and high *cis* selectivity[24] (Table 6, entries 5 and 6). Analogous *N*-acyliminium transformations could also be performed on 3-iodo-2-methoxypyrrolidine **2f** to give the substituted products **9g** and **9h** in good to excellent yields (Table 6, entries 7 and 8). These products were obtained exclusively as the *trans* diastereomers, presumably via the intermediacy of an iodonium ion, which exclusively directs the nucleophilic attack in an *anti* fashion.

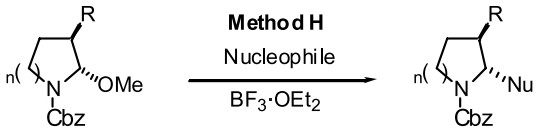
Pyrrolizidines are an important class of alkaloids, present in many plants and insects. They are important synthetic targets due to their toxicological and biological properties,[27] and indeed, synthesis of pyrrolizidines have been a fertile testing ground for new synthetic methodologies.[28] 1-Aminopyrrolizidines are a relatively rare subclass, and only a few representatives have been described.[29] There has been some synthetic effort to construct related structures.[30] Recently Potier and co-workers[31] described the first synthesis of two 1-amidopyrrolizidine alkaloids, absouline and laburnamine, through a pyrrolizidine-1-one hydrochloride intermediate.

The availability of 3-aminopyrrolidines through the methodology outlined in this paper, provides an alternative strategy for the formation of the 1-aminopyrrolizidine skeleton (Scheme 3). Thus, the major *trans*-isomer of **9d** was readily separated from the *cis*-isomer by flash column chromatography. Hydroboration of compound *trans*-**9d** using $BH_3 \cdot SMe_2$[32] followed by oxidative hydrolysis with $NaOH/H_2O_2$ afforded the alcohol **10**. Initial attempts using $BH_3 \cdot THF$[33] or 9-BBN[33] required long reaction times and, in the latter case, resulted in difficulties in purification. In an attempt to form a reductive amination precursor, oxidation of the primary alcohol **10** to the aldehyde was attempted using NMO/TPAP,[34] but this intermediate proved to be unstable. Alternatively tosylation[35] of the primary alcohol afforded compound **11** which upon hydrogenation[36] (5% Pd/C) cyclized to give 1-carbamate pyrrolizidine **12**. Carbamate deprotection was accomplished with TMSI followed by methanolysis[37] and the crude amine was immediately protected with methylbutyric acyl chloride to give (±)-laburnamine **13** in an overall yield of 6% starting from the enecarbamate **1a**.

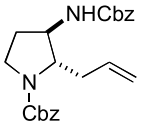
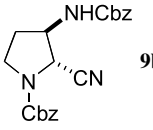
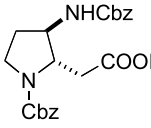
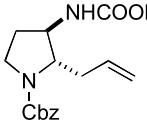
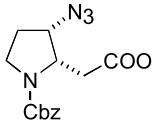
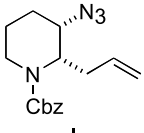
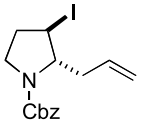
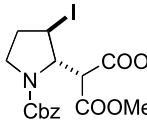
3. Conclusions

In summary, strategies for pyrrolidine and piperidine α,β-funcionalization have been developed, starting from readily available endocyclic enamine derivatives. A two step heteroannulation procedure involving iodoetherification of *N*-acyl-2-pyrrolines followed by radical cyclization, gave access to the bicyclic compounds **4** which can be used in further transformations to form substituted pyrrolidines. 3-Amino functionalization of pyrrolidines and piperidines can be accomplished by two different routes, from the corresponding endocyclic enamine derivatives. Iodoamination followed by aziridination/methanolysis afforded the 3-carbamate-2-methoxypyrrolidines **5** and azidomethoxylation with CAN/NaN_3 in methanol afforded the 3-azido-2-methoxypyrrolidines **6a** and piperidines **6b**. Stereoselective substitution of the 2-methoxy group by carbon nucleophiles via *N*-acyliminium intermediates afforded the 2-substituted-3-carbamate-pyrrolidines (**9a**–**9d**) with good *trans*-selectivity and the 2-substituted-3-azido-pyrrolidines and piperidines with good *cis*-selectivity (**9e** and **9f**). The resultant compounds are useful synthetic intermediates, as exemplified by the synthesis of the natural 1-aminopyrrolizidine alkaloid, (±)-laburnamine, starting from the pyrrolidine precursor **9d**. Overall, this study further establishes the utility of electron-rich endocyclic enecarbamates (or enamides) in electrophilic addition reactions.

Table 6. *N*-Acyliminium ion additions of 2-methoxy-3-substituted pyrrolidine precursors



9

Entry	Substrate	Nucleophile	Major product[a]	Yield (%)[b]	d.r.[c] *cis*/*trans*
1	**5b** ($n=1$, R=NHCbz)	$H_2C{=}CHCH_2SiMe_3$	 **9a**	60	24:76
2	**5b** ($n=1$, R=NHCbz)	Me_3SiCN	 **9b**	52	30:70
3	**5b** ($n=1$, R=NHCbz)	$CH_2{=}C(OTBDMS)OEt$	 **9c**	74	15:85
4	**5c** ($n=1$, R=$NHCO_2Me$)	$H_2C{=}CHCH_2SiMe_3$	 **9d**	79	23:77
5	**6a** ($n=1$, R=N_3)	$CH_2{=}C(OTBDMS)OEt$	 **9e**	49	88:12
6	**6b** ($n=2$, R=N_3)	$H_2C{=}CHCH_2SiMe_3$	 **9f**	50	88:12
7	**2f** ($n=1$, R=I)	$H_2C{=}CHCH_2SiMe_3$	 **9g**	93	≤2:98
8	**2f** ($n=1$, R=I)	$CH_2(CO_2Me)_2$	 **9h**	68[d]	≤2:98

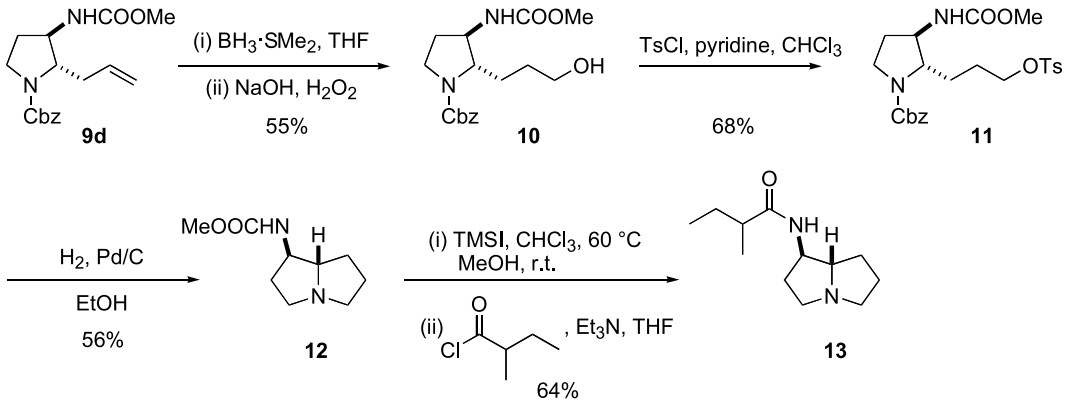
[a] The stereochemistry of the products were assigned by a combination of 1D and 2D NMR NOESY experiments performed at 360 K in 1,1,2,2-tetrachloroethane-d_2.
[b] Yield of purified pure product isolated by flash chromatography.
[c] Determined by ^{1}H NMR.
[d] Prepared at −78 °C and using $TiCl_4$ as the Lewis acid.

4. Experimental

4.1. General remarks

All chemicals were purchased from commercial sources and were used without further purification. Unless otherwise stated, all reactions were performed under nitrogen or argon atmosphere using flame or oven (120 °C) dried glassware. Diethyl ether, tetrahydrofuran (THF), benzene and toluene were distilled over sodium and benzophenone under argon or nitrogen. Dichloromethane, *t*-BuOH and acetonitrile were distilled over CaH_2. Analytical thin-layer chromatography (TLC) was performed on silica gel plates (Merck Kiesegel GF 254, 0.2 mm) and components were visualized by observation under UV light or by treating the plates with phosphomolybdic reagent followed by heating. Column chromatography was carried out using Merck 60H silica gel or Whatman 230–400 'mesh' silica gel. Solvent ratios for R_f values are reported as v/v.

Nuclear magnetic resonance spectra: ^{1}H and ^{13}C NMR spectra were recorded on either Varian Gemini 200, Bruker ARX 400 or Varian XL400 MHz spectrometers. The following abbreviations are used to indicate signal



Scheme 3. Synthesis of (±)-laburnamine.

multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; br, broad and *J*, coupling constant in Hz. Infrared spectra were recorded on either a Buck Scientific M-500 or a Fourier Perkin–Elmer 683 spectrometer. Melting points were measured on a Köpfler instrument, mod. Reichert Termovar and are uncorrected. Optical activities were measured on an Optical activity, Mod. AA-1000, with a 5 cm cell. Low-resolution mass spectra were performed on Bell and Howell 21-490 spectrometer and high resolution mass spectra were performed on a AEI MS3074 spectrometer (University of Toronto). X-ray crystallography analysis was performed by Dr. Alan Lough (Department of Chemistry, University of Toronto).

CCDC-249610 **8d** contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

4.2. Method A. General procedure for iodoetherification with alkynols

To a solution of *N*-iodosuccinimide (1.2 mequiv) and the alcohol (1.2 mequiv) in dry dichloromethane at −78 °C, was added dropwise *N*-acyl-2-pyrroline **1** (1.0 mequiv). The mixture was stirred under argon for 10 min and then poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted twice with dichloromethane. The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the iodoether **2** derivative, which was purified by flash chromatography.

4.2.1. *trans*-Benzyl-3-iodo-2-(2-propynyloxy)-1-pyrrolidine carboxylate (2a, Table 1, entry 1). Prepared following method A using propargyl alcohol (172 µl, 2.95 mmol), *N*-iodosuccinimide (698 mg, 2.95 mmol) and *N*-[(benzyloxy)carbonyl)]-2-pyrroline (**1a**) (500 mg, 2.46 mmol), to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2a** (760 mg, 80%) as a colorless oil; R_f=0.5 (10% EtOAc/90% hexane); IR (film) ν 3290, 3032, 2955, 2117, 1710, 1586, 1498, 1404, 1286, 1193, 1113, 1052, 972, 915, 772, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.33 (m, 5H, Ar), 5.63–5.54 (m, 1H, N–C*H*–O), 5.19 (s, 2H, –CH_2Ph), 4.33–4.31 (m, 2H, –OCH_2C≡C), 4.12 (d, J=3.6 Hz, 1H, –C*H*I), 3.71–3.49 (m, 2H, –NCH_2CH_2), 2.48–2.11 (m, 3H, –C≡C*H* and –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.4, 154.2, 136.7, 127.5, 128.5, 129.1, 95.4, 94.3, 80.2, 79.8, 75.2, 67.7, 56.6, 55.5, 45.2, 33.1, 32.5, 26.5, 26.0; HRMS (EI) *m/z* calcd for ($C_{15}H_{16}INO_3^+$): 385.0175, found: 385.0173.

4.2.2. *trans*-Benzyl-2-(3-butynyloxy)-3-iodo-1-pyrrolidine carboxylate (2b, Table 1, entry 2). Prepared following method A using 3-butyn-1-ol (295 µl, 3.03 mmol), *N*-iodosuccinimide (716 mg, 3.03 mmol) and **1a** (513 mg, 2.53 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2b** (760 mg, 75%) as a colorless oil; R_f=0.42 (20% EtOAc/80% hexane); IR (film) ν 3294, 3032, 2953, 1712, 1497, 1407, 1192, 1112, 916, 771, 697, 604 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, 7.35 (br, 5*H*, Ar), 5.42–5.54 (m, 1H, NC*H*–O), 5.22–5.18 (m, 2H, –CH_2Ph), 4.25 (d, J=4.8 Hz, 1H, –C*H*I), 3.76–3.53 (m, 4H, –NCH_2 and –OCH_2) 2.45–1.98 (m, 5H, –C≡C*H*, –NCH_2CH_2 and –CH_2C≡CH); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.2, 155.3, 136.3, 128.4, 128.3, 128.0, 127.9, 96.2, 96.1, 81.7, 81.5, 69.5, 69.4, 67.3, 67.1, 66.7, 66.4, 33.6, 32.7, 26.9, 26.3, 19.9, 19.8; HRMS (EI) *m/z* calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0316.

4.2.3. *trans*-Benzyl-3-iodo-2-[(1-methyl-2-propynyl)oxy]-1-pyrrolidinecarboxylate (2c, Table 1, entry 3). Prepared following method A using 3-butyn-2-ol (238 µl, 2.95 mmol), *N*-iodosuccinimide (698 mg, 2.95 mmol) and **1a** (500 mg, 2.46 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2c** (487 mg, 50%) as a colorless oil; R_f=0.22 (10% EtOAc/90% hexane); IR (film) ν 3294, 2983, 2895, 1706, 1558, 1539, 1505, 1456, 1405, 1358, 1338, 1282, 1259, 1212, 1186, 1113, 1045, 1008, 912, 734, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5H, Ar), 5.67 (s, 0.5H, NC*H*O), 5.53 (s, 0.5H, NC*H*O), 5.27–5.07 (m, 2H, –CH_2Ph), 4.57 (q, J=6.6 Hz, 0.5H, –C*H*CH$_3$), 4.38 (t, J=6.8 Hz, 1H, –C*H*I), 4.22 (q, J=6.7 Hz, 0.5H, –C*H*CH$_3$), 3.70–3.52 (m, 2H, –NCH_2), 2.56–2.39 (m, 2H, –NCH_2CH_2 and –C≡C*H*), 2.14–2.08 (m, 1H, –NCH_2CH_2), 1.38 (d, J=6.6 Hz, 1.5H, –CHCH_3), 1.24 (d,

J=6.8 Hz, 1.5H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 154.5, 136.2, 136.1, 128.4, 128.1, 128.1, 128.0, 127.7, 94.8, 94.3, 83.9, 94.3, 83.9, 83.7, 73.1, 67.4, 67.2, 64.5, 63.8, 44.8, 44.7, 33.6, 32.7, 27.8, 27.0, 22.1, 21.9; HRMS (EI) m/z calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0316.

4.2.4. *trans*-Benzyl-2-(2-butynyloxy)-3-iodo-1-pyrrolidinecarboxylate (2d, Table 1, entry 4). Prepared following method A using 2-butyn-1-ol (115 µl, 1.54 mmol), *N*-iodosuccinimide (362 mg, 1.54 mmol) and **1a** (260 mg, 1.28 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 5% EtOAc/95% hexane) affording **2d** (334 mg, 65%) as a colorless oil; R_f=0.68 (10% EtOAc/90% hexane); IR (film) ν 3032, 2954, 1712, 1498, 1407, 1359, 1285, 1192, 1113, 1043, 975, 912, 771, 698, 603 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5*H*, Ar), 5.9–5.7 (m, 0.4H, –NC*H*–O), 5.6 (s, 0.3H, –NC*H*–O), 5.5 (s, 0.3H, –NC*H*–O), 5.26–5.1 (m, 2H, –CH_2Ph), 4.56–4.20 (m, 2H, –OCH_2-C≡CH), 4.08–4.07 (m, 1H, –C*H*I), 3.72–3.5 (m, 2H, –NCH_2), 2.62–2.46 (m, 1H, –NCH$_2$CH_2), 2.14–2.04 (m, 1H, –NCH$_2$CH_2), 1.84 (s, 1.5H, –C≡CCH_3), 1.77(s, 1.5H, –C≡CCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.5, 136.1, 136.0, 128.5, 128.4, 128.3, 128.1, 127.8, 95.0, 94.2, 89.8, 89.2, 82.8, 82.7, 74.9, 74.6, 67.4, 67.2, 57.2, 56.5, 45.1, 44.7, 33.6, 33.0, 26.5, 26.3, 3.6, 3.5; HRMS (EI) m/z calcd for ($C_{16}H_{18}INO_3^+$): 399.0331, found: 399.0326.

4.2.5. *trans*-1-Acetyl-3-iodo-2-(2-propynyloxy)pyrrolidine (2e, Table 1, entry 5). Prepared following method A using propargyl alcohol (377 µl, 6.48 mmol), *N*-iodosuccinimide (1.53 g, 6.48 mmol) and *N*-[(methyl)carbonyl]-2-pyrroline **1b** (0.60 g, 5.4 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording **2e** (1.31 g, 83%) as a colorless oil; R_f=0.28 (30% EtOAc/70% hexane); IR (film) ν 3290, 2950, 1667, 1651, 1404, 1360, 1263, 1181, 1143, 1055, 921, 845 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$), rotamers, δ 5.41 (s, 0.5H, –NC*H*O), 5.16 (s, 0.5H, –NC*H*O), 4.24 (d, J=4.8 Hz, 0.5H, –C*H*I), 4.06–3.97 (m, 2.5H, –C*H*I and –OCH_2), 3.34–3.28 (m, 2H, N–CH_2), 2.51–2.50 (m, 0.4H, C≡C*H*), 2.36–2.14 (m, 2.6H, C≡C*H* and –NCH$_2$CH_2), 1.89 (s, 1.5H, CH_3), 1.84 (s, 1.5H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.5, 169.6, 93.9, 92.3, 79.3, 77.9, 75.8, 74.2, 56.3, 54.4, 45.0, 43.5, 33.2, 31.3, 26.0, 25.7, 21.8, 21.4; HRMS (EI) m/z calcd for ($C_9H_{12}INO_2+H^+$): 293.9991, found: 293.9976.

4.2.6. *trans*-Benzyl 3-iodo-2-methoxy-1-pyrrolidinecarboxylate (2f, Table 1, entry 6). Prepared following method A using *N*-iodosuccinimide (893 mg, 3.78 mmol), methanol (2 ml) and **1a** (630 mg, 3.15 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2f** (1.05 g, 92%) as a colorless oil; R_f=0.48 (20% EtOAc/80% hexane); IR (film) ν 3016, 2950, 2891, 2822, 1709, 1500, 1445, 1406, 1362, 1337, 1283, 1175, 1111, 1072, 954, 915, 773, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.31–7.19 (m, 5H, Ar), 5.38 (s, 0.6H, –NC*H*O), 5.27 (s, 0.4H, –NC*H*O), 5.18–5.06 (m, 2H, –CH_2Ph), 4.15 (d, J=4.6 Hz, 1H, –C*H*I), 3.66–3.59 (m, 1H, –NCH_2), 3.46 (t, J=8.8 Hz, 1H, –NCH_2), 3.36 (s, 1.5H, CH_3), 3.22 (s, 1.5H, CH_3), 2.48–2.41 (m, 1H, –NCH$_2$CH_2), 2.08–2.03 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.7, 155.9, 136.4, 128.5, 128.1, 127.8, 127.7, 96.7, 96.2, 67.4, 67.2, 66.7, 56.4, 56.0, 44.9, 44.7, 33.8, 32.9, 29.7, 26.5, 25.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.8(+), 127.7(+), 96.7(+), 96.2(+), 67.4(−), 67.2(−), 66.7(−), 56.4(+), 56.0(+), 44.9(−), 44.7(−), 33.8(−), 32.9(−), 29.7(−), 26.5(+), 25.8(+); HRMS (EI) m/z calcd for ($C_{13}H_{16}INO_3^+$): 361.0165, found: 361.0175.

4.2.7. 1-*tert*-Butyl-2-methyl-(2*S*(*R*),4*R*(*S*),5*S*)-4-iodo-5-(2-propynyloxy)-1,2-pyrrolidinecarboxylate (2g and 2g′, Table 1, entry 7). Prepared following method A using propargyl alcohol (78 µl, 1.35 mmol), *N*-iodosuccinimide (308 mg, 1.35 mmol) and **1c** (252 mg, 1.12 mmol) to yield the iodoether derivative which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording **2g** and **2g′** (260 mg, 57%) as a colorless oil; R_f=0.27 (10% EtOAc/90% hexane); $[\alpha]_D^{20}$=−25.0 ($CHCl_3$, c=0.105 g/100 ml); IR (film) ν 3269, 2977, 2952, 1760, 1713, 1478, 1439, 1378, 1320, 1258, 1203, 1165, 1054, 980, 903, 860, 804, 773, 749, 665 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.59–5.54 (m, 0.8H, –NC*H*O), 5.38 (s, 0.2H, –NC*H*O), 4.61–4.19 (m, 4H, –OCH_2, NC*H*CO$_2$CH$_3$ and –C*H*I), 3.70–3.68 (m, 3H, CO$_2$CH_3), 3.08–2.93 (m, 0.5H, –C≡C*H*), 2.63–2.54 (m, 0.5H, –C≡C*H*), 2.52–2.54 (m, 2H, –NCHCH_2), 1.45 (s, 4.5H, –C(CH_3)$_3$), 1.38 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 171.9, 171.8, 171.6, 171.3, 154.0, 153.3, 153.2, 96.5, 94.3, 93.9, 81.5, 81.2, 75.2, 74.8, 74.4, 74.3, 58.8, 58.5, 58.1, 57.6, 56.9, 55.5, 54.4, 52.3, 52.1, 38.6, 38.4, 37.7, 37.1, 28.3, 28.1, 25.2, 24.3, 22.1, 20.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 96.5(+), 94.3(+), 93.9(+), 81.5(+), 81.2(+), 75.2 (+), 74.8(+), 74.4(+), 74.3(+), 58.8(+), 58.5(+), 58.1(+), 57.6(−), 56.9(−), 55.5(−), 54.4(−), 52.4(+), 52.3(+), 52.1(+), 38.6(−), 38.4(−), 37.7(−), 37.1(−), 28.3(+), 28.1(+), 25.2(+), 24.3(+), 22.1(+), 20.7(+).

4.3. Method B. General procedure for iodoetherification with alkenols

To a solution *N*-acyl-2-pyrroline **1** (1.0 mequiv) and the alcohol (1.2 mequiv) in dry dichloromethane under argon at −78 °C was added via cannula a solution of *N*-iodosuccinimide (1.0 mequiv) in dry dichloromethane (50 ml) and cooled to −78 °C. The resulting mixture was stirred for 10 min and then poured into a cold saturated aqueous solution of $NaHCO_3$. The aqueous phase was extracted once with dichloromethane (40 ml). The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the iodoether derivative **2**, which was purified by flash column chromatography.

4.3.1. *trans*-Benzyl-2-(allyloxy)-3-iodo-1-pyrrolidinecarboxylate (2h, Table 1, entry 8). Prepared following method B using **1a** (1.5 g, 7.4 mmol), allyl alcohol (610 µl, 8.9 mmol) and *N*-iodosuccinimide (1.74 g, 7.39 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2h** (2.1 g, 74%) as a colorless oil; R_f=0.47 (10% EtOAc/90% hexane); IR (film) ν 3031, 2953, 2896, 1713,

1683, 1652, 1506, 1457, 1398, 1360, 1338, 1286, 1193, 1115, 1056, 917, 878, 771, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.24 (m, 5H, Ar), 5.92–5.84 (m, 0.5H, C*H*=CH_2), 5.82–5.70 (m, 0.5H, C*H*=CH_2), 5.54 (s, 0.5H, –NC*H*O), 5.42 (s, 0.5H, –NC*H*O), 5.30–5.07 (m, 4H, –CH_2Ph and –CH=CH_2), 4.23 (d, J=4.8 Hz, 2H, OCH_2), 3.94 (tt, J=6.8, 1.2 Hz, 1H, –C*H*I), 4.10 (tt, J=6.5, 1.2 Hz, 1H, –C*H*I), 3.74–3.65 (m, 1H, –NCH_2), 3.56–3.50 (m, 1H, –NCH_2), 2.61–2.50 (m, 1H, –NCH_2CH_2), 2.12 (ddd, J= 14.8, 6.8, 2.8 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.5, 154.6, 136.2, 136.1, 134.2, 133.8, 128.4, 128.1, 128.0, 127.9, 127.6, 117.4, 117.3, 95.1, 94.5, 69.9, 69.4, 67.3, 67.1, 44.8, 44.64, 33.68, 32.7, 27.0, 26.3; HRMS (EI) m/z calcd for ($C_{15}H_{18}INO_3^+$): 387.0331, found: 387.0323.

4.3.2. *trans*-Benzyl-2-(3-butenyloxy)-3-iodo-1-pyrrolidinecarboxylate (2i, Table 1, entry 9). Prepared following method B using **1a** (340 mg, 1.68 mmol), 3-buten-1-ol (177 µl, 2.02 mmol) and *N*-iodosuccinimide (397 mg, 1.68 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2i** (414 mg, 62%) as a colorless oil; R_f=0.38 (10% EtOAc/90% hexane); IR (film) ν 3067, 2951, 2895, 1711, 1640, 1105, 1360, 1335, 1283, 1210, 1192, 1112, 1062, 915, 876, 771, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.34–7.26 (m, 5H, Ar), 5.81–5.62 (m, 1H, C*H*=CH_2), 5.50 (s, 0.5H, –NC*H*O), 5.38 (s, 0.5H, –NC*H*O), 5.24–4.96 (m, 4H, –CH_2Ph and –CH=CH_2), 4.18 (d, J=3.6 Hz, 1H, –C*H*I), 3.72–3.40 (m, 4H, –OCH_2 and –NCH_2), 2.55–2.43 (m, 1H, –NCH_2CH_2), 2.28 (dq, J=6.8, 1.2 Hz, 1H, CH_2CH=CH_2), 2.18 (dq, J=6.8, 1.2 Hz, 2H, –CH_2CH=CH_2), 2.07 (dd, J=14.0, 6.4 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.2, 154.3, 136.1, 136.0, 134.6, 134.3, 128.2, 127.8, 127.7, 127.6, 127.4, 116.3, 95.1, 94.6, 67.8, 67.5, 67.0, 66.8, 44.6, 44.4, 33.9, 33.7, 33.5, 32.5, 26.9, 26.3; HRMS (EI) m/z calcd for ($C_{16}H_{20}INO_3^+$): 401.0488, found: 401.0494.

4.3.3. *trans*-Benyzl-3-iodo-2-([(2*E*)-3-phenyl-2-propenyl]oxy(-1-pyrrolidinecarboxylate (2j, Table 1, entry 10). Prepared following method B using **1a** (305 mg, 1.50 mmol), cinnamyl alcohol (241 mg, 1.8 mmol) and *N*-iodosuccinimide (353 mg, 1.5 mmol) to yield the iodoether derivative which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2j** (514 mg, 74%) as a yellow oil; R_f=0.24 (20% EtOAc/80% hexane); IR (film) ν 3028, 2951, 2895, 1712, 1496, 1448, 1403, 1356, 1328, 1267, 1210, 1177, 1112, 1070, 1050, 967, 913, 878, 735, 593 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.41–7.24 (m, 10H, Ar), 6.64 (d, J=16.0 Hz, 0.5H, CH=C*H*Ph), 6.46 (d, J=16.0 Hz, 0.5H, –CH=C*H*Ph), 6.33–6.26 (m, 0.5H, –C*H*=CHPh), 6.19–6.12 (m, 0.5H, –C*H*=CHPh), 5.66 (s, 0.5H, –NC*H*O), 5.54 (s, 0.5H, –NC*H*O), 5.32–5.16 (m, 2H, –CH_2Ph), 4.41–4.31 (m, 1H, –OCH_2), 4.29 (d, J=5.2 Hz, 1H, –C*H*I), 4.18–4.11 (m, 1H, –OCH_2), 3.80–3.63 (m, 1H, –NCH_2), 3.61–3.55 (m, 1H, –NCH_2), 2.66–2.53 (m, 1H, –NCH_2CH_2), 2.12 (dd, J= 14.4, 6.4 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 154.5, 136.4, 136.1, 136.0, 128.3, 127.9, 127.9, 127.8, 127.6, 127.5, 126.3, 126.3, 125.3, 124.8, 95.0, 94.3, 69.5, 68.9, 67.2, 67.0, 44.7, 44.5, 33.6, 32.6, 26.9, 26.3; HRMS (EI) m/z calcd for ($C_{12}H_{13}INO_3^+$, corresponds to β-iodopyrrolidine unit): 329.9991, found: 329.9994.

4.3.4. *trans*-Benzyl-2-([(2*E*)-4-ethoxy-4-oxo-2-butenyl]-oxy(-3-iodo-1-pyrrolidinecarboxylate (2k, Table 1, entry 11). Prepared following method B using **1a** (406 mg, 2.0 mmol), ethyl-(2*E*)-hydroxy-2-butenoate (312 mg, 2.4 mmol) and *N*-iodosuccinimide (460 mg, 2.0 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2k** (570 mg, 62%) as a yellow oil; R_f=0.42 (20% EtOAc/80% hexane); IR (film) ν 2979, 2898, 1737, 1716, 1661, 1446, 1403, 1360, 1281, 1179, 1281, 1179, 1109, 1031, 975, 915, 878, 772, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.24 (m, 5H, Ar), 6.88 (td, J=15.6, 4.4 Hz, 0.6H, –C*H*=CHC(=O)), 6.77 (td, J=15.6, 4.0 Hz, 0.4H, C*H*=CH–C(=O)), 6.00 (td, J= 1.6, 16.0 Hz, 0.6H, CH=C*H*–C(=O)), 5.90 (td, J=2.0, 16.0 Hz, 0.4H, CH=C*H*–C(=O)), 5.56 (s, 0.5H, –NC*H*O), 5.44 (s, 0.5H, –NC*H*O), 5.27–5.10 (m, 2H, –CH_2Ph), 4.36 (ddd, J=16.0, 4.4, 2.0 Hz, 0.5H, –CH_2CH=CH), 4.28 (ddd, J=16.0, 4.4, 2.0 Hz, 0.5H, –CH_2CH=CH),4.22 (d, J= 7.2 Hz, 1H, –C*H*I), 4.16 (q, J=4.8 Hz, 2H, –OCH_2), 4.12–4.07 (m, 1H, –CH_2CH=CH), 3.76–3.41 (m, 2H, –NCH_2), 2.61–2.48 (m, 1H, –NCH_2CH_2), 1.6–1.9 (m, 1H, –NCH_2CH_2), 1.26 (t, J=7.2 Hz, 3H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 173.3, 166.2, 166.0, 155.8, 155.6, 154.7, 143.7, 143.2, 136.2, 136.0, 128.6, 128.5, 128.5, 128.3, 128.1, 128.0, 127.9, 127.7, 121.3, 121.1, 95.5, 95.41, 94.9, 94.9, 67.8, 67.5, 67.4, 67.3, 67.3, 67.2, 66.8, 60.3, 60.4, 60.3, 45.0, 44.8, 44.6, 33.8, 33.7, 32.8, 32.8, 31.0, 30.8, 26.8, 26.3, 26.1, 25.7, 25.1, 24.9, 14.2; FAB m/z calcd for ($C_{18}H_{22}INO_5+Na^+$): 481.98, found: 482.20.

4.3.5. *trans*-Benzyl-3-iodo-2-phenoxy-1-pyrrolidinecarboxylate (2l, Table 1, entry 12). Prepared following method B using **1a** (554 mg, 2.73 mmol), phenol (309 mg, 3.28 mmol) and *N*-iodosuccinimide (774 mg, 3.28 mmol) to yield the iodoether derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **2l** (0.667 g, 57%) as a colorless oil; R_f=0.51 (20% EtOAc/80% hexane); IR (film) ν 3063, 3033, 2954, 2896, 1716, 1596, 1488, 1455, 1407, 1354, 1284, 1210, 1186, 1117, 1079, 1053, 1027, 1002, 969, 917, 810, 752, 732, 692 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.43–7.06 (m, 7H, Ar), 7.04 (t, J=8.0 Hz, 2H, Ar), 6.9 (d, J=7.6 Hz, 1H, Ar), 6.23 (s, 0.5H, –NC*H*O), 6.10 (s, 0.5H, –NC*H*O), 5.24–5.10 (m, 2H, –CH_2Ph), 4.36 (dt, J=8.4, 4.8 Hz, 1H, –C*H*I), 3.84–3.69 (m, 2H, –NCH_2), 2.71–2.57 (m, 1H, –NCH_2CH_2), 2.23–1.32 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.9, 154.5, 153.9, 135.9, 135.7, 129.5, 128.3, 128.1, 127.9, 127.6, 127.2, 122.2, 122.1, 116.6, 116.5, 94.5, 94.1, 67.2, 67.1, 45.0, 44.8, 33.2, 32.4, 26.3, 25.5; HRMS (EI) m/z calcd for ($C_{18}H_{18}INO_3^+$): 423.0331, found: 423.0316.

4.3.6. 1-*tert*-Butyl-2-methyl-(2*S*,4*R*(*S*),5*S*(*R*))-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m and 2m′, Table 1, entry 13). Prepared following method B using **1c** (520 mg, 2.32 mmol), 3-buten-1-ol (473 µl, 6.96 mmol) and *N*-iodosuccinimide (550 mg, 2.34 mmol). Purification by flash chromatography (SiO_2, 10% EtOAc/90% hexane)

afforded the two diastereomers **2m**, **2m′** (835 mg, 88%) as colorless oils

4.3.7. 1-*tert*-Butyl-2-methyl-(2*S*,4*R*,5*S*)-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m, Table 1, entry 13). (480 mg, 57%); R_f=0.30 (4% EtOAc/96% hexane); $[\alpha]_D^{20}$=+48.39 (c=0.81 g/100 ml, $CHCl_3$); IR (film) ν 3080, 2977, 2952, 2931, 2869, 1760, 1719, 1647, 1478, 1456, 1438, 1377, 1314, 1259, 1169, 1062, 1014, 972, 934, 903, 875, 852, 804, 772, 750, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.94–5.84 (m, 1H, –C*H*=CH_2), 5.54 (s, 0.5H, –NC*H*O), 5.45 (s, 0.5H, –NC*H*O), 5.28 (s, 0.5H, –CH=CH_2), 5.23 (s, 0.5H, –CH=CH_2), 5.16–5.12 (m, 1H, –CH=CH_2), 4.64 (t, J=8.6 Hz, 0.5H, –NC*H*CO_2CH_3), 4.65 (t, J=8.44 Hz, 0.5H, –NC*H*CO_2CH_3), 4.54 (t, J=7.6 Hz, 0.5H, –NC*H*CO_2CH_3), 4.25–4.21 (m, 2H, –OCH_2), 4.10 (dd, J=12.4, 5.9 Hz, 0.5H, –C*H*I), 4.01 (dd, J=12.3, 5.5 Hz, 0.5H, –C*H*I), 3.71 (s, 3H, –OCH_3), 2.68–2.62 (m, 1H, CH_2CHI), 2.49 (dt, J=7.5, 17.8 Hz, 1H, –CH_2CHI), 1.48 (s, 4.5H, –C(CH_3)$_3$), 1.42 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.2, 154.1, 134.4, 134.3, 117.0, 94.9, 94.5, 93.7, 81.6, 81.2, 70.9, 69.0, 68.3, 58.9, 58.2, 52.3, 52.2, 38.7, 37.9, 29.6, 28.3, 28.1, 25.6, 24.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 134.4(+), 117.0(−), 94.9(+), 94.5(+), 69.0(−), 68.3(−), 58.9(+), 58.2(+), 52.3(+), 52.2(+), 38.7(−), 37.9(−), 28.3(+), 28.1(+), 25.6(+), 24.8(+).

4.3.8. 1-*tert*-Butyl-2-methyl-(2*S*,4*S*,5*R*)-5-(allyloxy)-4-iodo-1,2-pyrrolidenecarboxylate (2m′, Table 1, entry 13). (355 mg, 43%); R_f=0.30 (7% EtOAc/93% hexane); $[\alpha]_D^{20}$=−56.38 (c=0.94 g/100 ml, $CHCl_3$); IR (film) ν 3080, 2928, 2858, 1763, 1714, 1647, 1478, 1456, 1437, 1375, 1323, 1296, 1258, 1166, 1122, 1053, 1011, 927, 904, 861, 843, 814, 772, 749, 700, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.89–5.85 (m, 1H, –C*H*=CH_2), 5.58 (s, 0.5H, –NC*H*O), 5.36 (s, 0.5H, –NC*H*O), 5.29 (s, 0.5H, –CH=CH_2), 5.25 (s, 0.5H, –CH=CH_2), 5.18 (1H, dd, J=9.8, 5.5 Hz, –CH=CH_2), 4.52 (d, J=9.7 Hz, 0.5H, –NC*H*CO_2CH_3), 4.43 (d, J=9.7 Hz, 0.5H, –NC*H*CO_2CH_3), 4.20–4.05 (m, 3H, –OCH_2 and –C*H*I), 3.74 (s, 3H, –OCH_3), 3.09–3.02 (m, 1H, –NCHCH_2), 2.48 (dd, J=15.0, 6.1 Hz, 1H, –NCHCH_2), 1.49 (s, 4.5H, –C(CH_3)$_3$), 1.42 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.0, 171.4, 153.3, 134.4, 134.0, 117.7, 117.6, 116.5, 96.5, 96.3, 81.2, 81.0, 71.1, 70.6, 58.6, 58.1, 52.3, 52.1, 38.4, 37.2, 31.88, 29.6, 29.3, 28.3, 28.1, 22.6, 22.1, 20.7, 14.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ δ 134.4(+), 134.0(+), 117.7(−), 96.5(+), 96.3(+), 71.1(−), 70.6(−), 58.6(+), 58.1(+), 52.3(+), 52.1(+), 38.4(−), 37.2(−), 29.6(−), 29.3(−), 28.3(+), 28.1(+), 22.1(+), 20.7(+).

4.4. Method C. General procedure for iodocarbamation

A solution of I_2 (1.2 mequiv) in dry THF was added dropwise to a stirred solution of the *N*-[(benzyloxy)carbonyl]-2-pyrrolidine **1a** (1.0 mequiv) and the corresponding carbamate (1 or 2 mequiv) in dry THF at −78 °C and under nitrogen. The resulting mixture was stirred for 10 min and then water and dichloromethane were added. The organic phase was separated and the aqueous phase washed with dichloromethane. The combined organic layers were washed with a $Na_2S_2O_3$ (0.5 M), and with saturated aqueous Na_2CO_3. The organic phase was dried over Na_2SO_4 and the solvent removed under vacuo. Purification by column chromatography afforded the 3-iodo-2-carbamate pyrrolidine derivative **3**.

4.4.1. Benzyl 2-[(*tert*-butoxycarbonyl)amino]-3-iodo-1-pyrrolidinecarboxylate (3a, Table 2, entry 1). Prepared following method C using **1a** (203 mg, 1 mmol), *tert*-butylcarbamate (119 mg, 1 mmol) and iodine (305 mg, 1.2 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *trans*/*cis* mixture of **3a** (72/28) (332 mg, 74%) as an orange foam; R_f=0.46 (30% EtOAc/70% hexane); IR (film) $\nu_{máx}$ 3320, 2978, 1696, 1499, 1412, 1365, 1280, 1249, 1158, 1117, 1050, 1025, 974, 910, 771, 731, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.19 (m, 5H, Ar), 5.66–5.55 (m, 1H, –NC*H*N–), 5.26 (br, 1H, –N*H*), 5.20–5.04 (m, 2H, –CH_2Ph), 4.36–4.24 (m, 1H, –C*H*I), 3.63–3.45 (m, 2H, –NC$H_2$$CH_2$), 2.31–2.01 (m, 2H, –$NCH_2CH_2$), 1.32 (br, 9H, –C(C$H_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.3, 153.9, 136.3, 128.5, 128.1, 127.9, 127.8, 127.4, 80.3, 75.7, 74.6, 67.2, 45.3, 33.8, 33.0, 28.3, 27.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.9(+), 127.8(+), 127.4(+), 80.3(+), 75.7(+), 74.6(+), 67.2(−), 45.3(−), 33.8(−), 33.0(−), 28.3(+), 27.1(+); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=360 K), rotamers, δ 7.39–7.35 (m, 5H, Ar), 5.67 (d, J=5.6 Hz, 0.73H, –NC*H*N–), 5.56 (d, J=6.0 Hz, 0.27H, –NC*H*N–), 5.27–5.2 (m, 2H, –CH_2Ph), 4.9 (d, J=4.3 Hz, 1H, –N*H*), 4.72 (s, 0.27H, –C*H*I), 4.46 (d, J=4.0 Hz, 0.73H, –C*H*I), 3.83–3.72 (m, 1H, –NC$H_2$$CH_2$), 3.63–3.54 (m, 1H, –NC$H_2$$CH_2$), 2.31–2.01 (m, 2H, –$NCH_2CH_2$), 1.48 (br, 9H, –C(C$H_3$)$_3$); HRMS (EI) *m*/*z* calcd for ($C_{17}H_{23}IN_2O_4$): 447.0703, found: 447.0791.

4.4.2. Benzyl 2-[(benzyloxycarbonyl)amino]-3-iodo-1-pyrrolidinecarboxylate (3b, Table 2, entry 2). Prepared following method C using **1a** (340 mg, 1.67 mmol), benzyl carbamate (504 mg, 3.34 mmol) and iodine (509 mg, 2.0 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 1:4:4, EtOAc:Hex:$CHCl_3$), followed by preparative thin layer chromatography (40% EtOAc/60% hexane) affording a *trans*/*cis* mixture (77/23) of **3b** (569 mg, 71%) as an orange foam; R_f=0.5 (30% EtOAc/70% hexane); IR (film) ν 3304, 3062, 3032, 2953, 2893, 1693, 1586, 1518, 1454, 1410, 1351, 1279, 1244, 1205, 1177, 1116, 1045, 1027, 976, 914, 870, 772, 736, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.19 (m, 10H, Ar), 5.66 (d, J=6.6 Hz, 0.45H, –NC*H*N–), 5.64 (s, 0.55H, –NC*H*N–), 5.33 (br, 0.45H, –N*H*), 5.29 (br, 0.55H, N*H*), 5.09–5.47 (m, 4H, 2×–CH_2Ph), 4.39 (br, 0.45H, –C*H*I), 4.28 (br, 0.55H, –C*H*I), 3.66–3.59 (m, 1H, –NC$H_2$$CH_2$), 3.51–3.41 (m, 1H, –NC$H_2$$CH_2$), 2.30–2.20 (m, 1H, –$NCH_2CH_2$), 2.07 (dd, J=13.9, 5.6 Hz, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 154.3, 136.2, 136.0, 128.6, 128.3, 128.0, 127.9, 127.6, 75.7, 74.9, 67.3, 67.0, 45.4, 34.1, 33.1, 27.2. 26.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.3(+), 128.3(+), 128.0(+) 127.9(+), 127.6(+), 75.7(+), 74.8(+), 67.3(−), 67.0(−), 45.4(−), 34.1(−), 33.1(−), 27.2(+), 26.3(+).

4.4.3. Benzyl-3-iodo-2-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (3c, Table 2, entry 3). Prepared following method C using **1a** (3.41 g, 16.8 mmol), methyl carbamate (2.6 g, 33.6 mmol) and iodine (5.12 g, 20.2 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane). The excess carbamate was further removed washing with Et_2O/hexane (20%/80%) to affording a *trans*/*cis* mixture (73/27) of **3c** (4.76 g, 70%) as an orange foam; R_f=0.26 (30% EtOAc/70% hexane); IR (film) ν 3301, 2954, 2885, 1703, 1699, 1694, 1683, 1520, 1418, 1353, 1250, 1179, 1114.6, 1044, 772, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.28 (m, 5H, Ar), 5.73–5.67 (m, 1H, –NC*H*N–), 5.58 (br, 1H, –N*H*), 5.21–5.10 (m, 2H, –CH_2Ph), 4.46 (br, 0.27H, –C*H*I), 4.34 (br, 0.73H, –C*H*I), 3.75–3.54 (m, 5H, –NCH_2 and –OCH_3), 2.43–2.37 (m, 1H, –NCH$_2$CH_2), 2.35–2.14 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.3, 154.5, 136.4, 128.7, 128.4, 128.3, 128.1, 127.9, 76.0, 75.1, 67.6, 52.5, 45.6, 34.5, 33.4, 27.2, 26.1; HRMS (EI) *m*/*z* calcd for ($C_{14}H_{17}IN_2O_4$+H^+) requires: 405.0311, found: 405.0314.

4.4.4. Benzyl-3-iodo-2-{[(4-methylphenyl)sulfonyl]-amino}-1-pyrrolidinecarboxylate (3d, Table 2, entry 4). Prepared following method C using **1a** (335 mg, 1.65 mmol), 4-methylbenzenesulfonamide ($TsNH_2$; 565 mg, 3.3 mmol) and iodine (503 mg, 1.98 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *trans*/*cis* mixture (69/31) of **3d** (258 mg, 32%) as a white solid which decomposed within a few days at 4 °C; R_f=0.26 (30% EtOAc/70% hexane); IR (film) ν 3250, 1701, 1698, 1597, 1496, 1410, 1337, 1278, 1161, 1118, 1094, 1038, 916, 814, 771, 733, 697, 667, 576, 542 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.79 (d, J=8.2 Hz, 2H, Ar), 7.66 (d, J=7.7 Hz, 1H, Ar), 7.32–7.10 (m, 7H, Ar), 5.67–5.65 (m, 1H, –NC*H*N–), 5.23–4.97 (m, 2H, –CH_2Ph), 4.69 (br, 0.31H, –C*H*I), 4.66 (br, 1H, –N*H*), 4.50 (d, J= 4.4 Hz, 0.69H, –C*H*I), 3.64–3.46 (m, 2H, –NCH_2), 2.57–2.29 (m, 1H, –NCH$_2$CH_2), 2.41 (s, 2.07H, Ar-CH_3), 2.34 (s, 0.93H, Ar-CH_3), 2.10 (dd, J=14.4, 5.6 Hz 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.1, 144.3, 143.7, 139.4, 136.5, 136.2, 130.0, 129.9, 128.7, 128.4, 128.3, 127.9, 127.7, 127.6, 127.4, 126.6, 67.7, 67.4, 45.5, 34.0, 32.7, 28.0, 26.4, 21.8, 21.7.

4.4.5. Benzyl-2-[(*tert*-butoxycarbonyl)amino]-3-iodo-1-piperidinecarboxylate (3e, Table 2, entry 5). Prepared following method C using benzyl 3,4-dihydro-1(2*H*)-pyridinecarboxylate **1d** (166 mg, 0.77 mmol), *tert*-butyl-carbamate (184 mg, 1.54 mmol) and iodine (196 mg, 0.77 mmol) to yield the iodocarbamate derivative which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording **3e** (0.57 mmol, 75%) as a colorless oil; R_f=0.3 (20% EtOAc/80% hexane); IR (film) ν 3485, 3323, 2976, 1694, 1597, 1515, 1423, 1165, 874, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.38–7.27 (m, 5H, Ph), 6.02 (d, J=6.4 Hz, 1H, –NC*H*N), 5.21–5.13 (m, 2H, –CH_2Ph), 4.83 (br, 1H, –N*H*), 4.52 (br, 1H, –C*H*I), 4.07 (d, J=11.2 Hz, 1H, –NCH_2CH$_2$), 3.0 (br, 1H, –NCH_2CH$_2$), 2.02–1.92 (m, 4H, –NCH$_2$(CH_2)$_2$CHI–), 1.42 (s, 9H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.1, 136.4, 128.3, 127.8, 127.6, 80.7, 79.4, 67.4, 65.1, 39.2, 29.6, 28.2, 21.2; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.3(+), 127.8(+), 127.6(+), 80.7(−), 67.4(−), 65.1(+), 39.2(−), 29.6(+), 28.2(+), 21.2(−); HRMS (EI) *m*/*z* calcd for ($C_{18}H_{25}IN_2O_4$+H^+): 461.0859, found: 461.0937.

4.5. Method D. General procedure for radical cyclizations

Iodoether derivative **2** (1.0 mequiv) in dry *t*-BuOH was added dropwise to a stirred mixture of $NaCNBH_3$ (1.2 mequiv), Bu_3SnH (0.05 mequiv) and AIBN (0.1 mequiv) in dry *t*-BuOH under nitrogen at 80 °C. After refluxing for 14 h the mixture was cooled to rt. Three portions of benzene were added and the azeotropic mixture was removed under reduced pressure. The residue was taken up in dichloromethane and filtered through celite. The solvent was removed in vacuo to yield the bicyclic derivative **4**, which was purified by flash column chromatography.

4.5.1. Benzyl-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4a, Table 3, entry 1). Prepared following method D using **2a** (400 mg, 1.04 mmol), $NaCNBH_3$ (82 mg, 1.25 mmol), Bu_3SnH (15 μl, 0.05 mmol) and AIBN (17.4 mg, 0.104 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 20% EtOAc/80% hexane) affording **4a** (192 mg, 71%) as a colorless oil; R_f=0.36 (20% EtOAc/80% hexane); IR (film) ν 2953, 1710, 1411, 1356, 1272, 1171, 1114, 1058, 1025, 888, 770, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.24 (m, 5H, Ar), 5.89–5.84 (m, 1H, –NC*H*O), 5.26–5.02 (m, 4H, –CH_2Ph and –C=CH_2), 4.4 (s, 2H, –OCH_2), 3.68–3.63 (m, 1H, –NCH_2), 3.42–3.29 (m, 2H, –CH$_2$C*H* and –NCH_2), 2.07–1.84 (m, 2H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.4, 154.2, 149.5, 136.5, 136.3, 128.2, 127.7, 127.6, 127.5, 105.4, 92.8, 92.2, 70.9, 66.7, 47.3, 46.4, 45.4, 45.2, 30.8, 30.4; HRMS (EI) *m*/*z* calcd for ($C_{15}H_{17}NO_3^+$): 259.1208, found: 259.1195.

4.5.2. Benzyl-4-methylene hexahydropyrano[2,3-*b*]pyrrole-7(2*H*)-carboxylate (4b, Table 3, entry 2). Prepared following method D using **2b** (261 mg, 0.65 mmol), $NaCNBH_3$ (52 mg, 0.78 mmol), Bu_3SnH (9 μl, 0.033 mmol) and AIBN (10 mg, 0.065 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **4b** (83 mg, 46%) as a colorless oil; R_f=0.53 (20% EtOAc/80% hexane); IR (film) ν 3067, 3033, 2954, 1713, 1651, 1498, 1450, 1415, 1354, 1285, 1271, 1256, 1235, 1178, 1121, 1085, 1055, 987, 922, 798, 771, 736, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.37–7.25 (m 5H, Ar), 5.29–5.26 (m, 1H, –NC*H*O), 5.19–5.03 (m, 2H, –CH_2Ph), 4.88–4.84 (m, 2H, C=CH_2), 4.00–3.95 (m, 1H, –NCH_2), 3.67–3.62 (m, 1H, –OCH_2), 3.46–3.35 (m, 2H, –OCH_2 and –NCH_2), 2.70–2.64 (m, 1H, –OCH$_2$CH_2), 2.46 (dt, J=14.0, 5.6 Hz, 1H, C*H*C=CH$_2$), 2.24–2.16 (m, 1H, –OCH$_2$CH_2), 2.07–2.03 (m, 1H, –NCH$_2$CH_2), 1.89–1.82 (m, 1H, and –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.9, 154.7, 154.3, 143.1, 137.1, 136.7, 136.4, 128.4, 128.4, 128.3, 128.0, 127.8, 127.8, 127.7, 111.7, 111.6, 110.3, 89.6, 86.7, 86.2, 67.0, 66.9, 66.5, 66.4, 65.4,

65.3, 47.3, 46.5, 46.2, 45.8, 45.5, 31.5, 30.5, 29.5, 27.7, 26.8, 25.7, 24.9; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1371; and the corresponding reduced product benzyl-2-(3-butynyloxy)-1-pyrrolidinecarboxylate (66 mg, 37%) as a colorless oil; R_f=0.44 (20% EtOAc/80% hexane); IR (film) ν 3296, 2955, 1714, 1640, 1506, 1456, 1404, 1382, 1288, 1180, 1102, 970, 917, 754, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.24 (m, 5H, Ar), 5.33 (d, J=4.8 Hz, 0.5H, –NC*H*O), 5.22 (d, J=5.2 Hz, 0.5H, –NC*H*O), 5.20–5.08 (m, 2H, –CH_2Ph), 3.75–3.67 (m, 1H, –NCH_2), 3.58–3.48 (m, 2H, –OCH_2), 3.40–3.33 (m, 1H, –NCH_2), 2.43 (tt, J=6.8, 2.4 Hz, 1H, –CH_2–C≡CH), 2.40 (dt, J=6.8, 4.4 Hz, 1H, –CH_2–C≡CH), 2.30–2.08 (m, 1H, –C≡C*H*), 2.07–1.73 (m, 4H, –NCH$_2$CH_2 and –NCH$_2$CH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ, 155.7, 154.7, 136.6, 136.3, 128.5, 128.2, 128.1, 128.0, 127.8, 87.9, 87.3, 87.5, 81.5, 81.2, 69.2, 69.0, 67.2, 66.9, 66.3, 65.8, 46.0, 45.8, 32.9, 32.4, 22.6, 21.7, 20.0, 19.8.

4.5.3. Benzyl-2-methyl-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4c, Table 3, entry 3). Prepared following method D using **2c** (180 mg, 0.45 mmol), $NaCNBH_3$ (35.6 mg, 0.54 mmol), Bu_3SnH (6.2 µl, 0.023 mmol) and AIBN (8 mg, 0.05 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording **4c** (75 mg, 61%) as a colorless oil; R_f=0.63 (20% EtOAc/80% hexane); IR (film) ν 2974, 2875, 1716, 1447, 1418, 1356, 1322, 1274, 1208, 1176, 1112, 1073, 1001, 900, 771, 737, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.39–7.24 (m, 5H, Ar), 5.88–5.72 (m, 1H, –NC*H*O), 5.32–5.28 (m, 1H, –C=CH_2), 5.26–4.91 (m, 3H, –CH_2Ph and C=CH_2), 4.55–4.52 (m, 1H, –OC*H*), 3.72–3.55 (1H, m, –NCH_2), 3.43–3.29 (m, 3H, –NCH_2 and C*H*C=CH$_2$), 2.11–2.02 (m, 1H, –NCH$_2$CH_2), 1.89–1.80 (m, 1H, –NCH$_2$CH_2), 1.33–1.28 (m, 3H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.8, 154.6, 154.4, 154.3, 154.2, 136.8, 136.4, 128.3, 128.0, 127.8, 105.7, 105.4, 105.2, 91.0, 90.5, 90.4, 77.9, 77.8, 76.4, 66.9, 66.8, 48.0, 47.1, 47.0, 45.6, 45.3, 45.1, 45.0, 31.8, 31.5, 30.8, 30.0, 20.9, 20.6, 19.9, 19.8; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1354.

4.5.4. Benzyl-(3*Z*)-ethylidinehexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4d, Table 3, entry 4). Prepared following method D using **2d** (140 mg, 0.35 mmol), $NaCNBH_3$ (63 mg, 0.42 mmol), Bu_3SnH (5 µl, 0.02 mmol) and AIBN (7 mg, 0.04 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 20% EtOAc/80% hexane) affording **4d** (69.0 mg, 74%) as a colorless oil; R_f=0.31 (20% EtOAc/80% hexane); IR (film) ν 2952, 1715, 1498, 1411, 1352, 1272, 1170, 1115, 882, 771, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.37–7.26 (m, 5H, Ar), 5.88–5.85 (m, 1H, –NC*H*O), 5.44–5.01 (m, 3H, –CH_2Ph and –C=C*H*CH$_3$), 4.44–4.31 (m, 2H, –OCH_2), 3.66–3.27 (m, 3H, –NCH_2 and C*H*C=CHCH$_3$), 2.10–1.80 (m, 2H, NCH$_2$CH_2), 1.64 (d, 1.5H, =CHCH_3), 1.59 (dd, J=5.4, 1.8 Hz, 1.5H, =CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 140.9, 136.8, 128.3, 127.9, 127.7, 116.2, 115.6, 110.3, 93.0, 92.8, 92.4, 92.2, 71.1, 68.9, 66.9, 66.8, 47.3, 46.4, 45.5, 45.3, 44.4, 43.5, 31.3, 30.9, 29.9, 29.4, 14.7, 14.4; HRMS (EI) *m/z* calcd for ($C_{16}H_{19}NO_3^+$): 273.1365, found: 273.1352.

4.5.5. 6-Acetyl-3-methylenehexahydro-2*H*-furo[2,3-*b*]pyrrole (4e, Table 3, entry 5). Prepared following method D using **2e** (1.08 g, 3.69 mmol), $NaCNBH_3$ (292 mg, 4.43 mmol), Bu_3SnH (50 µl, 0.18 mmol) and AIBN (62 mg, 0.4 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 60% EtOAc/40% hexane) affording **4e** (464 mg, 75%) as a colorless oil; R_f=0.19 (60% EtOAc/40% hexane); IR (film) ν 3079, 2951, 2876, 1657, 1417, 1348, 1208, 1169, 1051, 972, 895 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.78 (d, J=6.0 Hz, 0.15H, –NC*H*O), 5.55 (d, J=5.6 Hz, 0.85H, –NC*H*O), 4.89–4.83 (m, 2H, –C=CH_2), 4.21–4.18 (m, 2H, –OCH_2), 3.59–3.53 (m, 1H, –NCH_2), 3.38–3.29 (m, 0.3H, C*H*C=CH$_2$), 3.20–3.18 (m, 1H, –NCH_2), 3.11–3.04 (m, 0.7H, C*H*C=CH$_2$),1.96 (s, 2.6H, CHCH_3), 1.91–1.70 (m, 2.4H, CHCH_3 and N–CH$_2$–CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.0, 169.5, 149.1, 149.8, 105.5, 105.3, 92.7, 90.9, 70.8, 70.6, 70.5, 47.6, 47.4, 46.4, 45.7, 44.1, 30.6, 29.1, 22.5, 21.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 105.3(−), 92.7(+), 90.9(+), 70.8(−), 70.6(−), 70.5(+), 47.6(+), 47.4(+), 46.4(+), 45.7(−), 44.1(−), 30.6(−), 29.1(−), 22.5(+), 21.3(+); HRMS (EI) *m/z* calcd for ($C_9H_{13}NO_3^+$): 167.0946, found: 167.0945.

4.5.6. 6-*tert*-Butyl 5-methyl (3a*R*,5*S*,6a*S*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g, Table 3, entry 6) and 6-*tert*-butyl 5-methyl (3a*S*,5*S*,6a*R*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g′, Table 3, entry 6). Prepared following method D using a mixture of diastereomers **2g′** (240 mg, 0.59 mmol), $NaCNBH_3$ (46 mg, 0.71 mmol), Bu_3SnH (8 µl, 0.03 mmol) and AIBN (10 mg, 0.06 mmol) to yield the two bicyclic diastereomers. Purification by flash chromatography (SiO_2, 10% EtOAc/90% hexane) afforded the two diastereomers **4g** and **4g′** (101 mg, 61%) as a colorless oil.

4.5.7. 6-*tert*-Butyl 5-methyl (3a*R*,5*S*,6a*S*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g, Table 3, entry 6). (46 mg, 46%); R_f=0.3 (20%EtOAc/80% hexane); $[\alpha]_D^{20}$=−112.54 ($CDCl_3$, c=1.18 g/100 ml); IR (film) ν 2976, 1749, 1706, 1477, 1455, 1436, 1392, 1366, 1301, 1257, 1204, 1366, 1301, 1257, 1204, 1163, 1132, 1063, 1044, 1022, 980, 917, 856, 778, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.79 (d, J=5.4 Hz, 0.6H, –NC*H*O), 5.60 (d, J=5.2 Hz, 0.4H, –NC*H*O), 4.93 (s, 1H, –C=CH_2), 4.87 (s, 1H, –C=CH_2), 4.47–4.44 (m, 1H, NC*H*CO$_2$CH$_3$), 4.37–4.25 (m, 2H, –OCH_2), 3.65 (s, 3H, CO$_2$CH_3), 3.25 (br, 1H, –C*H*C=CH$_2$), 2.15–2.10 (m, 2H, –NCHCH_2), 1.41 (s, 4H, –C(CH_3)$_3$), 1.33 (s, 5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.8, 172.6, 153.9, 153.3, 148.6, 148.5, 106.0, 93.2, 93.9, 81.1, 81.0, 70.6, 70.4, 60.8, 60.4, 52.2, 52.1, 46.8, 45.8, 34.6, 33.9, 28.2, 28.1; DEPT (100 MHz, $CDCl_3$), rotamers, δ 106.0(−), 93.2(+), 93.9(+), 70.6(−), 70.4(−), 60.8(+), 60.4(+), 52.2(+), 52.1(+), 46.8(+), 45.8(+), 34.6(−), 33.9(−), 28.2(+), 28.1(+).

4.5.8. 6-*tert*-Butyl 5-methyl (3a*S*,5*S*,6a*R*)-3-methylenehexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4g′, Table 3, entry 6). (55 mg, 54%); R_f=0.3 (20%

EtOAc/80% hexane); $[\alpha]_D^{20}=+106.06$ ($CDCl_3$, $c=0.664$ g/100 ml); IR (film) ν 2953, 1755, 1706, 1456, 1436, 1392, 1366, 1280, 1257, 1164, 1122, 1069, 1053, 1034, 1008, 981, 937, 918, 890, 847, 808, 773, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.81 (d, $J=5.2$ Hz, 0.5H, –NC*H*O), 5.74 (d, $J=4.9$ Hz, 0.5H, –NC*H*O), 4.91 (d, $J=0.9$ Hz, 1H, –C=CH_2), 4.87 (d, $J=1.9$ Hz, 1H, C=CH_2), 4.53 (d, $J=1.5$ Hz, 0.5H, –NC*H*CO_2CH_3), 4.49 (d, $J=1.3$ Hz, 0.5H, –NC*H*CO_2CH_3), 4.39–4.25 (m, 2H, –OCH_2), 3.58 (s, 3H, –CO_2CH_3), 3.18 (br, 1H, –C*H*C=CH_2), 2.41–2.37 (m, 1H, –NCHCH_2), 2.13–2.10 (br, 1H, –NCHCH_2), 1.41 (s, 4.5H, –C(CH_3)$_3$), 1.34 (s, 4.5H, –C(CH_3)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.0, 149.9, 105.8, 93.7, 80.8, 70.9, 59.3, 58.7, 52.0, 46.9, 46.0, 34.4, 34.0, 29.7, 28.2.

4.5.9. Benzyl-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4h, Table 3, entry 7). Prepared following method D using **2h** (162 mg, 0.42 mmol), $NaCNBH_3$ (36 mg, 0.50 mmol), Bu_3SnH (7 μl, 0.02 mmol) and AIBN (8 mg, 0.05 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording a mixture of isomers *endo*/*exo* (95:5) **4h** (88 mg, 92%) as a white solid; mp: 42–44 °C; $R_f=0.45$ (20% EtOAc/80% hexane); IR (film) ν 2960, 2877, 1712, 1497, 1455, 1409, 1353, 1309, 1258, 1213, 185, 1118, 1096, 1050, 1006, 907, 677, 773, 737, 698, 512 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.23 (m, 5H, Ar), 5.74 (d, $J=4.8$ Hz, 0.5H, –NC*H*O), 5.68 (d, $J=5.2$ Hz, 0.5H, –NC*H*O), 5.30–5.24 (m, 0.6H, –CH_2Ph), 5.12–5.04 (m, 1.4H, –CH_2Ph), 3.92–3.88 (t, $J=7.5$ Hz, 1H, –OCH_2), 3.54–3.37 (m, 3H, –OCH_2 and –NCH_2), 2.76–2.72 (m, 1H, C*H*CHCH_3), 2.41–2.39 (m, 1H, CHC*H*CH_3), 1.98–1.72 (m, 2H, NCH_2CH_2), 1.02 (d, $J=6.8$ Hz, 0.15H, CHCH_3), 0.96 (d, $J=6.8$ Hz, 2.85H, CHCH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=350$ K) δ 7.42–7.35 (m, 5H, Ar), 5.78 (d, $J=5.4$ Hz, 1H, –NC*H*O), 5.26–5.17 (m, 2H, –CH_2Ph), 3.95 (t, $J=7.8$ Hz, 1H, –OCH_2), 3.55 (t, $J=7.8$ Hz, 2H, –NCH_2), 3.45 (t, $J=9.6$ Hz, 1H, –OCH_2), 2.83–2.76 (m, 1H, C*H*CHCH_3), 2.52–2.40 (m, 1H, CHC*H*CH_3), 1.96–1.72 (m, 2H, NCH_2CH_2), 1.11 (d, $J=6.8$ Hz, 0.15H, CHCH_3), 1.05 (d, $J=6.8$ Hz, 2.85H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.5, 136.6, 128.3, 127.7, 93.1, 92.4, 72.5, 66.8, 47.2, 46.9, 46.7, 45.7, 35.6, 23.2, 22.4, 10.9; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.3(+), 127.7(+), 93.1(+), 92.4(+), 72.5(−), 66.8(−), 47.2(−), 46.9(−), 46.7(+), 45.7(+), 35.6(+), 23.2(−), 22.4(−), 10.9(+); HRMS (EI) *m*/*z* calcd for ($C_{15}H_{19}NO_3$): 261.1365, found: 261.1372.

4.5.10. Benzyl-4-methylhexahydropyrano[2,3-*b*]pyrrole-7(2*H*)carboxylate (4i, Table 3, entry 8). Prepared following method D using **2i** (302 mg, 0.75 mmol), $NaCNBH_3$ (59 mg, 0.9 mmol), $SnBu_3H$ (10 μl, 0.04 mmol) and AIBN (12 mg, 0.07 mmol) to yield the bicyclic derivative **4i** which was purified by flash column chromatography (SiO_2, 10% EtOAc/90% hexane) affording a mixture of *endo*/*exo* isomers (40:60) (63 mg, 30%) as a colorless oil; $R_f=0.16$ (10% EtOAc/90% hexane); IR (film) ν 2954, 1712, 1453, 1411, 1352, 1271, 1213, 1185, 1116, 1077, 991, 971, 920, 771, 751, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.35–7.26 (m, 5H, Ar), 5.30–5.03 (m, 3H, –NC*H*O, –CH_2Ph), 3.92–3.30 (m, 4H, –OCH_2 and –NCH_2), 2.14–1.58 (m, 5H, –CHC*H*CH_3, –NCH_2CH_2 and –OCH_2CH_2), 1.48–1.30 (m, 1H, C*H*CHCH_3), 1.19–1.14 (m, 2H, CHCH_3), 0.96–0.90 (m, 1H, CHCH_3); ^1H NMR (400 MHz, d_2-tetracloroethane, $T=385$ K) δ 7.40–7.31 (m, 5H, Ar), 5.27 (d, $J=4.0$ Hz, 0.6H, –NC*H*O), 5.20 (br, 2H, –CH_2Ph), 5.12 (d, $J=2.2$ Hz, 0.4H, –NC*H*O), 3.89–3.86 (m, 4H, –OCH_2 and –NCH_2), 2.14–1.79 (m, 4H, –C*H*CHCH_3, –NCH_2CH_2 and –CHC*H*CH_3), 1.50–1.22 (m, 2H, –OCH_2CH_2), 1.20 (d, $J=7.2$ Hz, 1.8H, –CHCH_3), 1.02 (d, $J=6.4$ Hz, 1.2H, –CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.8, 154.4, 136.8, 136.5, 128.4, 128.3, 127.9, 127.8, 127.7, 85.8, 85.38, 82.9, 82.5, 66.8, 66.7, 65.3, 65.2, 60.5, 45.4, 45.2, 45.0, 44.8, 44.1, 43.3, 29.6, 29.5, 29.1, 28.5, 28.4, 27.4, 27.0, 26.6, 25.8, 21.3, 20.4, 20.04, 19.3, 16.4, 13.5; HRMS (EI) *m*/*z* calcd for ($C_{16}H_{21}NO_3^+$): 275.1521, found: 275.1521; and the corresponding reduced product benzyl-2-(3-butenyloxy)-1-pyrrolidinecarboxylate (13 mg, 6%) as a colorless oil; $R_f=0.37$ (10% EtOAc/90% hexane); ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.39–7.26 (m, 5H, Ar), 5.75 (br, 1H, CH_2-C*H*=CH_2), 5.14 (br, 5H, –NC*H*O, –CH_2Ph and CH_2-CH=CH_2), 3.53–3.43 (m, 4H, –NCH_2 and –OCH_2), 2.4–1.62 (m, 4H, NCH_2CH_2 and CH_2CH=CH_2); and benzyl-1-pyrrolidinecarboxylate (30 mg, 20%) as a colorless oil; $R_f=0.24$ (10% EtOAc/90% hexane); ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 7.36–7.15 (m, 5H, Ar), 5.14 (s, 2H, –CH_2Ph), 3.42–3.35 (m, 4H, –N(CH_2)$_2$), 1.86–1.79 (m, 4H, –N(CH_2CH_2)$_2$).

4.5.11. Benzyl-3-benzylhexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4j, Table 3; entry 9). Prepared following method D using **2j** (1.06 g, 2.23 mmol), $NaCNBH_3$ (181 mg, 2.75 mmol), Bu_3SnH (31 μl, 0.11 mmol) and AIBN (46 mg, 0.02 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, dichloromethane) affording a mixture of isomers *endo*/*exo*-**4j** (74:26) (510 mg, 66%) as a colorless oil; $R_f=0.16$ (dichloromethane); IR (film) ν 2941, 2875, 1712, 1602, 1500, 1454, 1410, 1353, 1278, 1213, 1187, 1091, 1038, 1006, 917, 748, 600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.16 (m, 10H, Ar), 5.75–5.70 (m, 1H, –NC*H*O), 5.32–5.08 (m, 2H, –(C=O)CH_2Ph), 3.92–3.90 (m, 1H, –OCH_2), 3.67–3.62 (m, 2H, –NCH_2), 3.48–3.43 (m, 1H, –OCH_2), 2.72–2.66 (m, 4H, C*H*CHCH_2Ph, CHC*H*CH_2Ph and CHCH_2Ph), 1.99–1.83 (m, 2H, –NCH_2CH_2); ^1H NMR (400 MHz, toluene, $T=370$ K) δ 7.38–6.93 (m, 10H, Ar), 5.78 (d, $J=5.8$ Hz, 0.24H, –NC*H*O), 5.71 (d, $J=5.04$ Hz, 0.76H, –NC*H*O), 5.17 (s, 2H, –(C=O)CH_2Ph), 3.78–3.71 (m, 1H, –OCH_2), 3.51–3.29 (m, 3H, –OCH_2 and –NCH_2), 2.48–2.32 (m, 3.52H, –CHCH_2Ph, C*H*CHCH_2Ph and CHC*H*CH_2Ph), 2.27–2.23 (m, 0.24H, C*H*CHCH_2Ph), 2.02–1.99 (m, 0.24H, CHC*H*CH_2Ph), 1.72–1.63 (m, 0.76H, CH_2CH_2N), 1.62–1.57 (m, 0.24H, –NCH_2CH_2), 1.51–1.39 (m, 0.76H, NCH_2CH_2), 1.32–1.27 (m, 0.24H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.0, 154.5, 139.8, 139.6, 128.7, 128.5, 128.4, 128.2, 127.9, 127.8, 126.2, 93.1, 92.4, 71.7, 71.0, 66.9, 47.2, 46.9, 45.6, 44.6, 43.3, 33.2, 23.3, 22.5; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.7(+), 128.5(+), 128.4,(+) 128.2(+),127.9(+), 127.8(+), 126.2(+), 93.1(+), 92.4(+), 71.7(−), 71.0(−), 66.9 (−), 47.2(−), 46.9(−), 45.6(+), 44.6(+), 43.3(+), 33.2(−),

23.3(−), 22.5(−); HRMS (EI) *m/z* calcd for ($C_{21}H_{23}NO_3^+$): 337.1678, found: 337.1696.

4.5.12. Benzyl-3-(2-ethoxy-2-oxoethyl)hexahydro-6*H*-furo[2,3-*b*]pyrrole-6-carboxylate (4k, Table 3, entry 10). Prepared following method D using **2k** (207 mg, 0.45 mmol), $NaCNBH_3$ (36 mg, 0.54 mmol), Bu_3SnH (6 μl, 0.02 mmol) and AIBN (7 mg, 0.04 mmol) to yield the bicyclic derivative which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording a mixture of isomers *endo*/*exo* (80:20) **4k** (123 mg, 82%) as a colorless oil; R_f=0.32 (30% EtOAc/70% hexane); IR (film) ν 2978, 1737, 1713, 1497, 1455, 1414, 1356, 1259, 1101, 1122, 1092, 1042, 1006, 920, 773, 736, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.34–7.24 (m, 5H, Ar), 5.73–5.68 (m, 1H, –NC*H*O), 5.27–5.04 (m, 2H, –CH_2-Ph), 4.10 (dq, J=7.7, 1.8 Hz, 2H, –OCH_2CH$_3$), 4.01 (t, J=7.9 Hz, 1H, –OCH_2), 3.57–3.40 (m, 3H, –OCH_2 and –NCH_2), 2.90–2.88 (m, 0.8H, C*H*CHCH$_2$), 2.72 (br, 0.8H, CHC*H*CH$_2$), 2.54 (br, 0.2H, C*H*CHCH$_3$), 2.41–2.30 (m, 2H, CHCH_2(C=O)), 2.05–1.20 (m, 0.2H, CHC*H*CH$_2$), 1.86–1.73 (m, 2H, –NCH$_2$CH_2), 1.22 (d, J=7.2 Hz, 3H, CH$_2$CH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=360 K) δ 7.40–7.34 (m, 5H, Ar), 5.90 (d, J=5.4 Hz, 1H, –NC*H*O), 5.25–5.20 (m, 2H, –CH_2Ph), 4.20 (q, J=7.1 Hz, 2H, –OCH_2CH$_3$), 4.05 (t, J=7.9 Hz, 1H, –OCH_2), 3.62–3.48 (m, 3H, –OCH_2 and –NCH_2), 2.96–2.92 (m, 0.8H, C*H*CHCH$_3$), 2.80–2.74 (m, 0.8H, CHC*H*CH$_3$), 2.57 (br, 0.2H, C*H*CHCH$_3$), 2.50–2.36 (m, 2H, CHCH_2(C=O)), 2.20–2.06 (m, 0.2H, CHC*H*CH$_3$), 1.90–1.81 (m, 2H, –NCH$_2$CH_2), 1.30 (d, J=7.1 Hz, 3H, CH$_2$CH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 171.8, 171.7, 154.8, 154.4, 136.5, 136.3, 128.4, 128.4, 128.32, 128.3, 128.2, 128.2, 128.1, 127.8, 92.8, 92.1, 91.4, 71.8, 70.5, 66.9, 60.6, 60.5, 48.7, 47.7, 47.1, 46.8, 45.7, 45.4, 44.4, 41.3, 37.6, 37.6, 32.0, 29.0, 28.4, 23.2, 22.6, 14.0; HRMS (EI) *m/z* calcd for ($C_{18}H_{23}NO_5^+$): 333.1576, found: 333.1590.

4.5.13. 6-*tert*-Butyl-5-methyl-(3a*R*,5*S*,6a*S*)-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4m, Table 3, entry 11). Prepared following method D using **2m** (480 mg, 1.18 mmol), $NaCNBH_3$ (93 mg, 1.4 mmol), Bu_3SnH (16 μl, 0.06 mmol) and AIBN (20 mg, 0.12 mmol) to yield the bicyclic derivative **4m** which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording a mixture of the *endo*/*exo* isomers (95:5) (320 mg, 96%) as a colorless oil; R_f=0.35 (20% EtOAc/80% hexane); $[\alpha]_D^{20}$=+55.06 (c=0.77 g/100 ml in $CHCl_3$); IR (film) ν 2974, 2879, 1756, 1710, 1478, 1454, 1436, 1366, 1315, 1258, 1198, 1170, 1124, 1099, 1045, 1001, 930, 906, 882, 858, 798, 772, 733, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.70 (br, 1H, –NC*H*O–), 4.15–4.30 (m, 1H, –NC*H*CO$_2$CH$_3$), 3.87 (t, J=7.9 Hz, 1H, –OCH_2), 3.70 (s, 3H, –OCH_3), 3.50 (dd, J=11.0, 8.6 Hz, 1H, –OCH$_2$), 2.75 (br, 1H, –NCHC*H*), 2.38 (br, 1H, –CHC*H*CH$_3$), 2.13–2.05 (m, 1H, –NCHCH_2), 1.84–1.75 (m, 1H, –NCHCH_2), 1.44 (s, 4.5H, C(CH_3)$_3$), 1.37 (s, 4.5H, –C(CH_3)$_3$), 0.93 (d, J=7.0 Hz, 0.05H, –CHCH_3), 0.85 (d, J=6.8 Hz, 0.95H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 172.0, 171.6, 153.4, 93.6, 92.8, 80.8, 71.7, 60.7, 60.4, 52.0, 46.4, 45.5, 35.9, 28.2, 27.1, 18.7, 10.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 93.6(+), 71.7(−), 60.7(+), 60.4(+), 52.0(+), 46.4(+), 45.5(+), 35.9(+), 28.2(+), 27.1(−), 18.7(+), 10.6(+).

4.5.14. 6-*tert*-Butyl-5-methyl-(3a*S*,5*S*,6a*R*)-3-methylhexahydro-6*H*-furo[2,3-*b*]pyrrole-5,6-dicarboxylate (4m′, Table 3, entry 12). Prepared following method D using **2m′** (323 mg, 0.79 mmol), $NaCNBH_3$ (62 mg, 0.95 mmol), Bu_3SnH (11 μl, 0.04 mmol) and AIBN (13 mg, 0.08 mmol) to yield the bicyclic derivative **4m′** which was purified by flash chromatography (SiO_2, 40% EtOAc/60%hexane) affording a mixture of the isomers *endo*/*exo* (95:5) (170 mg, 76%) as a colorless oil; R_f=0.5 (40% EtOAc/60% hexane); $[\alpha]_D^{20}$=−113.33 (c=1.043 g/100 ml, $CHCl_3$); IR (film) ν 2973, 1748, 1704, 1478, 1456, 1436, 1391, 1365, 1312, 1257, 1204, 1169, 1134, 1091, 1050, 1023, 1004, 983, 930, 877, 857, 781, 666 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$), rotamers, δ 5.61 (d, J=5.4 Hz, 0.5H, –NC*H*O–), 5.53 (d, J=5.3 Hz, 0.5H, –NC*H*O–), 4.23 (dd, J=19.5, 9.0 Hz, 1H, –NC*H*CO$_2$CH$_3$), 3.70 (t, J=7.7 Hz, 1H, –OCH_2), 3.52 (s, 3H, –OCH_3), 3.32–3.26 (m, 1H, –OCH_2), 2.68–2.62 (m, 1H, –NCHC*H*), 2.29–2.22 (m, 1H, –CHC*H*CH$_3$), 2.02–1.92 (m, 1H, –NCHCH_2), 1.68–1.63 (m, 1H, –NCHCH_2), 1.29 (s, 4.5H, –C(CH_3)$_3$), 0.77 (s, 4.5H, –C(CH_3)$_3$), 0.86 (d, J=6.9 Hz, 0.05H, –CHCH_3), 0.77 (d, J=6.8 Hz, 0.95H, CHCH_3); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 173.0, 172.7, 153.6, 93.4, 93.1, 80.5, 80.3, 71.5, 60.6, 60.3, 51.9, 51.8, 45.7, 4.6, 35.5, 28.1, 27.9, 27.4, 26.6, 10.20, 10.16; DEPT (100 MHz, $CDCl_3$), rotamers, δ 93.4(+), 93.1(+), 71.5(−), 60.6(+), 60.3(+), 51.9 (+), 51.8(+), 45.7(+), 4.6(+), 35.5(+), 28.1(+), 27.9(+), 27.4(−), 26.6(−), 10.2(+).

4.6. Method E. General procedure for aziridination/methanolysis

A solution of NaN(SiMe$_3$)$_2$ (1.1 mequiv) in THF was added dropwise to a stirred solution of the iodocarbamate **3** in dry THF and dry methanol (excess) at −78 °C and under nitrogen. The mixture was stirred for 5 min at −78 °C and then allowed to reach rt. A saturated aqueous solution of $NaHCO_3$ and diethyl ether were added, the organic layer separated and the aqueous layer extracted with diethyl ether. The combined organic phases were dried (Na_2SO_4) and the solvent removed in vacuo to yield the 3-carbamoyl-2-methoxy derivative **5**, which was purified by flash chromatography.

4.6.1. Benzyl-3-[*tert*-butoxycarbonyl)amino]-2-methoxy-1-pyrrolidinecarboxylate (5a, Table 4, entry 1). Prepared following method E using **3a** (298 mg, 0.67 mmol) and NaN(SiMe$_3$)$_2$ (0.5 M in toluene, 1.46 ml, 0.73 mmol) to yield the crude product which was purified by flash chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *cis*/*trans* mixture (15:85) of **5a** (184 mg, 82%) as a yellow oil; R_f=0.3 (20% EtOAc/80% hexane); IR (filme) ν 3336, 2976, 1711, 1518, 1453, 1410, 1365, 1285, 1247, 1169, 1116, 1078, 1048, 1020, 973, 915, 881, 750, 698, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.32–7.23 (m, 5H, Ar), 5.19–5.07 (m, 2H, –CH_2Ph), 5.02 (s, 0.5H, –NC*H*O), 4.95 (s, 0.5H, –NC*H*O), 4.85 (br, 1H, –N*H*), 4.10 (br, 0.3H, –C*H*NHBoc), 3.98 (br, 0.7H, –C*H*NHBoc), 3.51–3.30 (m, 5H, –NCH_2 and –OCH_3), 2.28 (br, 1H, –NCH$_2$CH_2), 1.76 (br, 1H, –NCH$_2$CH_2), 1.41 (br, 9H, –C(CH_3)$_3$); ^{13}C NMR

(100 MHz, $CDCl_3$), rotamers, δ 155.0, 136.3, 133.1, 130.9, 128.5, 128.1, 127.9, 93.0, 92.4, 67.2, 56.4, 55.9, 55.2, 54.4, 43.9, 43.7, 28.3, 28.2, 27.5, 18.5; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.1(+), 127.9(+), 93.0(+), 92.4(+), 67.2(−), 56.4(+), 55.9(+), 55.2(+), 54.4(+), 43.9(−), 43.7(−), 28.3(+), 28.2(+), 27.5(−).

4.6.2. Benzyl-3-[(benzyloxycarbonyl)amino]-2-methoxy-1-pyrrolidinecarboxylate (5b, Table 4, entry 2). Prepared following method E using **3b** (298 mg, 0.62 mmol) and $NaN(SiMe3)_2$ (0.5 M in toluene, 1.49 ml, 0.74 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 30% EtOAc/70% hexane) affording a *cis*/*trans* mixture (23:77) of **5b** (173 mg, 73%) as a yellow oil; R_f=0.38 (30% EtOAc/70% hexane); IR (film) ν 3323, 3032, 2952, 1704, 1531, 1454, 1408, 1338, 1295, 1240, 1112, 1240, 1078, 968, 912, 773, 739, 697, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.26–7.20 (m, 5H, Ar), 5.24–4.94 (m, 5.5H, –NC*H*O–, N*H* and 2×(–CH_2Ph)), 4.59 (s, 0.5H, –N*H*), 4.01 (br, 0.8H, –C*H*NHCbz), 3.89 (br, 0.2H, –C*H*NHCbz), 3.44–3.23 (m, 5H, –NCH_2CH_2 and –OCH_3), 2.26–2.16 (m, 1H, –NCH$_2$CH_2), 1.74–1.71 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.9, 155.8, 155.2, 154.9, 141.3, 136.3, 128.5, 128.4, 128.2, 128.1, 127.9, 127.6, 127.4, 126.9, 92.9, 92.4, 86.8, 86.3, 67.5, 67.3, 67.2, 66.9, 64.9, 57.2, 56.6, 56.3, 55.8, 55.7, 55.1, 53.2, 52.5, 44.1, 43.8, 43.4, 28.5, 28.3, 27.3; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.4(+), 128.2(+), 128.1(+), 127.9(+), 127.4(+), 126.9(+), 92.9(+), 92.4(+), 86.8(+), 86.3(+), 67.5(−), 67.3(−), 67.2(−), 66.9(−), 57.2(+), 56.6(+), 56.3(+), 55.8(+), 55.7(+), 55.1(+), 53.2(+), 52.5(+), 44.1(−), 43.8(−), 43.4(−), 28.5(−), 28.3(−), 27.3(−).

4.6.3. Benzyl-2-methoxy-3-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (5c, Table 4, entry 3). Prepared following method E using **3c** (4.76 g, 11.8 mmol) and $NaN(SiMe_3)_2$ (0.5 M in toluene, 25.9 ml, 12.9 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *cis*/*trans* mixture (22:77) of **5c** (3.1 g, 85%). as a yellow oil; R_f=0.23 (30% EtOAc/70% hexane); IR (film) ν 3321, 2954, 1683, 1694, 1699, 1713, 1538, 1455, 1418, 1348, 1246, 1082, 974, 773, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.31–7.26 (m, 5H, Ar), 5.45 (d, J= 5.2 Hz, 0.78H, –NC*H*O–), 5.35 (br, 0.22H, –NC*H*O–), 5.19–4.95 (m, 3H, –CH_2Ph and –N*H*), 4.01 (br, 0.78H, –C*H*NH(CO$_2$Me)), 3.86 (br, 0.22H, –C*H*NH(CO$_2$Me)), 3.66–3.29 (m, 4H, 1×–NCH_2CH$_2$ and –OCH_3), 2.29 (br, 1H, –NCH_2CH$_2$), 1.76 (br, 1H, –NCH$_2$CH_2), 1.83–1.74 (m, 1H, –NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.6, 156.0, 155.4, 136.5, 128.7, 128.3, 128.1, 93.1, 92.6, 67.5, 67.4, 56.5, 56.0, 55.8, 55.2, 52.4, 44.2, 44.0, 28.6, 27.6.

4.7. Method F. General procedure for azidomethoxylation

CAN (3 mequiv) dissolved in acetonitrile was added dropwise to a cooled (ice-bath) mixture of sodium azide (1.5 mequiv) and the enecarbamate (1 mequiv), in dry acetonitrile and dry methanol and under nitrogen. The mixture was gradually brought to rt and stirred overnight. Water and diethyl ether were added and the organic layers separated and washed with ice-cold water. The aqueous layer was extracted once again with diethyl ether, the combined organic layers dried (Na_2SO_4) and the solvent removed in vacuo. Purification by column chromatography afforded the 3-azido-2-methoxy derivative **6**.

4.7.1. Benzyl-3-azido 2-methoxy-1-pyrrolidinecarboxylate (6a, Scheme 1). Prepared following method F using **1a** (1.0 g, 4.93 mmol), sodium azide (480 mg, 7.4 mmol), and CAN (5.4 g, 9.8 mmol) to yield the crude product which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane), affording a mixture of *cis*/*trans*-**6a** (30/70) (372 mg, 27%) as a colorless oil; R_f=0.44 (20% EtOAc/80% hexane); IR (film) ν 3033, 2954, 2835, 2105, 1716, 1694, 1699, 1641, 1498, 1455, 1418, 1337.5, 1176, 1115, 1029, 985, 931, 772, 753, 698, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.29 (m, 5H, Ar), 5.25–4.89 (m, 3H, –CH_2Ph and –NC*H*O–), 3.93 (d, J= 6.4 Hz, 0.7H, –C*H*N$_3$), 3.54–3.42 (m, 5.3H, –OCH_3, 0.3×–C*H*N$_3$ and –NCH_2), 2.31–2.24 (m, 1H, –NCH$_2$CH_2), 2.20–1.96 (m, 1H, –NCH$_2$CH_2); ^1H NMR (300 MHz, d_2-tetrachloroethane, T=365 K), rotamers, δ 7.40–7.35 (m, 5H, Ar), 5.24–5.19 (m, 2.7H, –CH_2Ph and 0.7×–NC*H*O–), 5.08 (br, 0.3H, –NC*H*O–), 3.97 (d, J=5.1 Hz, 0.7H, –C*H*N$_3$), 3.63–3.39 (m, 5.3H, –OCH_3, 0.3×–C*H*N$_3$ and –NCH_2), 2.36–2.00 (m, 2H, NCH$_2$CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.0, 136.6, 128.8, 128.7, 128.4, 128.3, 128.2, 128.0, 92.2, 91.6, 88.5, 88.2, 67.6, 67.4, 64.8, 64.2, 60.8, 60.2, 57.4, 56.9, 56.5, 55.9, 44.4, 44.2, 43.3, 43.2, 28.2, 27.3, 26.3, 25.3; HRMS (EI) *m*/*z* calcd for ($C_{13}H_{16}N_4O_3^+$) requires: 275.1144, found: 275.1108.

4.7.2. Benzyl-3-azido-2-methoxy-1-piperidinecarboxylate (6b, Scheme 1). Prepared following method F using **1d** (0.76 g, 3.5 mmol), sodium azide (0.34 g, 5.25 mmol) and CAN (5.82 g, 10.5 mmol) to yield the crude product which was purified by flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a mixture of *cis*/*trans*-**6b** (40/60) (0.69 g, 71%) as a colorless oil; R_f=0.65 (20% EtOAc/80% hexane); IR (film) ν 3032, 2946, 2103, 1699, 1498, 1418, 1345, 1307, 1263, 1162, 1121, 1079, 1039, 965 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.37–7.26 (m, 5H, Ar), 5.5 (br, 0.6H, –NC*H*–O), 5.36 (br, 0.4H, –NC*H*O–), 5.24–5.08 (m, 2H, –CH_2Ph), 3.96–3.87 (m, 1H, –NCH_2), 3.76 (br, 0.4H, –C*H*N$_3$), 3.35–2.91 (m, 4.6H, –OCH_3, 0.6×–C*H*N$_3$ and 1×–NCH_2), 2.03–1.43 (m, 4H, –NCH$_2$(CH_2)$_2$);^1H NMR (300 MHz, d_2-tetrachloroethane, T=350 K), rotamers, δ 7.43–7.39 (m, 5H, Ar), 5.46 (br, 0.6H, –NC*H*O–), 5.31 (br, 0.4H, –NC*H*O–), 5.23–5.20 (m, 2H, –CH_2Ph), 4.03–3.93 (m, 1H, –NCH_2), 3.77 (br, 0.4H, –C*H*N$_3$), 3.37 (s, 1.8H, –OCH_3), 3.30 (s, 1.2H, –OCH_3), 3.15 (d, J=12.3 Hz, 0.6H, –C*H*N$_3$), 3.02–2.94 (m, 1H, NCH_2), 2.05–1.51 (m, 4H, NCH$_2$(CH_2)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.8, 155.2, 128.8, 128.7, 128.6, 128.4, 128.3, 128.1, 84.1, 83.8, 83.1, 67.8, 67.9, 59.2, 59.1, 58.2, 55.6, 55.2, 38.0, 37.6, 24.5, 24.2, 23.5, 23.3, 23.2, 19.6.

4.8. Method G. General procedure for $LiAlH_4$ reduction

To a stirred suspension of $LiAlH_4$ (5 mequiv) in dry THF at

0 °C and under nitrogen was slowly added a solution of the bicyclic compound **4** (1 mequiv) in THF. After refluxing for 14 h, the mixture was cooled to rt and carefully treated with H_2O, aqueous NaOH (15%), and again with H_2O. The white precipitate was filtered and washed several times with Et_2O. After acidification with aqueous H_2SO_4 (10%), the ethereal phase was separated, the aqueous layer basified (pH=14) and extracted with dichloromethane. Removal of the solvent in vacuo afforded the *N*-alkyl-3-alkyl-pyrrolidine derivative **7**.

4.8.1. 2-(1-Methyl-3-pyrrolidinyl)-2-propen-1-ol (7a, Scheme 2). Prepared following method G using **4a** (128 mg, 0.49 mmol) and $LiAlH_4$ (93 mg, 2.45 mmol) to yield the **7a** (43.6 mg, 62%) as a colorless oil; IR (film) ν 3367 (O–H), 2945, 2789, 1648, 1450, 1349, 1233, 1151, 1081, 1037, 894, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.84–4.83 (m, 1H, C=CH_2), 4.78 (m, 1H, –C=CH_2), 4.18–4.14 (dd, J=13.6, 1.2 Hz, 1H, –CH_2=CCH_2OH), 4.00–3.96 (dd, J=13.6, 1.2 Hz, 1H, –CH_2=CCH_2OH), 3.01–2.96 (m, 1H, –NCH_2CH_2), 2.93 (dt, J=8.8, 3.6 Hz, 1H, –NCH_2CH), 2.72 (dd, J=9.6, 2.8 Hz, 1H, –NCH_2CH), 2.48–2.31 (m, 1H, –NCH_2CH), 2.32 (s, 3H, N–CH_3), 2.24–2.14 (m, 1H, NCH_2CH), 2.10–2.01 (m, 1H, –NCH_2CH_2), 1.85–1.39 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 111.5, 64.3, 61.8, 55.5, 43.3, 41.2, 29.2; HRMS (EI) m/z calcd for ($C_8H_{15}NO^+$): 141.1154, found: 141.1151.

4.8.2. 2-(1-Ethyl-3-pyrrolidinyl)-2-propen-1-ol (7b, Scheme 2). Prepared following method G using **4e** (117 mg, 0.7 mmol) and $LiAlH_4$ (133 mg, 3.5 mmol) to yield **7b** (63.3 mg, 58%) as a colorless oil; IR (film) ν 3359, 2960, 2927, 2808, 1652, 1483, 1455, 1390, 1346, 1216, 1158, 1106, 1042, 896 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.82 (s, 1H, –C=CH_2), 4.7 (d, J=1.4 Hz, 1H, –C=CH_2), 4.15–4.12 (dd, J=13.2, 0.7 Hz, 1H, CH_2=CCH_2–OH), 3.95 (d, J=13.2 Hz, 1H, CH_2=CCH_2–OH), 2.98–2.92 (m, 2H, –NCH_2CH_2 and –NCH_2CH), 2.76 (dd, 1H, J=9.5, 2.6 Hz, –NCH_2CH_2), 2.31 (q, J=7.2 Hz, 2H, –NCH_2CH_3), 2.28–2.25 (m, 1H, –NCH_2CH_3), 2.23–2.16 (m, 1H, –CHC=CH_2), 2.14–2.00 (m, 1H, –NCH_2CH_2), 1.79–1.76 (m, 1H, –NCH_2CH_2), 1.06 (t, J=7.3 Hz, 3H, –NCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.6, 111.4, 64.2, 59.3, 53.0, 49.2, 42.6, 28.4, 13.6; HRMS (EI) m/z calcd for ($C_9H_{17}NO^+$): 155.1310, found: 155.1308.

4.9. Method H. General procedure for nucleophilic substitution of 4 via *N*-acyl-iminium formation

To a stirred solution of the bicyclic compound (1 quiv) and the nucleophile (5 quiv) in dry dichloromethane at 0 °C was added BF_3.OEt_2 (4 quiv). The resulting mixture was stirred at rt (1 h for the *N*-Cbz-bicyclic substrate and 2 days for the *N*-acetyl-bicyclic substrate). Na_2CO_3 (sat. aq. soln) was then added, the phases were separated and the aqueous phase extracted with dichloromethane. The combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo to yield the 2,3-dialkylsubstituted pyrrolidine derivative **8**, which was purified by flash chromatography.

4.9.1. Benzyl-2-allyl-3-[1-hydroxymethy)vinyl]-1-pyrrolidinecarboxylate (8a, Table 5, entry 1). Prepared following method H using **4a** (453 mg, 1.75 mmol), allyltrimethylsilane (1.39 ml, 8.75 mmol) and $BF_3 \cdot OEt_2$ (0.887 ml, 7.0 mmol) to yield the 2,3-dialkylsubstituted pyrrolidine derivative which was purified flash column chromatography (SiO_2, 40% EtOAc/60% hexane) affording a mixture of *cis*/*trans*-**8a** (76/24) (450 mg, 89%) as a colorless oil; R_f=0.18 (30% EtOAc/70% hexane); IR (film) ν 3431, 3074, 2952, 1685, 1420, 1357, 1185, 1113, 913, 767, 735, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.34–7.24 (m, 5H, Ar), 5.86–5.64 (m, 1H, –CH_2CH=CH_2), 5.29–4.93 (m, 5H, –CH_2Ph and 3×(–C=CH_2)$_2$), 4.85 (d, J=12.8 Hz, 1H, 1×–C=CH_2), 4.18–4.15 (m, 0.4H, –NCHCH), 4.06 (s, 2H, –CH_2OH), 3.93–3.85 (m, 0.6H, –NCHCH), 3.77–3.28 (m, 2H, –NCH_2CH_2), 2.79–2.76 (m, 0.4H, –NCHCH), 2.64 (br, 0.8H, CH_2CH=CH_2), 2.47–2.39 (m, 0.6H, –NCHCH), 2.36–1.79 (m, 2.2H, 1.2×CH_2-CH=CH_2 and 1×–NCH_2CH_2), 1.78–1.72 (m, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 154.5, 154.3, 149.0, 149.0, 145.4, 145.3, 136.5, 136.4, 136.2, 136.1, 135.2, 135.2, 134.0, 133.8, 128.0, 128.0, 127.8, 127.6, 127.6, 127.5, 127.4, 127.21, 117.5, 117.5, 116.4, 111.0, 110.7, 108.9, 66.6, 66.2, 65.3, 65.2, 64.3, 61.0, 60.6, 57.7, 57.4, 45.6, 45.3, 44.4, 44.3, 43.6, 38.0, 37.0, 35.0, 34.7, 28.8, 28.0, 25.8, 24.9; HRMS (EI) m/z calcd for ($C_{18}H_{23}NO_3+H^+$): 302.1756, found: 302.1748.

4.9.2. 2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (8b, Table 5, entry 2). Prepared following method H using **4e** (205 mg, 1.23 mmol), allyltrimethylsilane (0.98 ml, 6.15 mmol) and $BF_3 \cdot OEt_2$ (0.623 ml, 4.92 mmol) to yield a mixture of the *cis*/*trans*-2,3-dialkylsubstituted pyrrolidine derivative which was purified by flash chromatography (SiO_2, 80% EtOAc/20% hexane) affording the *cis*-**8b** and *trans*-**8b**(combined yield 58%).

4.9.3. *trans*-2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (*trans*-8b). (56 mg, 21%) as a yellow oil; R_f=0.43 (EtOAc); IR (film) ν 3392, 3077, 2926, 1620, 1446, 1430, 1358, 1036, 912 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.65–5.56 (m, 1H, –CH_2CH=CH_2), 5.13–4.94 (m, 2.8H, –C=CH_2), 4.73 (s, 0.9H, –C=CH_2), 4.67 (s, 0.3H, –C=CH_2), 4.15 (dt, J=8.5, 3.5 Hz, 0.67H, –NCHCH), 4.07 (s, 2H, –CH_2OH), 3.80 (ddd, J=8.8, 4.0, 1.7 Hz, 0.33H, N–CHCH), 3.69–3.61 (m, 0.32H, –NCH_2CH_2), 3.52–3.36 (m, 1.68H, N–CH_2CH_2), 2.72–2.71 (m, 0.35H, –NCHCH), 2.66 (dt, J=7.0, 4.0 Hz, 0.65H, –NCHCH), 2.53–2.46 (m, 0.84H, –CH_2CH=CH_2), 2.38–1.78 (m, 3.16H, 1.16×–CH_2CH=CH_2 and –NCH_2CH_2), 2.08 (s, 0.78H, –CH_3), 2.02 (s, 2.22H, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 169.2, 149.8, 149.2, 145.4, 134.3, 133.4, 118.4, 118.0, 117.5, 116.6, 111.7, 109.0, 67.9, 64.7, 64.6, 64.4, 62.6, 60.4, 50.2, 46.8, 46.3, 45.5, 45.1, 44.6, 44.5, 43.2, 39.4, 36.9, 29.6, 28.9, 27.8, 27.1, 22.6, 21.9; DEPT (100 MHz, $CDCl_3$), rotamers, δ 134.3(+), 133.4(+), 118.4(−), 118.0(−), 117.5(−), 116.6(−), 111.7(−), 109.0(−), 64.6(−), 64.4(−), 62.6(+), 60.4(+), 50.2(+), 46.8(−), 46.3(−), 45.5(+), 45.1(+), 44.6(+), 44.5(+), 43.2(+), 39.4(−), 36.9(−), 29.6(−), 28.9(−), 27.8(−), 27.1(−), 22.6(+), 21.9(+); HRMS (EI) m/z calcd for ($C_{12}H_{19}NO_2+H^+$): 210.1494, found: 210.1483.

4.9.4. *cis*-2-(1-Acetyl-2-allyl-3-pyrrolidinyl)-2-propen-1-ol (*cis*-8b). (94 mg, 37%) as a yellow oil; R_f=0.26 (EtOAc); IR (film) ν 3390, 3077, 2932, 2887, 1619, 1445,

1429, 1352, 1184, 1067, 1040, 999, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.83–5.66 (m, 1H, $-CH_2CH{=}CH_2$), 5.27–4.25 (m, 1H, $-C{=}CH_2$), 5.04–4.90 (m, 3H, $-C{=}CH_2$), 4.34 (q, $J=6.5$ Hz, 0.68H, –NCHCH), 4.18–4.06 (m, 2H, $-CH_2OH$), 4.01 (q, $J=6.5$ Hz, 0.32H, –NCHCH), 3.57–3.65 (m, 2H, $-NCH_2CH_2$), 2.90 (dt, $J=$ 13.2, 7.5 Hz, 0.32H, –NCHCH), 2.75 (dt, $J=13.0$, 7.5 Hz, 0.68H, –NCHCH), 2.28–1.84 (m, 4H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 2.07 (s, 0.94H, $-CH_3$), 2.01 (s, 2.06H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 169.5, 145.6, 135.6, 134.6, 118.0, 117.4, 116.3, 112.0, 111.0, 65.7, 65.3, 59.4, 56.8, 46.0, 45.4, 45.3, 43.6, 43.4, 34.9, 34.2, 26.2, 25.8, 24.4, 22.4, 22.1; DEPT (100 MHz, $CDCl_3$) δ 135.6(+), 134.6(+), 118.0(−), 117.4(−), 116.3(−),112.0(−), 111.0(−), 65.7(−), 65.3(−), 59.4(+), 56.8(+), 46.0(−), 45.4(+), 45.3(−), 43.6(+), 43.4(+), 34.9(−), 34.2(−), 26.2(−), 25.8(−), 24.4(−), 22.4(+), 22.1(+); HRMS (EI) m/z calcd for ($C_{12}H_{19}NO_2+H^+$): 210.1494, found: 210.1489

4.9.5. Benzyl-2-cyano-3-[1-hydroxymethyl)vinyl]-1-pyrrolidinecarboxylate (8c, Table 5, entry 3). Prepared following method H using **4a** (150 mg, 0.58 mmol), cyanotrimethylsilane (386 µl, 2.9 mmol) and $BF_3{\cdot}OEt_2$ (293 µl, 2.32 mmol) to yield the 2,3-dialkyl-substituted pyrrolidine derivative which was purified by flash column chromatography (SiO_2, 60% EtOAc/40% hexane) affording a mixture of *cis*/*trans*-**8c** (67:33) (125 mg, 76%) as a colorless oil; $R_f=0.32$ (50% EtOAc/50% hexane); IR (film) ν 3440, 2950, 2891, 1705, 1494, 1416, 1357, 1214, 1190, 1126, 1057, 1028, 915, 763, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.39–7.31 (m, 5H, Ar), 5.34 (s, 1H, $-C{=}CH_2$), 5.27–5.13 (m, 3H, $1\times-C{=}CH_2$ and CH_2Ph), 4.99–4.89 (m, 0.67H, –NCHCN), 4.57–4.49 (m, 0.33H, –NCHCN), 4.19–4.10 (m, 2H, $-CH_2OH$), 3.72–3.36 (m, 1H, $-NCH_2CH_2$), 3.52–3.50 (m, 0.33H, $-NCH_2CH_2$), 3.43–3.35 (m, 0.67H, $-NCH_2CH_2$), 3.26–3.22 (m, 0.33H, $-CHC{=}CH_2$), 3.09–3.04 (m, 0.67H, $-CHC{=}CH_2$), 2.27–2.10 (m, 2H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 153.6, 145.1, 135.8, 128.5, 128.2, 128.1, 128.0, 118.8, 118.4, 116.8, 116.7, 115.2, 114.8, 112.8, 112.6, 68.6, 68.0, 67.8, 67.7, 67.6, 66.6, 66.4, 65.0, 52.2, 51.8, 51.6, 51.2, 47.5, 46.4, 45.8, 45.4, 45.2, 45.1, 45.0, 44.2, 29.6, 28.8, 27.6, 26.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.5(+), 128.2(+), 128.1(+), 128.0(+), 118.8(−), 118.4(−), 116.8(−), 116.7(−), 115.2(−), 114.8(−), 112.8(−), 112.6(−), 68.6(−), 68.0(−), 67.8(−), 67.7(−), 67.6(−), 66.6(−), 66.4(−), 65.0(−), 52.2(+), 51.8(+), 51.6(+), 51.2(+), 47.5(+), 46.4(+), 45.8(−), 45.4(−), 45.2(−), 45.1(−), 45.0(−), 44.2(+), 29.6(−), 28.8(−), 27.6(−), 26.7(−); HRMS (EI) m/z calcd for ($C_{16}H_{18}N_2O_3^+$): 286.1317, found: 286.1330.

4.9.6. 1-Acetyl-3-[1-(hydroxymethyl)vinyl]-2-pyrrolidinecarbonitrile (8d, Table 5, entry 4). Prepared following method H using **4e** (160 mg, 0.96 mmol), cyanotrimethylsilane (638 µl, 4.8 mmol) and $BF_3{\cdot}OEt_2$ (486 µl, 3.84 mmol) to yield the 2,3-dialkylsubstituted pyrrolidine derivative which was purified by flash column chromatography (SiO_2, 90%EtOAc/10% hexane) affording a mixture of *cis*/*trans*-**8d** (74:26) (120 mg, 64%) as a colorless oil; $R_f=0.26$ (EtOAc); IR (film) ν 3390, 2947, 2892, 1644, 1651, 1417, 1359, 1300, 1260, 1184, 1037, 917, 834 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 5.38 (br, 1H, $C{=}CH_2$), 5.21–5.13 (m, 1.74H, $C{=}CH_2$ and –NCHCN), 4.92 (d, $J=7.1$ Hz, 0.26H, –NCHCN), 4.28–4.16 (m, 2H, $-CH_2OH$), 3.79–3.70 (m, 1H, $-NCH_2CH_2$), 3.53–3.39 (m, 1H, $-NCH_2CH_2$), 3.17–3.13 (m, 0.26H, $-CHC{=}CH_2$), 3.10–3.04 (m, 0.74H, $-CHC{=}CH_2$), 2.38–2.33 (m, 1H, $-NCH_2CH_2$), 2.26–2.19 (m, 1H, $-NCH_2CH_2$), 2.22 (s, 0.5H, $-CH_3$), 2.09 (s, 2.5H, $-CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 169.5, 143.4, 143.1, 116.2, 115.8, 114.6, 114.0, 66.1, 65.6, 52.5, 50.3, 45.9, 45.0, 44.5, 27.8, 26.1, 22.3, 21.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 115.7(+), 114.8(+), 67.0(+), 66.3(+), 52.5(−), 50.3(−), 46.1(+), 45.0(−), 44.7(+), 44.5(−), 29.6(+), 28.1(+), 26.3(+), 22.3(−), 21.6(−); HRMS (EI) m/z calcd for ($C_{10}H_{14}N_2O_2^+$): 194.1055, found: 194.1053.

4.9.7. Benzyl-2-allyl-3[(benzyloxycarbonyl)amino]-1-pyrrolidinecarboxylate (9a, Table 6, entry 1). Prepared following method H using **5b** (55 mg, 0.14 mmol), allyltrimethylsilane (46 µl, 0.28 mmol, 2 quiv) and $BF_3{\cdot}OEt_2$ (36 µl, 0.28 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by preparative thin layer chromatography (SiO_2, 40%EtOAc/60% hexane) affording the *cis* (24%) and *trans* (76%) isomers of **9a** (35 mg, 60%) as colorless oils.

4.9.8. *trans*-Benzyl-2-allyl-3-[(benzyloxycarbonyl)-amino]-1-pyrrolidinecarboxylate (*trans*-9a). $R_f=0.37$ (30% AcOE/70% hexane); IR (film) ν 3313, 3064, 3032, 2952, 1698, 1586, 1532, 1498, 1454, 1415, 1349, 1278, 1244, 1114, 1028, 1002, 916, 846, 769, 697, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers δ 7.27–7.16 (m, 5H, Ar), 5.70 (br, 1H, $-CH_2CH{=}CH_2$), 5.13–4.93 (m, 7H, N*H*, $2\times(-CH_2Ph)$ and $-C{=}CH_2$), 4.29 (br, 1H, –NH), 4.00 (br, 1H, –CHNH), 3.74 (br, 1H, –NCHCH), 3.47–3.32 (m, 2H, $-NCH_2CH_2$), 2.46 (br, 0.5H, $-CH_2CH{=}CH_2$), 2.33 (br, 0.5H, $-CH_2CH{=}CH_2$), 2.13–2.11 (br, 2H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 1.77 (br, 1H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.6, 136.2, 133.6, 128.5, 128.2, 128.0, 127.9, 118.2, 67.0, 66.8, 63.6, 54.9, 54.0, 44.4, 44.1, 37.7, 36.8, 29.9, 29.0; DEPT (100 MHz, $CDCl_3$), rotamers, δ 133.6(+), 128.5(+), 128.2(+), 128.0(+), 127.9(+), 118.2(−), 67.0(−), 66.8(−), 63.6(+), 54.9(+), 54.0(+), 44.4(−), 44.1(−), 37.7(−), 36.8(−), 29.9 (−), 29.0(−).

4.9.9. *cis*-Benzyl-2-allyl-3-[(benzyloxycarbonyl)amino]-1-pyrrolidinecarboxylate (*cis*-9a). $R_f=0.26$ (30% EtOAc/70% hexane); IR (film) ν 3304, 3065, 3031, 2915, 1693, 1538, 1452, 1412, 1358, 1239, 1113, 1026, 916, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.28–7.19 (m, 5H, Ar), 5.70 (br, 1H, $-CH_2CH{=}CH_2$), 5.09–4.84 (m, 7H, N*H*, $2\times(-CH_2Ph)$ and $-CH{=}CH_2$), 4.24 (br, 1H, $-CH_2CHNH$), 4.15–4.12 (m, 1H, –NCHCH–), 3.40 (dt, $J=$ 8.8, 2.0 Hz, 2H, $-NCH_2CH_2$), 2.20 (br, 3H, $-CH_2CH{=}CH_2$ and $-NCH_2CH_2$), 1.74–1.69 (m, 1H, $-NCH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.7, 155.1, 135.1, 128.6, 128.5, 128.3, 128.2, 128.0, 117.3, 77.2, 67.0, 56.8, 52.5, 43.4, 34.3, 29.7; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.5(+), 128.3(+), 128.2(+), 128.0(+), 117.3(−), 77.2(+), 67.0(−), 56.8(+), 52.5(+), 43.4(−),

34.3(−), 29.7(−); HRMS (EI) *m/z* calcd for ($C_{23}H_{26}N_2O_4+H^+$): 395.1970, found: 395.1971.

4.9.10. Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (9b, Table 6, entry 2). Prepared following method H using **5b** (89 mg, 0.23 mmol), cyanotrimethylsilane (63 μl, 0.46 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (58 μl, 0.46 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 40%EtOAc/60% hexane) affording the *cis* (30%) and *trans* (70%) isomers of **9b** (44.8 mg, 52%) as colorless oils.

4.9.11. *trans*-Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (*trans*-9b). R_f=0.29 (30% EtOAc/70%hexane); IR (film) ν 3307, 3071, 3031, 2956, 1710, 1536, 1454, 1413, 1358, 1284, 1244, 1218, 1172, 1133, 1027, 913, 738, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.19 (m, 5H, Ar), 5.36–5.30 (m, 1H, –NC*H*CN), 5.21–5.05 (m, 4H, 2×(–CH_2Ph)), 4.63–4.57 (m, 1H, –N*H*), 4.47 (br, 1H, –CH_2C*H*NH), 3.61–3.20 (m, 2H, –NC$H_2$$CH_2$), 1.27–1.79 (m, 2H, –NC$H_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.4, 155.3, 135.7, 128.6, 128.5, 128.4, 128.2, 128.0, 116.9, 76.7, 68.0, 67.9, 66.3, 58.9, 56.3, 55.3, 53.1, 44.5, 44.1, 30.3, 29.2, 18.6; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.6(+), 128.5(+), 128.4(+), 128.2(+), 128.0(+), 76.7(−), 68.0(−), 67.9(−), 66.3(−), 58.9(+), 56.3(+), 55.3(+), 53.1(+), 44.5(−), 44.1(−), 30.3(−), 29.2(−),18.6(−).

4.9.12. *cis*-Benzyl-3-[(benzyloxycarbonyl)amino]-2-cyano-1-pyrrolidinecarboxylate (*cis*-9b). R_f=0.22 (30% EtOAc/70% hexane); IR (film) ν 3321, 3033, 2957, 1711, 1532, 1454, 1413, 1357, 1284, 1241, 1177, 1114, 1040, 980, 913, 738, 698, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.28–7.19 (m, 5H, Ar), 5.23–5.19 (m, 1H, –NC*H*CN), 5.15–5.05 (m, 4H, 2×(–CH_2Ph)), 4.85 (br, 1H, –N*H*), 4.34 (br, 1H, –CH_2C*H*NH), 3.59–3.57 (m, 1H, –NC$H_2$$CH_2$), 3.35–3.32 (m, 1H, –NC$H_2$$CH_2$), 2.25–2.20 (m, 1H, –NC$H_2CH_2$), 1.93–1.91 (m, 1H, NC$H_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.6, 153.6, 135.7, 128.6, 128.4, 128.2, 115.9, 68.1, 67.9, 67.5, 53.4, 52.5, 52.3, 51.5, 51.3, 43.8, 29.6, 28.5.

4.9.13. Benzyl-3-[(benzyloxycarbonyl)amino]-2-(ethoxy-2-oxoethyl)-1-pyrrolidinecarboxylate (9c, Table 6, entry 3). Prepared following method H using **5b** (58 mg, 0.15 mmol), *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane (202 mg, 0.6 mmol, 4 quiv) and $BF_3\cdot OEt_2$ (38 μl, 0.30 mmol, 2 quiv) to yield the 2,3-disubstituted pyrrolidine which was purified by flash chromatography (SiO_2, 40% EtOAc/60% hexane) affording a *cis*/*trans*-**9c** mixture (15/85) (49 mg, 74%) as a colorless oil; R_f=0.56 (40% EtOAc/60% hexane); IR (film) ν 3322, 3032, 2980, 2897, 1703, 1586, 1532, 1498, 1454, 1416, 1350, 1288, 1241, 1204, 1116, 1057, 1028, 978, 915, 770, 739 cm^{-1}; ^1H NMR (400 MHz, d_2-tetrachloroethane, T=340 K) δ 7.41–7.34 (m, 5H, Ar), 5.17 (s, 2H, –CH_2Ph), 5.14 (s, 2H, –CH_2Ph), 4.98 (d, J=5.0 Hz, 1H, –N*H*), 4.32–4.07 (m, 4H, –C*H*NH, NC*H*CH_2, –OC$H_2$$CH_3$), 3.65–3.59 (m, 1H, –NC$H_2$$CH_2$), 3.53–3.47 (m, 1H, –NC$H_2$$CH_2$), 2.88–2.84 (m, 1H, –$CH_2$(C=O)), 2.56–2.50 (m, 1H, –CH_2(C=O)), 2.26–2.20 (m, 1H, –NCH_2CH_2), 1.94–1.86 (m, 1H, –NCH_2CH_2), 1.32–1.24 (m, 3H, –OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 155.6, 154.5, 136.7, 136.5, 128.4, 127.9, 127.8, 127.7, 66.9, 66.8, 60.8, 60.4, 56.1, 50.4, 44.4, 43.6, 37.7, 29.9, 13.9; DEPT (100 MHz, $CDCl_3$) δ 128.4(+), 127.9(+), 127.8(+), 127.7(+), 66.9(−), 66.8(−), 60.8(−), 60.4(+), 56.1(+), 50.4(−), 44.4(−), 43.6(−), 37.7(−), 29.9(−), 13.9(+); HRMS (EI) *m/z* calcd ($C_{24}H_{28}N_2O_6$–H^+): 439.1869, found: 439.1866.

4.9.14. Benzyl-2-allyl-3-[(methoxycarbonyl)amino]-1-pyrrolidinecarboxylate (9d, Table 6, entry 4). Prepared following method H using **5c** (475 mg, 1.54 mmol), allyltrimethylsilane (489 μl, 3.08 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (782 μl, 6.2 mmol, 4 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 40%EtOAc/60% hexane) affording a *cis*/*trans*-**9d** mixture (23/77) (385 mg, 79%) as a colorless oil; R_f=(10% EtOAc/90% hexane); IR (film) ν 3316, 3061, 3030, 2951, 1703, 1699, 1694, 1683, 1538, 1455, 1418, 1350, 1280, 1248, 1194, 1114, 918, 770, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.34–7.26 (m, 5H, Ar), 5.82–5.20 (m, 1H, –C*H*=CH_2), 5.16–5.04 (m, 5H, –CH_2Ph and –CH=CH_2 and –N*H*), 4.04 (br, 1H, –C*H*NH(CO_2Me)), 3.79 (br, 1H, –NC*H*CH_2), 3.68 (s, 3H, –OCH_3), 3.64–3.43 (m, 2H, –NC$H_2$$CH_2$), 2.55–2.38 (m, 1H, C$H_2$CH=$CH_2$), 2.21–2.14 (m, 2H, 1×C$H_2$CH=$CH_2$ and 1×–NCH_2CH_2), 2.12–1.83 (m, 1H, –NCH_2CH_2); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=365 K), δ 7.39–7.31 (m, 5H, Ar), 5.81–5.78 (m, 1H, –C*H*=CH_2), 5.19–5.06 (m, 5H, –CH_2Ph and –CH=CH_2 and –N*H*), 4.00 (br, 1H, –C*H*NH(CO_2Me)), 3.79 (d, J=4.8 Hz, 1H, –NC*H*CH_2), 3.64 (s, 3H, –OCH_3), 3.51–3.45 (m, 2H, –NC$H_2$$CH_2$), 2.53 (br, 0.5H, C$H_2$-CH=$CH_2$), 2.42 (br, 0.5H, C$H_2$CH=$CH_2$), 2.19–2.18 (m, 2H, 1×C$H_2$CH=$CH_2$ and 1×–NCH_2CH_2), 1.83 (br, 1H, –NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.5, 133.9, 128.7, 128.2, 128.1, 118.3, 67.2, 67.0, 63.9, 55.1, 54.3, 52.3, 44.7, 44.4, 37.9, 37.0, 30.2, 29.2; HRMS (EI) *m/z* calcd for ($C_{17}H_{22}N_2O_4+H^+$): 319.1658, found: 319.1665.

4.9.15. Benzyl-3-azido-2-(2-ethoxy-2-oxoethyl)-1-pyrrolidinecarboxylate (9e, Table 6, entry 5). Prepared following method H using **6a** (237 mg, 0.86 mmol), *tert*-butyl[1-ethoxyvinyl)oxy]dimethylsilane (347 mg, 1.72 mmol) and $BF_3\cdot OEt_2$ (435 μl, 3.4 mmol) to yield the pyrrolidine derivative which was purified by flash chromatography (SiO_2, 20% EtOAc/80% hexane) affording a *cis*/*trans* mixture (88/12) **9e** (140 mg, 49%) as a colorless oil; R_f=0.24 (10% EtOAc/90% hexane); IR (film) ν 2977, 2893, 2099, 1726, 1691, 1448, 1413, 1352, 1261, 1189, 1117, 1029, 899, 766, 694, 598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.26 (m, 5H, Ar), 5.12 (br, 2H, –CH_2Ph), 4.34 (br, 2H, –NC*H* and C*H*N_3), 4.19–4.09 (m, 2H, –OC$H_2$$CH_3$), 3.62–3.56 (m, 1H, –NC$H_2$), 3.56–3.39 (m, 1H, –NC$H_2$), 2.66–2.49 (m, 2H, –C$H_2$(C=O)), 2.13–2.19 (m, 2H, –NCH_2CH_2), 1.29–1.25 (m, 3H, CH_2CH_3); ^1H NMR (400 MHz, d_2-tetrachloroethane, T=365 K) δ 7.42–7.34 (m, 5H, Ar), 5.19 (br, 2H, –CH_2Ph), 4.45–4.41 (m, 1H, –NC*H*), 4.32 (q, J=6.4 Hz, 0.88H, –C*H*N_3), 4.21 (dq, J=7.2, 1.6 Hz, 2H, –OC$H_2$$CH_3$), 4.88–4.87 (m, 0.12H, –C*H*N_3), 3.67–3.61 (m, 1H, –NCH_2), 3.58–3.45 (m, 1H, –NCH_2), 2.99 (dd, J=16.4, 4.0 Hz, 0.88H, –CH_2(C=O)),

2.91 (dd, $J=15.6$, 3.6 Hz, 0.12H, $-CH_2(C{=}O)$), 2.70–2.61 (m, 0.88H, $-CH_2(C{=}O)$), 2.48–2.41 (m, 0.12H, $-CH_2(C{=}O)$), 2.22–2.00 (m, 2H, $-NCH_2CH_2$), 1.31 (t, $J=7.2$ Hz, 3H, $-OCH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 170.4, 169.7, 168.3, 157.4, 153.7, 135.6, 127.6, 127.2, 127.1, 66.1, 61.8, 60.0, 59.8, 56.3, 55.4, 44.1, 43.4, 34.2, 33.1, 29.0, 28.1, 13.4; HRMS (EI) m/z calcd for ($C_{16}H_{20}N_4O_4+H^+$): 333.1576, found: 333.1571.

4.9.16. Benzyl-2-allyl-3-azido-1-piperidinecarboxylate (9f, Table 6, entry 6). Prepared following method H using **6b** (70 mg, 0.24 mmol), allyltrimethylsilane (77 µl, 0.48 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (122 µl, 0.96 mmol, 4 quiv) to yield the 3-azido-2-allyl-piperidine which was purified by flash chromatography (SiO_2, 10% EtOAc/90% hexane) affording a *cis*/*trans* mixture (88/12) **9f** (36 mg, 50%) as a colorless oil; $R_f=0.32$ (10% EtOAc/90% hexane); IR (film) ν 2949, 2855, 2100, 1698, 1425, 1347, 1252, 1196, 1146, 1028, 917, 763, 698, 666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.36–7.26 (m, 5H, Ar), 5.68 (br, 1H, $-CH{=}CH_2$), 5.15–5.03 (m, 4H, $-CH_2Ph$ and $-CH{=}CH_2$), 4.38 (br, 1H, $-NCH$), 4.12 (d, $J=12.8$ Hz, 1H, $-NCH_2$), 3.69 (br, 1H, $-NCHN_3$), 2.86 (dt, $J=12.8$, 4.0 Hz, 1H, $-NCH_2$), 2.47–2.24 (m, 3H, $CH_2CH{=}CH_2$ and 1×$-NCH_2CH_2$), 1.82–1.49 (m, 3H, 1×$-NCH_2CH_2$ and $-NCH_2CH_2CH_2$); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=365$ K), rotamers, δ 7.40–7.33 (m, 5H, Ar), 5.78–5.72 (m, 1H, $-CH{=}CH_2$), 5.19–5.09 (m, 4H, $-CH_2Ph$ and $-CH{=}CH_2$), 4.43 (t, $J=7.2$ Hz, 0.88H, $-NCH$), 4.30–4.20 (m, 0.12H, $-NCH$), 4.13 (d, $J=11.4$ Hz, 1H, $-NCH_2$), 3.68 (d, $J=1.4$ Hz, 1H, $-NCHN_3$), 2.91 (dt, $J=12.0$, 4.0 Hz, 1H, $-NCH_2$), 2.51–2.41 (m, 1H, $CH_2CH{=}CH_2$), 2.37–2.27 (m, 1H, $CH_2CH{=}CH_2$), 1.83–1.77 (m, 4H, $-NCH_2CH_2$ and $-NCH_2CH_2CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.0, 137.0, 133.8, 128.8, 128.6, 128.4, 128.2, 128.1, 128.1, 128.0, 118.2, 70.4, 67.6, 67.4, 58.3, 56.3, 55.6, 54.3, 53.9, 40.4, 38.7, 34.3, 26.05, 23.5, 22.1, 19.8; HRMS (EI) m/z calcd for ($C_{16}H_{20}N_4O_2+H^+$): 301.1664, found: 301.1663.

4.9.17. *trans*-Benzyl-2-allyl-3-iodo-1-pyrrolidinecarboxylate (9g, Table 6, entry 7). Prepared following method H using **2f** (525 mg, 1.45 mmol), allyltrimethylsilane (467 µl, 2.9 mmol, 2 quiv) and $BF_3\cdot OEt_2$ (369 µl, 2.9 mmol, 2 quiv) to yield the substituted pyrrolidine which was purified by flash chromatography (SiO_2, 20%EtOAc/80% hexane) affording **9g** (500 mg, 93%) as a colorless oil; $R_f=0.43$ (20% EtOAc/80% hexane); IR (film) ν 3068, 3033, 2891, 1703, 1641, 1498, 1445, 1411, 1358, 1336, 1287, 1267, 1155, 1110, 916, 875, 768, 735, 697, 665 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) rotamers δ 7.29–7.19 (m, 5H, Ar), 5.70–5.68 (m, 1H, $-CH_2CH{=}CH_2$), 5.16–4.95 (m, 4H, $-CH_2Ph$ and $-CH_2CH{=}CH_2$), 4.20 (br, 2H, CHI and $-NCHCH_2$), 3.72–3.70 (m, 1H, $-NCH_2CH_2$), 3.46–3.43 (m, 1H, $-NCH_2CH_2$), 2.43–2.03 (m, 4H, $-CH_2CH{=}CH_2$ and NCH_2CH_2); ^1H NMR (400 MHz, d_2-tetrachloroethane, $T=360$ K) δ 7.41–7.35 (m, 5H, Ar), 5.83–5.76 (m, 1H, $-CH_2CH{=}CH_2$), 5.22 (s, 2H, $-CH_2Ph$), 5.19–5.10 (m, 2H, $-CH_2CH{=}CH_2$), 4.39–4.26 (m, 2H, $-CHI$ and $-NCHCH_2$), 3.87–3.81 (m, 1H, $-NCH_2CH_2$), 3.54 (dt, $J=8.4$, 2.8 Hz, 1H, $-NCH_2CH_2$), 2.51–2.47 (m, 1H, $-CH_2CH{=}CH_2$), 2.42–2.33 (m, 1H, $-NCH_2CH_2$), 2.26–2.19 (m, 2H, 1×$CH_2CH{=}CH_2$ and 1×NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 154.6, 136.5, 136.3, 133.6, 133.4, 128.5, 128.0, 127.7, 118.4, 69.0, 68.6, 67.0, 66.9, 45.6, 45.3, 38.8, 38.0, 35.6, 35.8, 25.5, 24.8; DEPT (100 MHz, $CDCl_3$), rotamers, δ 133.6(+), 133.4(+), 128.5(+), 128.0(+), 127.7(+), 118.4(−), 69.0(+), 68.6(+), 67.0(−), 66.9(−), 45.6(−), 45.3(−), 38.8(−), 38.0(−), 35.6(−), 35.8(−), 25.5(+), 24.8(+).

4.9.18. *trans*-Dimethyl-2-{[(benzyloxy)carbonyl]-3-iodo-2-pyrrolidinyl}malonate (9h, Table 6, entry 8). To a stirred solution of **2f** (191 mg, 0.53 mmol) and dimethylmalonate (92 µl, 0.79 mmol, 1.5 quiv) in dry dichloromethane, under argon and cooled to −78 °C was slowly added a solution of $TiCl_4$ (100 µl, 0.53 mmol) in dry dichloromethane. The resulting mixture was stirred at −78 °C for 2 h, warmed to rt and stirred for an additional 2 h. A basic work-up (method F) yielded the substituted pyrrolidine which was purified by preparative thin layer chromatography (40% EtOAc/60% hexane) affording **9h** (165 mg, 68%) as a colorless oil; $R_f=0.35$ (30% EtOAc/70% hexane); IR (film) ν 3037, 2952, 2894, 1735, 1704, 1498, 1435, 1410, 1360, 1335, 1307, 1261, 1198, 1152, 1113, 1028, 974, 753, 698, 665; ^1H NMR (400 MHz, $CDCl_3$) δ 7.28–7.22 (m, 5H, Ar), 5.09–5.06 (m, 2H, $-CH_2Ph$), 4.73 (d, $J=5.5$ Hz, 0.5H, $-CH(CO_2Me)_2$), 4.59 (br, 0.5H, $-CH(CO_2Me)_2$), 3.90–3.31 (m, 10H, $-CHI$, $-NCHCH(CO_2Me)_2$, $-O(CH_3)_2$ and $-NCH_2CH_2$), 2.20–2.14 (m, 2H, NCH_2CH_2); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 167.7, 166.8, 155.4, 137.0, 136.5, 128.8, 128.2, 127.7, 68.6, 68.0, 67.4, 67.1, 54.2, 53.4, 52.7, 52.5, 52.4, 45.9, 45.6, 41.1, 36.3, 35.5, 22.7, 22.0; DEPT (100 MHz, $CDCl_3$), rotamers, δ 128.8(+), 128.2(+), 127.7(+), 68.6(+), 68.0(+), 67.4(−), 67.1(−), 54.2(+), 53.4(+), 52.7(+), 52.5(+), 52.4(+), 45.9(−), 45.6(−), 41.1(−), 36.3(−), 35.5(−), 22.7(+), 22.0(+).

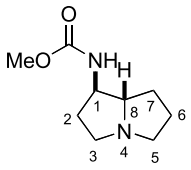
4.10. Synthesis of (±)-laburnamine

4.10.1. *trans*-Benzyl-2-(3-hydroxypropyl)-3-[(methoxycarbonyl)-amino]-1-pyrrolidinecarboxylate (10, Scheme 3). $BH_3\cdot SMe_2$ (30 µl, 0.31 mmol) was added dropwise to a solution of *trans*-**9d** (300 mg, 0.94 mmol) in dry THF (9 ml), cooled in an ice-bath and under nitrogen. The mixture was stirred at rt for 1 h and the solvent removed in vacuo yielding the boronate as a white foam which was dissolved in THF (9 ml). The solution was cooled with an ice-bath and an aqueous 3 M NaOH solution (346 µl, 1.04 mmol) followed by a dropwise addition of an aqueous 30% H_2O_2 solution (343 µl, 3.02 mmol) were added. The mixture was stirred at 40 °C for 2 h and then cold water (10 ml) together with diethyl ether were added (10 ml). The aqueous phase was extracted with diethyl ether, the combined organic layers were dried (Na_2SO_4) and the solvent removed in vacuo. The crude mixture was purified by flash chromatography (SiO_2, 80% EtOAc/20% hexane) affording **10** (170 mg, 55%) as a colorless oil; $R_f=$(10% EtOAc/90% hexane); IR (film) ν 3427, 3313, 3064, 3033, 2951, 1694, 1542, 1498, 1455, 1420, 1351, 1285, 1251, 1116, 1045, 987, 916, 877, 770, 739, 698, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.33–7.26 (m, 5H, Ar), 5.30, 5.29 (s, 1H, NH), 5.19–5.01 (m, 2H, $-CH_2Ph$), 3.96 (br, 1H, $-CHNH(CO_2Me)$), 3.80–3.79 (m, 1H,

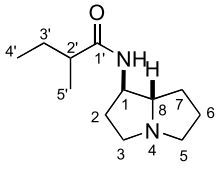
–NC*H*CH_2), 3.62 (s, 3H, CO_2CH_3), 3.67–3.23 (m, 4H, –NCH_2CH_2 and –CH_2CH_2–OH), 2.18–2.15 (m, 1H, –NCH_2CH_2), 1.83–1.77 (m, 1H, –NCH_2CH_2), 1.65–1.24 (m, 4H, –$CH_2CH_2CH_2$–OH); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 155.8, 155.3, 136.8, 128.7, 128.3, 128.1, 128.0, 67.2, 67.1, 64.4, 64.2, 62.3, 55.6, 55.1, 52.3, 44.5, 44.2, 30.1, 29.8, 29.3, 29.0; HRMS (EI) *m/z* calcd for ($C_{17}H_{24}N_2O_5+H^+$): 337.1763, found: 337.1767.

4.10.2. *trans*-Benzyl-3-[(methoxycarbonyl)amino]-2-(3-{[(4-methylphenyl)sulfonyl]oxy}propyl)-1-pyrrolidinecarboxylate (11, Scheme 3). To a solution of **10** (170 mg, 0.5 mmol) in dry chloroform (0.5 ml) cooled with an ice bath and under argon was added tosyl chloride (194 mg, 1.0 mmol) and right after, pyridine (82 μl, 1.0 mmol). The reaction mixture was stirred for 3 h at rt and water (2 ml) was then added followed by diethyl ether (5 ml). The organic phase was washed with an HCl (2 M, 3 ml), 5% $NaHCO_3$ aqueous solution (3 ml), water (3 ml) and dried with anhydrous $MgSO_4$. The reaction mixture was stirred for 3 h at rt. The solvent was removed in vacuo and the residue purified by preparative thin layer chromatography (60% EtOAc/40% hexane) to yield **11** (60 mg, 68%) as a colorless oil; R_f=0.64 (80% EtOAc/20% hexane); IR (film) ν 3319, 2956, 1704, 1532, 1435, 1359, 1175, 1097, 925, 664 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$), rotamers, δ 7.73–7.67 (m, 2H, Ar), 7.29–7.20 (m, 7H, Ar), 5.11–4.83 (m, 2H, CH_2Ph), 4.83 (br, 1H, N*H*), 4.02–3.93 (m, 1H, –CH_2OTs), 3.89 (br, 1H, –*C*HNH(CO_2Me)), 3.82 (br, 1H, –NC*H*CH_2), 3.57 (s, 3H, –OCH_3), 3.66–3.36 (m, 2H, –CH_2OTs and –NCH_2CH_2), 2.38 (s, 3H, Ar-CH_3), 2.25–2.06 (m, 1H, –NCH_2CH_2), 1.79–1.19 (m, 5H, 1×–NCH_2CH_2 and –$CH_2CH_2CH_2$OTs); ^{13}C NMR (100 MHz, $CDCl_3$), rotamers, δ 156.2, 154.9, 144.7, 136.6, 133.0, 129.8, 129.5, 128.8, 128.5, 128.0, 127.8, 126.0, 125.7, 70.5, 70.3, 70.02, 67.05, 66.9, 63.7, 55.4, 54.7, 52.1, 44.2, 43.9, 29.8, 29.6, 29.3, 28.8, 25.6, 21.6; HRMS (EI) *m/z* calcd for ($C_{24}H_{30}N_2O_7S+H^+$): 491.1851, found: 491.1844.

4.10.3. *trans*-Methyl-hexahydro-1*H*-pyrrolizin-1-ylcarbamate (12, Scheme 3). To a solution of **11** (96 mg, 0.196 mmol) in dry ethanol (0.2 ml), cooled in an ice bath and under argon, was added palladium over carbon (19 mg). The reaction mixture was placed in a hydrogen atmosphere and stirred vigorously overnight. The solvent was removed and a KOH 2 M aqueous NaCl saturated solution (5 ml) was added to the residue and extracted with diethyl ether (4× 5 ml). The combined organic layers were dried under Na_2SO_4 and the solvent removed in vacuo. The residue was purified by preparative thin layer chromatography (MeOH/CH_2Cl_2/NH_4OH, 10:89:1) to yield **12** (20 mg, 56%) as an orange oil; R_f=0.2 (CH_2Cl_2/MeOH/NH_4OH: 8/2/0.1, I_2); IR (film) ν 3451, 2951, 2514, 1711, 1536, 1452, 1254, 1193, 909, 780, 666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.2–4.15 (m, 2H, H_1 and H_8), 3.93–3.68 (m, 1H, H_3), 3.9–3.63 (m, 1H, H_5), 3.6 (s, 3H, –OCH_3), 2.98–2.87 (m, 2H, H_3 and H_5), 2.32–2.18 (m, 2×H_2 and 1×H_7), 2.05–1.97 (m, 1×H_6 and 1×H_7), 1.84–1.76 (m, 1×H_6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.1, 71.5, 55.9, 55.2, 53.2, 52.4, 31.7, 31.1, 30.0, 25.4; HRMS (EI) *m/z* calcd for ($C_9H_{16}N_2O_2+H^+$): 185.1290, found: 185.1280.



4.10.4. *trans*-*N*-Hexahydro-1*H*-pyrrolizin-1-yl-2-methylbutanamide((±)-laburnamine) (13, Scheme 3). To a solution of **12** (50 mg, 0.27 mmol) in dry chloroform (0.27 ml) under argon was added iodo(trimethyl)silane (47 μl, 0.32 mmol). The mixture was heated to 60 °C and stirred for 4 h. Methanol (0.1 ml) was then added and the volatile components removed in vacuo. The residue was redissolved in methanol and sodium methoxide was added (8 mg, 0.14 mmol). The mixture was stirred for 10 min at 60 °C and the volatile components removed in vacuo, to yield the crude amine, which was immediately used in the next reaction. To a solution of crude amine (50 mg, 0.27 mmol) in THF (2,7 ml), cooled in an ice bath and under argon, was added triethylamine (56 μl, 0.4 mmol) followed by (±)-2-methylbutyric acyl chloride (40 μl, 0.32 mmol). The reaction mixture was stirred for 4 h at rt and the solvent removed in vacuo. The residue was dissolved in methanol (5 ml) and a KOH pellet was added. After stirring for 10 min the solvent was removed in vacuo and the crude reaction mixture was purified by preparative thin layer chromatography (MeOH/CH_2Cl_2/NH_4OH, 10:89:1), to yield the (±)-laburnamine **13** (36.4 mg, 64%) as an orange oil; R_f=0.3 (CH_2Cl_2/MeOH/NH_4OH: 8/2/0.1, I_2); IR (film) ν 3437, 3270, 2965, 2934, 1704, 1645, 1548, 1463, 1386, 1289, 1238, 1089, 1013 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (br, 1H, NH), 3.71–3.65 (m, 1H, H_1), 3.58–3.43 (m, 1H, H_8), 3.39–3.19 (m, 1H, H_3), 2.81–2.67 (m, 2H, H_3, H_5), 2.21–2.14 (m, 3H, 2×H_2, H_5), 2.01–1.81 (m, 4H, 2×H_6, H_7, $H_{2'}$), 1.75–1.57 (m, 2H, H_7, $H_{3'}$), 1.46–1.36 (m, 1H, $H_{3'}$), 1.11–1.09 (m, 3H, 3×$H_{5'}$), 0.89–0.71 (m, 3H, 3×$H_{4'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.2, 55.0, 53.8, 53.0, 42.6, 31.7, 30.1, 27.2, 25.3, 17.3, 11.8; DEPT (100 MHz, $CDCl_3$) δ 71.2(+), 55.0(−), 53.8(+), 53.0(−), 42.6(+), 31.7(−), 30.1(−), 27.2(−), 25.3(−), 17.3(+), 11.8(+); HRMS (EI) *m/z* calcd for ($C_{12}H_{22}N_2O+H^+$): 211.1810, found: 211.1812.



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A novel synthesis, including asymmetric synthesis, of 2,4,4-trisubstituted 2-cyclopentenones based on the reaction of 1-chlorovinyl *p*-tolyl sulfoxides with acetonitrile and its homologues

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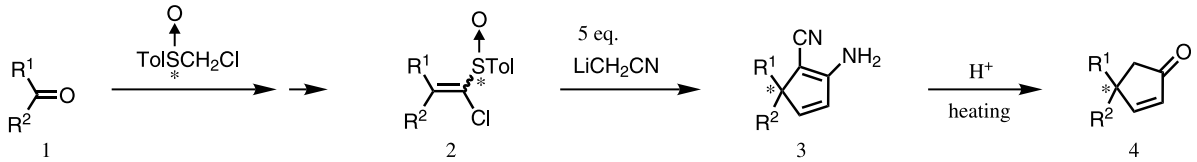
Abstract—Reaction of 1-chlorovinyl *p*-tolyl sulfoxides, which were synthesized from chloromethyl *p*-tolyl sulfoxide and ketones in high overall yields, with cyanomethyllithium (lithium α-carbanion of acetonitrile) gave adducts in high to quantitative yields. The adducts were treated with LDA followed by lithium α-carbanion of the homologues of acetonitrile to give 3,5,5-trisubstituted enaminonitriles in good to high yields. Hydrolysis of the enaminonitriles under acidic conditions gave 2,4,4-trisubstituted 2-cyclopentenones in good yields. By using the optically active chloromethyl *p*-tolyl sulfoxide and unsymmetrical ketones, this procedure gave the optically pure 2,4,4-trisubstituted 2-cyclopentenones. The scope and limitations of this method and the mechanism of the reactions are also discussed. These procedures offer a new and effective method for the synthesis of 2,4,4-trisubstituted 2-cyclopentenones from four components, ketones, chloromethyl *p*-tolyl sulfoxide, acetonitrile, and its homologues.

1. Introduction

The cyclopentane, including cyclopentanone and cyclopentenone, ring system is among the most widely found structures in natural compounds, especially in cyclopentanoid natural products.[1] 2-Cyclopentenones are undoubtedly one of the most versatile intermediates in the synthesis of cyclopentanes, because, the 3- and 5-positions of the 2-cyclopentenones are quite easily modified by a general method, for example, 1,4-addition of the enone system and aldol-type reaction, respectively. However, modification of the 2-position of the 2-cyclopentenones has been recognized to be relatively difficult.[2] In view of the importance of 2-cyclopentenones in organic synthesis, several methods such as the Nazarov cyclization[3] and the Pauson–Khand reaction[4] have been reported.

Recently, we reported a reaction of 1-chlorovinyl *p*-tolyl sulfoxides **2**, derived from ketones **1** and chloromethyl *p*-tolyl sulfoxide in three steps, with cyanomethyllithium to give 5,5-disubstituted enaminonitrile **3** in high to quantitative yield.[5] Acidic hydrolysis of **3** gave 4,4-disubstituted 2-cyclopentenones **4** in good yield (Scheme 1). Further, when unsymmetrical ketones and optically active chloromethyl *p*-tolyl sulfoxide were used in this procedure, an asymmetric synthesis of optically pure 4,4-disubstituted 2-cyclopentenones **4** was realized.[6]

Considering the usefulness of this procedure in the synthesis of 4,4-disubstitued 2-cyclopentenones and the proposed mechanism of the reaction from **2** to **3**,[5] we anticipated that if we used several kinds of nitriles other than acetonitrile in this reaction, highly substituted 2-cyclopentenones could be



1 2 3 4

Scheme 1.

Keywords: 2-Cyclopentenone; 2,4,4-Trisubstituted 2-cyclopentenone; Conjugate addition; Sulfoxide; Asymmetric synthesis.
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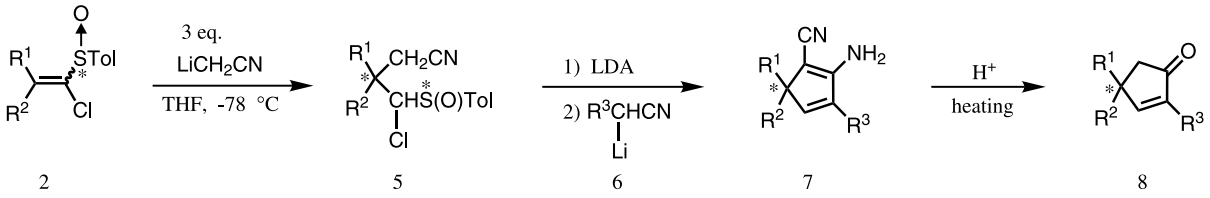


Scheme 2.

obtained. We investigated the reaction of 1-chlorovinyl *p*-tolyl sulfoxides **2** with several lithium α-carbanion of nitriles and found a quite versatile method for synthesis of 3,5,5-trisubstituted enaminonitriles **7** and 2,4,4-trisubstituted 2-cyclopentenones **8**. The whole sequence is shown in Scheme 2. Thus, the vinyl sulfoxides **2** was first treated with cyanomethyllithium at −78 °C to give the adducts **5**, which were treated with LDA followed by the lithium α-carbanion of the homologues of acetonitrile to afford 3,5,5-trisubstituted enaminonitriles **7**. The enaminonitriles were hydrolyzed to give 2,4,4-trisubstituted 2-cyclopentenones **8** in good to high yields. Herein we describe the details of this investigation and the application of this procedure to an asymmetric synthesis of optically active 2,4,4-trisubstituted 2-cyclopentenones.[7]

2. Results and discussion

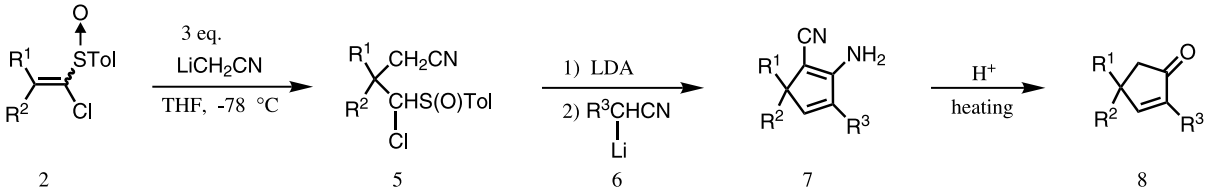
2.1. The reaction of lithium α-carbanion of acetonitrile and propionitrile with 1-chlorovinyl *p*-tolyl sulfoxides

As the substrate used in this investigation we selected three 1-chlorovinyl *p*-tolyl sulfoxides **2a–c** and synthesized them from the corresponding ketones and chloromethyl *p*-tolyl sulfoxide (see Table 1).[5,6] First, we studied the reaction of **2c** with lithium carbanion of propionitrile. We anticipated a product like **9** if the expected reaction worked (Scheme 3). Thus, 5 equiv of lithium α-carbanion of propionitrile was generated from propionitrile and *n*-butyllithium in THF at −78 °C. In this solution, a solution of **2c** in THF was added and the temperature of the reaction mixture was slowly allowed to warm to room temperature. However, only a complex mixture was obtained.

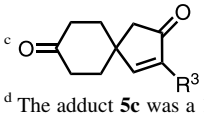
Next, to a solution of 3 equiv of lithium α-carbanion of propionitrile was added a solution of **2c** at −78 °C. The reaction was quenched with water after 10 min to give the adduct **10** in 91% yield.[5b] The adduct was treated with 3 equiv of LDA at −78 °C and to the solution was added a solution of 4 equiv of cyanomethyllithium. The reaction mixture was stirred and allowed to warm to room temperature. We anticipated a product like **11** in this treatment; however, we obtained a rather complex mixture with 27% of the enaminonitrile **3a**.

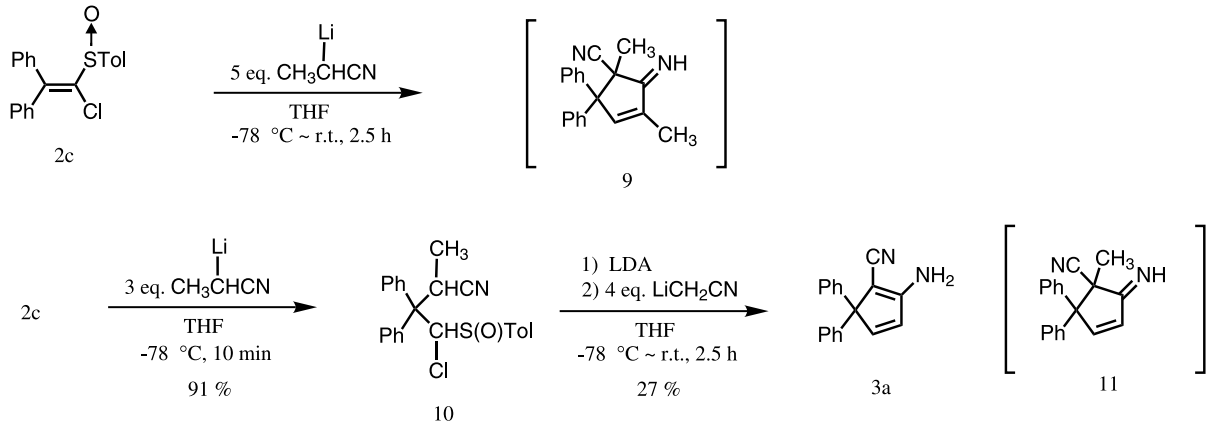
This rather unexpected result was explained as follows. Treatment of **10** with LDA afforded α-sulfinyl carbanion of **10**, from which the lithium α-carbanion of propionitrile was eliminated to give the vinyl sulfoxide **2c**. The cyanomethyllithium in the reaction mixture reacted with **2c** to give the enaminonitrile **3a**.[5]

Table 1. Synthesis of 3,5,5-trisubstituted enaminoitriles **7** and 2,4,4-trisubstituted 2- cyclopentenones **8** from the vinyl sulfoxides **2** by the reaction with acetonitrile followed by the homologues of acetonitrile



Entry	Vinyl sulfoxide **2**		Adduct **5**		R^3	Examinonitrile **7**		2-Cyclopentenone **8**	
	R^1	R^2		Yield/%			Yield/%		Yield/%
1	**2a**	$-(CH_2)_{14}-$	**5a**[a]	97	CH_3	**7a**	80	**8a**	93
2					CH_3CH_2	**7b**	76	**8b**	83
3	**2b**	$-(CH_2)_2C(CH_2)_2-$ (O,O)	**5b**[b]	99	CH_3	**7c**	76	**8c**[c]	87
4					CH_3CH_2	**7d**	75	**8d**[c]	89
5	**2c** Ph	Ph	**5c**[d]	93	CH_3	**7e**	62	**8e**	74
6					CH_3CH_2	**7f**	55	**8f**	72

[a] The adduct **5a** was 3:1 mixture of two diastereomers.
[b] The adduct **5b** was a 7:3 mixture of two diastereomers.
[c] 
[d] The adduct **5c** was a 13:3 mixture of two diastereomers.



Scheme 3.

2.2. Consecutive reaction of 1-chlorovinyl *p*-tolyl sulfoxides with cyanomethyllithium and lithium α-carbanion of the homologues of acetonitrile.[7]

Finally, we tried the reaction shown in Table 1. 1-Chlorovinyl *p*-tolyl sulfoxide **2a**, derived from cyclopentadecanone, was treated with 3 equiv of cyanomethyllithium at −78 °C for 10 min to give the adduct **5a** in 97% yield as a 3:1 mixture of two diastereomers (Table 1, entry 1). A diastereomeric mixture of the adduct **5a** was treated with 3 equiv of LDA followed by lithium α-carbanion of propionitrile and the reaction mixture was stirred and slowly allowed to warm to room temperature. Fortunately, this reaction gave the desired 3,5,5-trisubstituted enaminonitrile **7a** in 80% yield as colorless crystals.

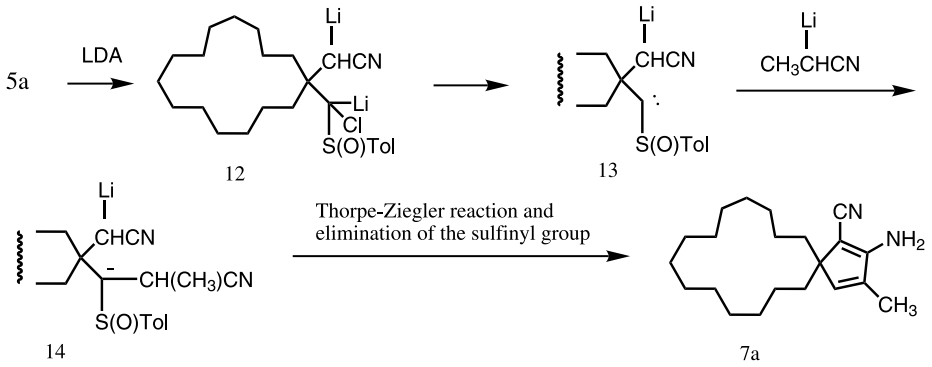
The presumed mechanism of this reaction is as follows (Scheme 4). Treatment of the adduct **5a** with 3 equiv of LDA afforded the lithium α-sulfinyl carbanion **12**. Upon warming the reaction mixture, α-elimination of LiCl took place to give α-sulfinyl carbenoid **13**. Addition of lithium α-carbanion of propionitrile to the electrophilic carbon of the carbenoid **13** resulted in the formation of the dinitrile **14**. Finally, the Thorpe–Ziegler reaction[8] of the dinitrile **14** with concomitant elimination of the *p*-tolylsulfinyl group took place to afford the enaminonitrile **7a**.

The enaminonitrile **7a** was heated under reflux in acetic acid containing H_3PO_4 and a small amount of water for 30 h to afford the desired 2,4,4-trisubstituted 2-cyclopentenone **8a** in 93% yield (Table 1, entry 1). The same reaction of **5a** with butyronitrile was carried out. As shown in Table 1, entry 2, the reaction of **5a** with lithium α-carbanion of butyronitrile gave **7b** in 76% yield, which was hydrolyzed to afford **8b** in somewhat lower yield compared with the yield in entry 1.

To ascertain the generality of this procedure, we investigated the reaction with other 1-chlorovinyl *p*-tolyl sulfoxides **2b** and **2c** with propionitrile and butyronitrile. The results are summarized in Table 1, entries 3–6. The addition reaction of **2b** and **2c** with cyanomethyllithium gave almost quantitative yields of **5b** and **5c**, respectively. In the next two steps, similar results were obtained with the adduct **5b** (entries 3 and 4). However, the reactions starting from the adduct **5c** (entries 5 and 6) showed somewhat lower yields of the enaminonitrile (**7e** and **7f**) and the 2-substituted 2-cyclopentenone (**8e** and **8f**). In any event, generality of this procedure was confirmed from the results described above.

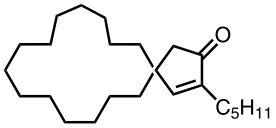
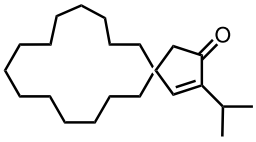
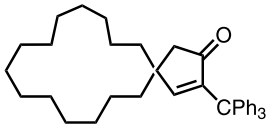
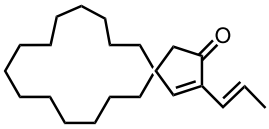
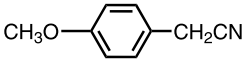
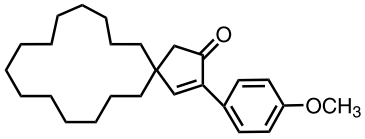
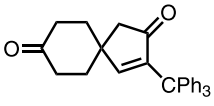
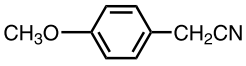
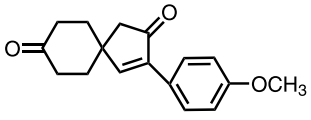
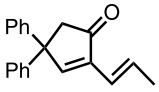
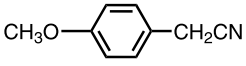
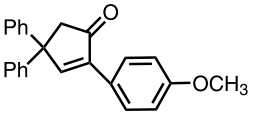
2.3. Investigation of the scope and limitation of the nitriles (R^3CH_2CN) used in this procedure

As described above, this procedure is quite a good way for the synthesis of 2,4,4-trisubstituted 2-cyclopentenones. It is interesting to investigate what kind of substituents could be introduced at the 2-position. We studied this procedure with heptanenitrile, isovaleronitrile, 3,3,3-triphenylpropionitrile,[9]



Scheme 4.

Table 2. Synthesis of 3,5,5-trisubstituted enaminonitriles **7** and 2,4,4-trisubstituted 2-cyclopentenones **8** from the adducts **5** and the homologues of acetonitrile

Entry	Adduct **5**	R^3CH_3CN	Enaminonitrile **7**		2,4,4-Trisubstituted 2-cyclopentenone **8**		Yield/%
			Yield/%				
1	**5a**	$C_6H_{13}CN$	**7g**	72	**8g**		87
2	**5a**	$(CH_3)_2CHCH_2CN$	**7h**	79	**8h**		91
3	**5a**	Ph_3CCH_2CN	**7i**	46	**8i**		51
4	**5a**	$CH_3CH{=}CHCH_2CN$	**7j**	76	**8j**		33
5	**5a**		**7k**	64	**8k**		93
6	**5b**	Ph_3CCH_2CN	**7l**	78	**8l**		89
7	**5b**		**7m**	90	**8m**		99
8	**5c**	Ph_3CCH_2CN	Complex mixture			—	
9	**5c**	$CH_3CH{=}CHCH_2CN$	**7n**	81	**8n**		61
10	**5c**		**7o**	91	**8o**		62

trans-3-pentenenitrile, and (4-methoxyphenyl)acetonitrile and the results are summarized in Table 2.

As shown in Table 2, entries 1–5, the reaction of the adduct **5a** with the five nitriles mentioned above gave the desired enaminonitriles **7g–k** in variable yields (46–79%). The acidic hydrolysis of **7g–k** gave the enones **8g–k**, respectively, in good to high yields except **8j**. Long-chain and branched-chain hydrocarbons were placed on the 2-position in good overall yields (entries 1 and 2). 2-Cyclopentenone having a quite bulky substituent (triphenylmethyl group) **8i** was also synthesized by this procedure though the overall yield was not satisfactory (entry 3). The enaminonitrile having an unsaturated carbon chain on the 2-position, **7j**, could be synthesized without problem (entry 4); however, the acidic hydrolysis gave a rather complex reaction mixture and only 33% of the 2-cyclopentenone **8j** could be obtained. Acetonitrile having an aromatic group could be used in this reaction and the 2-cyclopentenone directly combined with the aromatic ring at the 2-position **8k** could be obtained in good overall yield (entry 5).

Entries 6 and 7 show the results of the reaction of **5b** with 3,3,3-triphenylpropionitrile and (4-methoxyphenyl)acetonitrile. The desired enones **8l** and **8m** were obtained in high overall yields. Entries 8–10 show the results of the reaction of **5c** with 3,3,3-triphenylpropionitrile, *trans*-3-pentenenitrile, and (4-methoxyphenyl)acetonitrile. Interestingly, the reaction of **5c** with 3,3,3-triphenylpropionitrile only gave a complex mixture (entry 8). Two other reactions gave the desired enones **8n** and **8o** in moderate overall yields.

2.4. Synthesis of 2-(3-hydroxypropyl)-4,4-dimethyl-2-cyclopentenone from acetone by this procedure

Many cyclopentanoid natural products have geminal methyl groups on the cyclopentane ring.[1] As an application of our method described above, we planned to synthesize 2-(3-hydroxypropyl)-4,4-dimethyl-2-cyclopentenone **8q**, which was reported to be an intermediate in the total synthesis of alliacolide,[10] from acetone (Scheme 5).

1-Chlorovinyl *p*-tolyl sulfoxide **2d** was synthesized from acetone in high overall yield.[5b] The vinyl sulfoxide **2d** was treated with cyanomethyllithium to give the adduct **5d** in quantitative yield as a 17:4 mixture of two diastereomers. First, **5d** was treated with 3 equiv of LDA followed by the dianion of 5-hydroxypentanenitrile under the conditions described above. The desired enaminonitrile bearing a 3-hydroxypropyl group at the 3-position **7p** was obtained; however, the yield was not satisfactory. The presence of the free hydroxyl group in the reaction was thought to be the reason for the lowered yield.

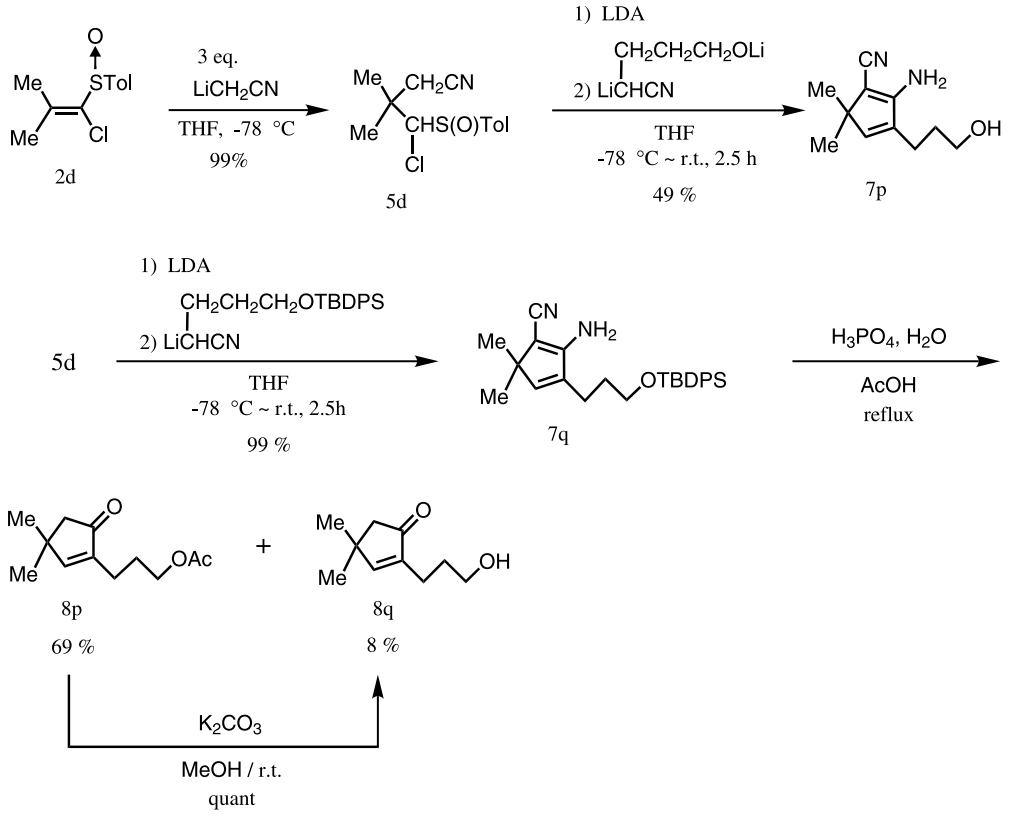
Next, O-protected 5-hydroxypentanenitrile was reacted with **5d** under the same conditions described above. As expected, the desired enaminonitrile **7q** was obtained in quantitative yield. Finally, **7q** was heated under reflux in acetic acid containing H_3PO_4 and water. We obtained the desired 2-(3-hydroxypropyl)-4,4-dimethyl-2-cyclopentenone **8q**; however, the main product was found to be the acetate **8p**. The acetate **8p** was transformed, in the usual manner, to give the alcohol **8q** in a quantitative yield. As a whole, the desired **8q**[10] was obtained from **7q** in 77% yield.

2.5. Asymmetric synthesis of optically active 3,5,5-trisubstituted enaminonitriles and 2,4,4-trisubstituted 2-cyclopentenones

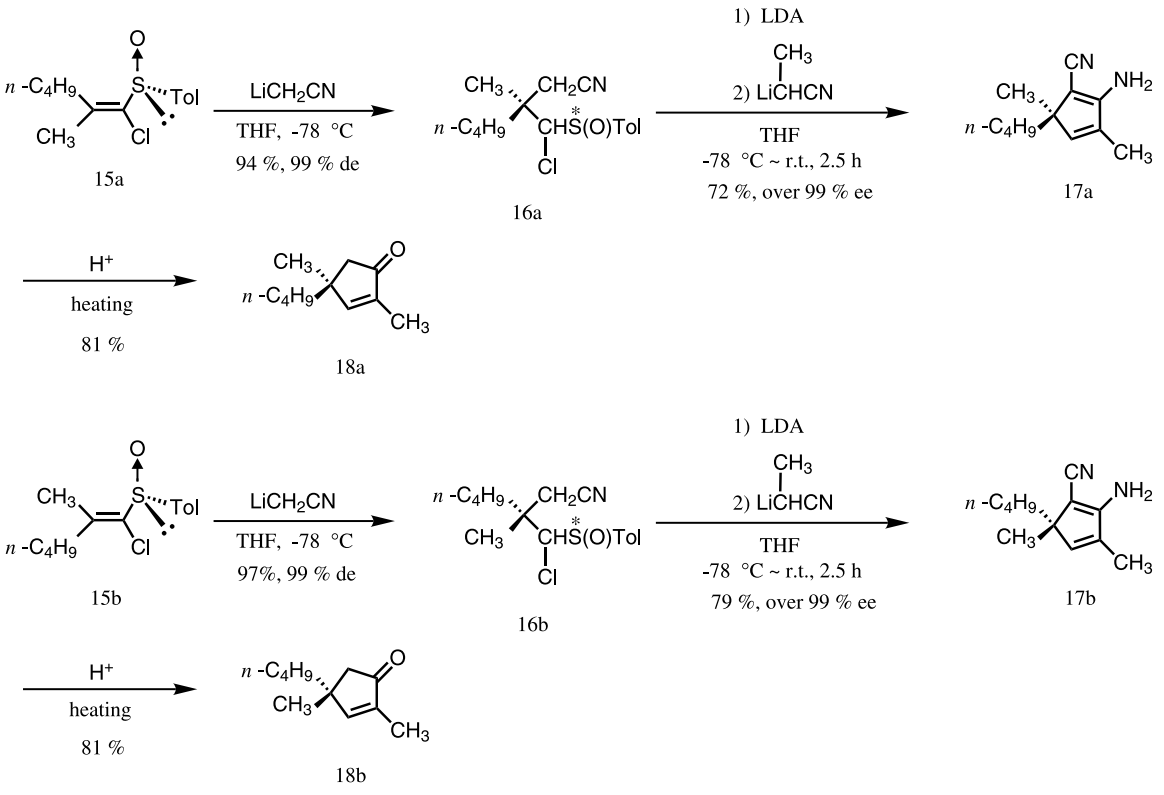
We previously reported an asymmetric synthesis of 4,4-disubstituted 2-pentenones **4** from the optically active 1-chlorovinyl *p*-tolyl sulfoxides **2** via the optically active enaminonitriles **3** (Scheme 1).[6] As an extension of our new synthetic method described above, we investigated the feasibility for the asymmetric synthesis of the 2,4,4-trisubstituted 2-cyclopentenones (Scheme 6).

Optically pure *E*-1-chloro-1-hexenyl *p*-tolyl sulfoxide **15a** and its *Z*-isomer **15b** were synthesized from 2-hexanone and (*R*)-chloromethyl *p*-tolyl sulfoxide[11] as reported before.[6b] First, **15a** was treated with cyanomethyllithium at −78 °C for 10 min to afford the adduct **16a** as a 17:4 mixture of two diastereomers. These diastereomers could be separated by column chromatography and from the ^{1}H NMR spectrum of each diastereomers, they were found to be diastereomerically pure. The diastereomers are thought to be based on the two chiral carbons. This meant that the diastereomeric excess of these isomers was over 99%.

Next, a mixture of the adduct **16a** was treated with 3 equiv of LDA at −78 °C followed by lithium α-carbanion of propionitrile in a similar manner described above. This reaction gave optically active **17a** as an oil in 72% yield. We measured the optical purity of the product using HPLC with CHIRALCEL OD and found that it was over 99%. As the stereochemistry of the asymmetric induction of the reaction of the vinyl sulfoxides **15** and cyanomethyllithium was

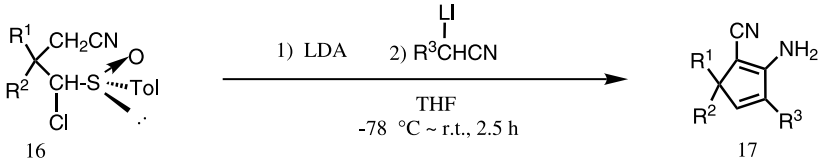


Scheme 5.



Scheme 6.

Table 3. Synthesis of optically 3,5,5-trisubstituted cyclopentadienyl enaminonitriles **17** from the optically active adduct **16** with lithium α-carbanion of heptanenitrile and isovaleronitrile



Entry	Adduct **16**	Nitrile	Enaminonitrile **17**	Yield/%	Enantiomeric excess/% ee[a]
1	**16a**	$C_6H_{13}CN$	**17c**	88	98
2	**16b**	$C_6H_{13}CN$	**17d**	81	99
3	**16a**	$(CH_3)_2CHCH_2CN$	**17e**	83	>99
4	**16b**	$(CH_3)_2CHCH_2CN$	**17f**	89	>99

[a] The enantiomeric excess was measured by using HPLC with CHIRALCEL OD (hexane/2-propanol=20:1).

already established by our previous work,[6b] the absolute configuration of **17a** is *R*. Finally, the optically active **17a** was treated in the acidic media to give optically pure (*S*)-4-butyl-2,4-dimethyl-2-cyclopentenone **18a** in 81% yield ($[\alpha]_D^{30} = -46.7$).

In a similar way, the addition reaction of **15b** with cyanomethyllithium gave the adduct **16b** as a 7:2 mixture of two diastereomers with 99% diastereomeric excess. From **16b** the enaminonitrile **17b** and the optically pure (*R*)-4-butyl-2,4-dimethyl-2-cyclopentenone **18b** (the enantiomer of **18a**) were synthesized in similar chemical yields. The specific rotation of **18b** showed +43.4.

Table 3 shows the results for the asymmetric synthesis of optically active enaminonitriles **17c–f** from **16a** and **16b** with hexanenitrile and isovaleronitrile. As shown in the table, both enantiomers of the enaminonitriles were obtained in 81–89% yield with over 98% enantiomeric excess. These results show that the procedure described above is a quite versatile and reliable method for the preparation of optically active 2,4,4-trisubstituted 2-cyclopentenones.

3. Experimental

3.1. General

All melting points are uncorrected. ^{1}H NMR spectra were measured in a $CDCl_3$ solution with JEOL JNM-LA 500 spectrometer. Electron-impact mass spectra (MS) were obtained at 70 eV by direct insertion. Silica gel 60 (Merck) containing 0.5% fluorescence reagent 254 and a quartz column were used for column chromatography and the products having UV absorption were detected by UV irradiation. In experiments requiring a dry reagent and solvent, diisopropylamine was distilled from CaH_2 and THF was distilled from diphenylketyl. Acetone was dried over $CaSO_4$ and distilled before use. 1-Chlorovinyl *p*-tolyl sulfoxides **2** used in this study were synthesized from the corresponding ketones and chloromethyl *p*-tolyl sulfoxide as reported before.[5,6]

2a, **2b**, **2c**, **2d**, **3a**, **10**, **15a**, and **15b** are known compounds.[5,6]

3.1.1. {1-[Chloro(*p*-tolylsulfinyl)methyl]cyclopentadecyl}acetonitrile (5a). Acetonitrile (0.096 ml; 1.80 mmol) was added to a solution of *n*-BuLi (1.80 mmol) in 10 ml of dry THF at −78 °C with stirring. The solution was stirred for 10 min and a solution of **2a** (237.0 mg; 0.60 mmol) in 2 ml of dry THF was added. The reaction mixture was stirred for 10 min and the reaction was quenched by adding satd aq. NH_4Cl. The whole was extracted with $CHCl_3$. The products (less polar product **5a-L** and more polar product **5a-P**) were isolated by silica gel column chromatography to give **5a-L** (190.8 mg; 73%) and **5a-P** (61.9 mg; 23%) as a colorless oil.

Compound **5a-L**. IR (neat) 2930, 2858, 2243 (CN), 1461, 1083, 1054 (SO), 812, 756 cm^{-1}; ^{1}H NMR δ 1.31–1.44 (24H, m), 1.73 (2H, br t, J=11.6 Hz), 1.99 (2H, br quintet, J=14.3 Hz), 2.44 (3H, s), 2.65, 3.24 (each 1H, d, J=17.1 Hz), 4.56 (1H, s), 7.35, 7.74 (each 2H, d, J=8.3 Hz). MS *m*/*z* (%) 435 (M^+, 1.4), 419 (1.8), 385 (4), 296 (4), 260 (7), 248 (5), 141 (9), 140 (100), 139 (10). Calcd for $C_{25}H_{38}ClNOS$: M, 435.2363. Found: *m*/*z* 435.2376.

Compound **5a-P**. IR (neat) 2929, 2858, 2242 (CN), 1461, 1089, 1060 (SO), 811, 756 cm^{-1}; ^{1}H NMR δ 1.31–1.59 (24H, m), 1.76–1.79 (2H, m), 1.88–1.98 (2H, m), 2.44 (3H, s), 2.80, 2.85 (each 1H, d, J=17.1 Hz), 4.26 (1H, s), 7.36, 7.48 (each 2H, d, J=8.3 Hz). MS *m*/*z* (%) 435 (M^+, 1.5), 419 (2.2), 385 (7), 296 (4), 260 (7), 248 (4), 221 (4), 140 (100), 139 (10). Calcd for $C_{25}H_{38}ClNOS$: M, 435.2363. Found: *m*/*z* 435.2372.

3.1.2. {8-[Chloro(*p*-tolylsulfinyl)methyl]-1,4-dioxaspiro[4.5]dec-8-yl}acetonitrile (5b). *Compound* **5b-L**. Colorless crystals, mp 110–111 °C (AcOEt–hexane); IR (KBr) 2948, 2881, 2243 (CN), 1454, 1107, 1082, 1053 (SO), 813, 503 cm^{-1}; ^{1}H NMR δ 1.61–1.79 (4H, m), 1.85–1.88 (1H, m), 2.01–2.05 (1H, m), 2.25–2.31 (1H, m), 2.36–2.41 (1H, m), 2.44 (3H, s), 2.90, 3.46 (each 1H, d, J=17.1 Hz), 3.96 (4H, s), 4.69 (1H, s), 7.35, 7.75 (each 2H, d, J=8.3 Hz). MS *m*/*z* (%) 367 (M^+, 11), 230 (32), 228 (100), 200 (16), 192 (49), 184 (40), 148 (26), 140 (66), 139 (35), 120 (16). Anal. Calcd for $C_{18}H_{22}ClNO_3S$: C, 58.77; H, 6.03; Cl, 9.64; N, 3.81; S, 8.72%. Found: C, 58.80; H, 5.78; Cl, 9.55; N, 3.74; S, 8.70%.

Compound **5b-P**. Colorless crystals, mp 166–167 °C (AcOEt–hexane); IR (KBr) 2940, 2897, 2239 (CN), 1114, 1085, 1053 (SO), 820, 515 cm^{-1}; ^{1}H NMR δ 1.67–2.20 (6H, m), 2.32–2.42 (2H, m), 2.44 (3H, s), 2.90, 2.99 (each 1H, d, J=17.4 Hz), 3.97 (4H, s), 4.48 (1H, s), 7.36, 7.48 (each 2H, d, J=8.2 Hz). MS *m*/*z* (%) 367 (M^+, 15), 230 (32), 228 (100), 192 (61), 184 (38), 148 (30), 140 (68), 139 (34), 120 (16). Anal. Calcd for $C_{18}H_{22}ClNO_3S$: C, 58.77; H, 6.03; Cl, 9.64; N, 3.81; S, 8.72%. Found: C, 58.77; H, 5.91; Cl, 9.55; N, 3.73; S, 8.72%.

3.1.3. 4-Chloro-3,3-diphenyl-4-(*p*-tolylsulfinyl)butyronitrile (5c). *Compound* **5c-L**. Colorless crystals, mp 198–199 °C (AcOEt–hexane); IR (KBr) 2950, 2926, 2247 (CN), 1595, 1494, 1443, 1083, 1051 (SO), 705 cm^{-1}; ^{1}H NMR δ 2.44 (3H, s), 3.54, 4.34 (each 1H, d, J=16.2 Hz), 5.31 (1H, s), 7.22 (2H, d, J=6.7 Hz), 7.29–7.35 (5H, m), 7.49 (3H, m), 7.60–7.63 (2H, m), 7.72 (2H, d, J=8.0 Hz). MS *m*/*z* (%) 393 (M^+, trace), 254 (73), 214 (54), 179 (66), 178 (65), 140 (100), 139 (26). Anal. Calcd for $C_{23}H_{20}ClNOS$: C, 70.13; H, 5.12; Cl, 9.00; N, 3.56; S, 8.14%. Found: C, 70.01; H, 4.94; Cl, 8.93; N, 3.57; S, 8.16%.

Compound **5c-P**. Colorless crystals, mp 68–69 °C (AcOEt–hexane); IR (KBr) 2926, 2852, 2241 (CN), 1632, 1495, 1447, 1087, 1058 (SO), 700 cm^{-1}; ^{1}H NMR δ 2.41 (3H, s), 3.57, 3.85 (each 1H, d, J=17.1 Hz), 5.01 (1H, s), 7.26–7.48 (14H, m). MS *m*/*z* (%) 393 (M^+, trace), 256 (31), 254 (95), 218 (40), 214 (69), 179 (78), 178 (77), 140 (100), 139 (30). Anal. Calcd for $C_{23}H_{20}ClNOS$: C, 70.13; H, 5.12; Cl, 9.00; N, 3.56; S, 8.14%. Found: C, 69.94; H, 5.25; Cl, 8.94; N, 3.58; S, 7.76%.

3.1.4. 2-Amino-3-methylspiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7a). To a solution of LDA (0.23 mmol) in

2 ml of dry THF was added a solution **5a** (33.1 mg; 0.076 mmol) in 1 ml of dry THF at −78 °C and the reaction mixture was stirred for 30 min. To the reaction mixture was added lithium α-carbanion of propionitrile (0.30 mmol), which was generated from propionitrile and *n*-BuLi at −78 °C, through a cannula and the temperature of the reaction mixture was slowly allowed to warm to room temperature for 2.5 h. The reaction mixture was quenched by satd aq. NH_4Cl. The whole was extracted with $CHCl_3$. The product was isolated by silica gel column chromatography to give 19.0 mg (80%) of **7a** as colorless crystals; mp 162–164 °C (AcOEt–hexane); IR (KBr) 3424 (NH), 3346 (NH), 2930, 2854, 2168 (CN), 1648, 1623, 1565, 1451, 1421 cm^{-1}; ^1H NMR δ 1.34–1.59 (28H, m), 1.85 (3H, d, $J=1.3$ Hz), 4.42 (2H, br s, NH), 6.20 (1H, q, $J=1.3$ Hz). MS *m/z* (%) 315 (25), 314 (M^+, 100), 147 (20), 134 (24), 133 (38), 132 (17). Anal. Calcd for $C_{21}H_{34}N_2$: C, 80.20; H, 10.90; N, 8.91%. Found: C, 80.18; H, 10.94; N, 8.91%.

3.1.5. 2-Amino-3-ethylspiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7b). Colorless crystals; mp 132–134 °C (AcOEt–hexane); IR (KBr) 3427 (NH), 3347 (NH), 2932, 2855, 2166 (CN), 1646, 1563, 1459, 1423, 842 cm^{-1}; ^1H NMR δ 1.16 (3H, t, $J=7.3$ Hz), 1.26–1.54 (28H, m), 2.16 (2H, q, $J=7.3$ Hz), 4.40 (2H, br s, NH), 6.18 (1H, s). MS *m/z* (%) 329 (26), 328 (M^+, 100), 161 (18), 159 (15), 148 (24), 147 (43), 146 (22). Anal. Calcd for $C_{22}H_{36}N_2$: C, 80.43; H, 11.04; N, 8.53%. Found: C, 80.30; H, 11.10; N, 8.43%.

3.1.6. 10-Amino-11-methyl-1,4-dioxa-dispiro[4.2.4.2]-tetradeca-9,11-diene-9-carbonitrile (7c). Colorless crystals; mp 243–244 °C ($CHCl_3$–hexane); IR (KBr) 3405 (NH), 3356 (NH), 3245, 2929, 2165 (CN), 1663, 1560, 1452, 1092 cm^{-1}; ^1H NMR δ 1.45 (2H, br d, $J=12.8$ Hz), 1.73 (2H, dt, $J=12.8$, 4.1 Hz), 1.89 (3H, s), 1.92 (2H, m), 2.02 (2H, br t, $J=12.4$ Hz), 3.97 (4H, s), 4.46 (2H, br s, NH), 6.49 (1H, s). MS *m/z* (%) 246 (M^+, 32), 218 (26), 145 (15), 133 (15), 132 (100), 131 (14). Anal. Calcd for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37%. Found: C, 67.88; H, 7.32; N, 11.30%.

3.1.7. 10-Amino-11-ethyl-1,4-dioxa-dispiro[4.2.4.2]tetradeca-9,11-diene-9-carbonitrile (7d). Colorless crystals; mp 195–196 °C (AcOEt–hexane); IR (KBr) 3410 (NH), 3354 (NH), 3245, 2964, 2162 (CN), 1661, 1557, 1436, 1090 cm^{-1}; ^1H NMR δ 1.18 (3H, t, $J=7.3$ Hz), 1.45 (2H, br d, $J=12.9$ Hz), 1.75 (2H, dt, $J=12.9$, 4.2 Hz), 1.92 (2H, br d, $J=13.2$ Hz), 2.03 (2H, br t, $J=10.4$ Hz), 2.19 (2H, dt, $J=7.3$, 1.8 Hz), 3.97 (4H, s), 4.48 (2H, br s, NH), 6.46 (1H, br s). MS *m/z* (%) 261 (9), 260 (M^+, 40), 232 (27), 147 (20), 146 (100), 131 (15). Calcd for $C_{15}H_{20}N_2O_2$: M, 260.1524. Found: *m/z* 260.1525.

3.1.8. 2-Amino-3-methyl-5,5-diphenylcyclopenta-1,3-diene-1-carbonitrile (7e). Colorless crystals; mp 171–172 °C (AcOEt–hexane); IR (KBr) 3456 (NH), 3366 (NH), 3232, 2166 (CN), 1654, 1624, 1563, 1445, 698 cm^{-1}; ^1H NMR δ 1.96 (3H, d, $J=1.5$ Hz), 4.69 (2H, br s, NH), 6.62 (1H, q, $J=1.5$ Hz), 7.21–7.29 (10H, m). MS *m/z* (%) 273 (23), 272 (M^+, 100), 258 (21), 257 (52), 195 (15). Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.79; H, 5.92; N, 10.29%. Found: C, 83.38; H, 5.76; N, 10.19%.

3.1.9. 2-Amino-3-ethyl-5,5-diphenylcyclopenta-1,3-diene-1-carbonitrile (7f). Colorless crystals; mp 164–165 °C (AcOEt–hexane); IR (KBr) 3352 (NH), 3232 (NH), 2969, 2175 (CN), 1651, 1562, 1490, 1445, 758, 699 cm^{-1}; ^1H NMR δ 1.24 (3H, t, $J=7.3$ Hz), 2.26 (2H, q, $J=7.3$ Hz), 4.69 (2H, br s, NH), 6.58 (1H, s), 7.22–7.29 (10H, m). MS *m/z* (%) 287 (25), 286 (M^+, 95), 271 (62), 256 (34), 257 (100). Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.34; N, 9.78%. Found: C, 83.63; H, 6.09; N, 9.75%.

3.1.10. 3-Methylspiro[4.14]nonadec-3-en-2-one (8a). To a solution **7a** (97.2 mg; 0.31 mmol) in 21 ml acetic acid was added phosphoric acid (85%, 9 ml) and water (2 ml). The reaction mixture was stirred and heated under reflux for 32 h. The reaction mixture was neutralized with 10% aq. NaOH and the whole was extracted with $CHCl_3$. The product was isolated by silica gel column chromatography to give 83.3 mg (93%) of **8a** as a colorless oil; IR (neat) 2929, 2857, 1709 (CO), 1639, 1459, 1330, 756 cm^{-1}; ^1H NMR δ 1.31–1.44 (28H, m), 1.73 (3H, d, $J=1.3$ Hz), 2.19 (2H, s), 7.23 (1H, q, $J=1.3$ Hz). MS *m/z* (%) 291 (16), 290 (M^+, 69), 262 (28), 123 (27), 110 (39), 109 (100), 108 (35). Calcd for $C_{20}H_{34}O$: M, 290.2608. Found: *m/z* 290.2625.

3.1.11. 3-Ethylspiro[4.14]nonadec-3-en-2-one (8b). Colorless oil; IR (neat) 2930, 2857, 1709 (CO), 1460 cm^{-1}; ^1H NMR δ 1.07 (3H, t, $J=7.5$ Hz), 1.33–1.44 (28H, m), 2.15 (2H, dq, $J=7.5$, 1.1 Hz), 2.21 (2H, s), 7.19 (1H, t, $J=1.1$ Hz). MS *m/z* (%) 305 (25), 304 (M^+, 100), 137 (24), 124 (53), 123 (80), 122 (24). Calcd for $C_{21}H_{36}O$: M, 304.2764. Found: *m/z* 304.2774.

3.1.12. 3-Methylspiro[4.5]dec-3-ene-2,8-dione (8c). Colorless crystals; mp 84–85 °C (AcOEt–hexane); IR (KBr) 2963, 2946, 2868, 1712 (CO), 1701 (CO), 1637, 1069, 977 cm^{-1}; ^1H NMR δ 1.80 (3H, d, $J=1.2$ Hz), 1.82–1.86 (2H, m), 1.94–2.00 (2H, m), 2.44–2.51 (4H, m), 2.49 (2H, s), 7.21 (1H, q, $J=1.2$ Hz). MS *m/z* (%) 179 (14), 178 (M^+, 100), 122 (42), 121 (31), 108 (92). Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92%. Found: C, 73.90; H, 7.80%.

3.1.13. 3-Ethylspiro[4.5]dec-3-ene-2,8-dione (8d). Colorless crystals; mp 58–59 °C (AcOEt–hexane); IR (KBr) 2970, 2933, 1698 (CO), 1337, 970 cm^{-1}; ^1H NMR δ 1.11 (3H, t, $J=7.5$ Hz), 1.81–1.85 (2H, m), 1.94–2.00 (2H, m), 2.21 (2H, q, $J=7.5$ Hz), 2.44–2.48 (4H, m), 2.50 (2H, s), 7.15 (1H, s). MS *m/z* (%) 193 (10), 192 (M^+, 100), 164 (32), 136 (73), 135 (45), 123 (18), 122 (74), 121 (20), 107 (23). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39%. Found: C, 74.92; H, 8.30%.

3.1.14. 2-Methyl-4,4-diphenyl-2-cyclopentenone (8e). Colorless crystals; mp 91–92 °C (hexane); IR (KBr) 1697 (CO), 1493, 1445, 752, 704 cm^{-1}; ^1H NMR δ 1.88 (3H, d, $J=1.2$ Hz), 3.17 (2H, s), 7.14–7.33 (10H, m), 7.63 (1H, d, $J=1.2$ Hz). MS *m/z* (%) 249 (22), 248 (M^+, 100), 220 (39), 205 (93), 171 (35), 129 (21), 128 (35), 115 (25). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49%. Found: C, 86.83; H, 6.26%.

3.1.15. 2-Ethyl-4,4-diphenyl-2-cyclopentenone (8f). Colorless oil; IR (neat) 3059, 3026, 2969, 2935, 1709 (CO), 1634, 1597, 1493, 1446, 761, 700 cm^{-1}; ^1H NMR δ

1.17 (3H, t, J=7.4 Hz), 2.30 (2H, dq, J=7.4, 1.2 Hz), 3.18 (2H, s), 7.13–7.33 (10H, m), 7.58 (1H, br t, J=1.2 Hz). MS *m/z* (%) 263 (22), 262 (M^+, 100), 261 (53), 233 (39), 205 (68), 185 (18), 157 (39), 129 (18), 115 (26). Calcd for $C_{19}H_{18}O$: M, 262.1356. Found: *m/z* 262.1342.

3.1.16. 2-Amino-3-pentylspiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7g). Colorless crystals; mp 109–110 °C (hexane); IR (KBr) 3424 (NH), 3359 (NH), 2929, 2857, 2165 (CN), 1673, 1648, 1557 cm^{-1}; ^1H NMR δ 0.91 (3H, t, J=6.9 Hz), 1.33–1.57 (34H, m), 2.12 (2H, dt, J=7.7, 1.4 Hz), 4.39 (2H, br s, NH), 6.17 (1H, t, J=1.4 Hz). MS *m/z* (%) 371 (29), 370 (M^+, 100), 313 (32), 189 (18), 145 (10), 132 (12). Anal. Calcd for $C_{25}H_{42}N_2$: C, 81.02; H, 11.42; N, 7.56%. Found: C, 81.12; H, 11.63; N, 7.48%.

3.1.17. 2-Amino-3-isopropylspiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7h). Colorless crystals; mp 113–115 °C (AcOEt–hexane); IR (KBr) 3434 (NH), 3349 (NH), 2932, 2852, 2165 (CN), 1643, 1559, 1459, 1420 cm^{-1}; ^1H NMR δ 1.14 (6H, d, J=6.7 Hz), 1.34–1.55 (28H, m), 2.41 (1H, septet, J=6.7 Hz), 4.44 (2H, br s, NH), 6.17 (1H, s). MS *m/z* (%) 343 (28), 342 (M^+, 100), 327 (28), 299 (22), 161 (24). Anal. Calcd for $C_{23}H_{38}N_2$: C, 80.64; H, 11.18; N, 8.18%. Found: C, 80.77; H, 11.41; N, 8.08%.

3.1.18. 2-Amino-3-(triphenylmethyl)spiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7i). Colorless crystals; mp 202–203 °C (AcOEt–hexane); IR (KBr) 3483 (NH), 2930, 2856, 2182 (CN), 1637, 1552, 1492, 1445, 702 cm^{-1}; ^1H NMR δ 1.26–1.66 (28H, m), 3.87 (2H, br s, NH), 6.18 (1H, s), 7.16 (6H, m), 7.24–7.34 (9H, m). MS *m/z* (%) 543 (43), 542 (M^+, 100), 456 (16), 243 (37), 165 (11). Anal. Calcd for $C_{39}H_{46}N_2$: C, 86.30; H, 8.54; N, 5.16%. Found: C, 85.83; H, 8.50; N, 5.00%.

3.1.19. (*E*)-2-Amino-3-propenylspiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7j). Colorless crystals; mp 92–93 °C (hexane); IR (KBr) 3484 (NH), 3342 (NH), 2930, 2856, 2177 (CN), 1662, 1557, 1423, 961 cm^{-1}; ^1H NMR δ 1.34–1.54 (28H, m), 1.84 (3H, d, J=6.4 Hz), 4.50 (2H, br s, NH), 5.97 (1H, d, J=15.9 Hz), 6.06 (1H, dq, J=15.9, 6.4 Hz), 6.37 (1H, s). MS *m/z* (%) 341 (26), 340 (M^+, 100), 173 (16), 160 (18), 159 (18), 111 (13). Anal. Calcd for $C_{23}H_{36}N_2$: C, 81.12; H, 10.66; N, 8.23%. Found: C, 81.20; H, 10.89; N, 8.07%.

3.1.20. 2-Amino-3-(4-methoxyphenyl)spiro[4.14]nonadeca-1,3-diene-1-carbonitrile (7k). Colorless crystals; mp 164–165 °C (AcOEt–hexane); IR (KBr) 3459 (NH), 2930, 2855, 2173 (CN), 1645, 1603, 1509, 1247, 832 cm^{-1}; ^1H NMR δ 1.27–1.70 (28H, m), 3.84 (3H, s), 4.55 (2H, br s, NH), 6.44 (1H, s), 6.94, 7.28 (each 2H, d, J=8.6 Hz). MS *m/z* (%) 407 (29), 406 (M^+, 100), 304 (7), 225 (12), 224 (5), 146 (6). Anal. Calcd for $C_{27}H_{38}N_2O$: C, 79.76; H, 9.42; N, 6.89%. Found: C, 79.79; H, 9.47; N, 6.74%.

3.1.21. 10-Amino-11-(triphenylmethyl)-1,4-dioxa-dispiro[4.2.4.2]tetradeca-9,11-diene-9-carbonitrile (7l). Colorless crystals; mp > 300 °C (AcOEt–hexane); IR (KBr) 3478 (NH), 3336 (NH), 2941, 2893, 2180 (CN), 1653, 1556, 1491, 1099, 750, 703 cm^{-1}; ^1H NMR δ 1.57–1.67 (4H, m), 1.90–1.93 (2H, m), 2.05–2.10 (2H, m), 3.91 (2H, br s, NH), 3.92–3.98 (4H, m), 6.43 (1H, s), 7.14–7.32 (15H, m). MS *m/z* (%) 475 (37), 474 (M^+, 100), 360 (17), 242 (15), 243 (57), 165 (17). Calcd for $C_{32}H_{30}N_2O_2$: M, 474.2305. Found: *m/z* 474.2299.

3.1.22. 10-Amino-11-(4-methoxyphenyl)-1,4-dioxa-dispiro[4.2.4.2]tetradeca-9,11-diene-9-carbonitrile (7m). Colorless crystals; mp 223 °C (AcOEt–hexane); IR (KBr) 3462 (NH), 3353 (NH), 2937, 2893, 2169 (CN), 1647, 1509, 1247, 1106, 1031, 837 cm^{-1}; ^1H NMR δ 1.55–1.62 (2H, m), 1.79 (2H, dt, J=12.7, 3.7 Hz), 1.96 (2H, br d, J=13.1 Hz), 2.12 (2H, br t, J=11.3 Hz), 3.84 (3H, s), 3.98 (4H, s), 4.61 (2H, br s, NH), 6.71 (1H, s), 6.96, 7.29 (each 2H, d, J=8.9 Hz). MS *m/z* (%) 339 (24), 338 (M^+, 100), 294 (28), 293 (22), 276 (28), 237 (35), 246 (66). Anal. Calcd for $C_{20}H_{22}N_2O_3$: C, 70.99; H, 6.55; N, 8.28%. Found: C, 71.04; H, 6.59; N, 8.14%.

3.1.23. (*E*)-2-Amino-5,5-diphenyl-3-propenylcyclopenta-1,3-diene-1-carbonitrile (7n). Colorless crystals; mp 146–147 °C (AcOEt–hexane); IR (KBr) 3474 (NH), 3421 (NH), 3330 (NH), 3230 (NH), 3026, 2183 (CN), 1657, 1557, 761, 701 cm^{-1}; ^1H NMR δ 1.86 (3H, d, J=6.4 Hz), 4.77 (2H, br s, NH), 6.03 (1H, d, J=15.9 Hz), 6.17 (1H, dq, J=15.9, 6.4 Hz), 6.75 (1H, s), 7.22–7.30 (10H, m). MS *m/z* (%) 299 (25), 298 (M^+, 100), 297 (38), 283 (26), 205 (13). Calcd for $C_{21}H_{18}N_2$: M, 298.1468. Found: *m/z* 298.1462.

3.1.24. 2-Amino-3-(4-methoxyphenyl)-5,5-diphenylcyclopenta-1,3-diene-1-carbonitrile (7o). Colorless crystals; mp 171–173 °C (AcOEt–hexane); IR (KBr) 3465 (NH), 3344 (NH), 3058, 2179 (CN), 1650, 1621, 1604, 1508, 1242, 1027, 831, 701 cm^{-1}; ^1H NMR δ 3.84 (3H, s), 4.84 (2H, br s, NH), 6.84 (1H, s), 6.96 (2H, d, J=8.6 Hz), 7.25–7.32 (10H, m), 7.34 (2H, d, J=8.6 Hz). MS *m/z* (%) 365 (28), 364 (M^+, 100), 349 (8), 287 (11). Anal. Calcd for $C_{25}H_{20}N_2O$: C, 82.39; H, 5.53; N, 7.69%. Found: C, 82.35; H, 5.47; N, 7.63%.

3.1.25. 3-Pentylspiro[4.14]nonadec-3-en-2-one (8g). Colorless oil; IR (neat) 2929, 2857, 1709 (CO), 1460 cm^{-1}; ^1H NMR δ 0.89 (3H, t, J=7.0 Hz), 1.24–1.49 (34H, m), 2.11 (2H, dt, J=15.4, 1.3 Hz), 2.20 (2H, s), 7.19 (1H, t, J=1.3 Hz). MS *m/z* (%) 347 (28), 346 (M^+, 100), 166 (13), 165 (32), 163 (12), 151 (12), 109 (10). Calcd for $C_{24}H_{42}O$: M, 346.3233. Found: *m/z* 346.3226.

3.1.26. 3-Isopropylspiro[4.14]nonadec-3-en-2-one (8h). Colorless oil; IR (neat) 2930, 2858, 1708 (CO), 1460, 1369, 1002 cm^{-1}; ^1H NMR δ 1.07 (6H, d, J=6.7 Hz), 1.33–1.44 (28H, m), 2.20 (2H, s), 2.59 (1H, double septet, J=6.7, 1.0 Hz), 7.15 (1H, d, J=1.0 Hz). MS *m/z* (%) 319 (26), 318 (M^+, 100), 276 (20), 275 (15), 138 (32), 137 (40). Calcd for $C_{22}H_{38}O$: M, 318.2920. Found: *m/z* 318.2913.

3.1.27. 3-(Triphenylmethyl)spiro[4.14]nonadec-3-en-2-one (8i). Colorless crystals; mp 144–145 °C (AcOEt–hexane); IR (KBr) 3056, 3029, 2928, 2855, 1715 (CO), 1492, 1446, 746, 699 cm^{-1}; ^1H NMR δ 1.27–1.50 (28H, m), 2.30 (2H, s), 7.12–7.26 (15H, m), 7.32 (1H, s). MS *m/z* (%) 519 (40), 518 (M^+, 100), 441 (8), 296 (30), 268 (9), 243 (11), 215 (7), 165 (10). Anal. Calcd for $C_{38}H_{46}O$: C, 87.98; H, 8.94%. Found: C, 88.06; H, 8.97%.

3.1.28. (*E*)-3-Propenylspiro[4.14]nonadec-3-en-2-one (8j). Colorless oil; IR (neat) 2930, 2857, 1709 (CO), 1459, 971 cm^{-1}; ^1H NMR δ 1.33–1.46 (28H, m), 1.78 (3H, dd, J=6.7, 1.5 Hz), 2.25 (2H, s), 6.04 (1H, dd, J=15.3, 1.5 Hz), 6.62 (1H, dq, J=15.3, 6.7 Hz), 7.26 (1H, s). MS *m/z* (%) 317 (26), 316 (M^+, 100), 149 (18), 136 (25), 121 (9), 105 (8). Calcd for $C_{22}H_{36}O$: M, 316.2765. Found: *m/z* 316.2772.

3.1.29. 3-(4-Methoxyphenyl)spiro[4.14]nonadec-3-en-2-one (8k). Colorless crystals; mp 54–55 °C (hexane); IR (KBr) 2928, 2854, 1698 (CO), 1600, 1509, 831 cm^{-1}; ^1H NMR δ 1.35–1.54 (28H, m), 2.38 (2H, s), 3.82 (3H, s), 6.90 (2H, d, J=8.6 Hz), 7.64 (1H, s), 7.67 (2H, d, J=8.6 Hz). MS *m/z* (%) 383 (29), 382 (M^+, 100), 354 (18), 201 (18), 159 (7), 121 (8). Anal. Calcd for $C_{26}H_{38}O_2$: C, 81.62; H, 10.01%. Found: C, 81.74; H, 10.14%.

3.1.30. 3-(Triphenylmethyl)spiro[4.5]dec-3-ene-2,8-dione (8l). Colorless crystals; mp 242–243 °C (AcOEt–hexane); IR (KBr) 3050, 2933, 1712 (CO), 1490, 1444, 751, 702 cm^{-1}; ^1H NMR δ 1.88 (2H, m), 1.96–2.04 (2H, m), 2.40–2.46 (4H, m), 2.60 (2H, s), 7.11–7.28 (16H, m). MS *m/z* (%) 407 (33), 406 (M^+, 100), 329 (28), 296 (68), 268 (30), 243 (24), 165 (31). Anal. Calcd for $C_{29}H_{26}O_2$: C, 85.68; H, 6.45%. Found: C, 85.30; H, 6.51%.

3.1.31. 3-(4-Methoxyphenyl)spiro[4.5]dec-3-ene-2,8-dione (8m). Colorless crystals; mp 106–107 °C (AcOEt–hexane); IR (KBr) 2944, 2872, 1709 (CO), 1693 (CO), 1612, 1599, 1510, 1256, 833 cm^{-1}; ^1H NMR δ 1.91–1.95 (2H, m), 2.03–2.09 (2H, m), 2.45–2.56 (4H, m), 2.68 (2H, s), 3.83 (3H, s), 6.93 (2H, d, J=9.2 Hz), 7.59 (1H, s), 7.71 (2H, d, J=9.2 Hz). MS *m/z* (%) 271 (19), 270 (M^+, 100), 212 (63), 213 (88), 200 (28). Anal. Calcd for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71%. Found: C, 75.69; H, 6.73%.

3.1.32. (*E*)-4,4-Diphenyl-2-propenyl-2-cyclopentenone (8n). Colorless crystals; mp 59–60 °C (AcOEt–hexane); IR (KBr) 3023, 2933, 1705 (CO), 1489, 1444, 976, 764, 701 cm^{-1}; ^1H NMR δ 1.84 (3H, dd, J=6.7, 1.5 Hz), 3.21 (2H, s), 6.15 (1H, dd, J=15.9, 1.5 Hz), 6.75 (1H, dq, J=15.9, 6.7 Hz), 7.14–7.32 (10H, m), 7.62 (1H, s). MS *m/z* (%) 275 (25), 274 (M^+, 100), 231 (72), 217 (48), 170 (45), 155 (38), 142 (32), 128 (38), 115 (37). Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61%. Found: C, 87.64; H, 6.46%.

3.1.33. 2-(4-Methoxyphenyl)-4,4-diphenyl-2-cyclopentenone (8o). Colorless crystals; mp 159–160 °C (AcOEt–hexane); IR (KBr) 2835, 1702 (CO), 1605, 1509, 1254, 1035, 835, 758, 701 cm^{-1}; ^1H NMR δ 3.34 (2H, s), 3.83 (3H, s), 6.93 (2H, d, J=8.9 Hz), 7.21–7.27 (6H, m), 7.32–7.35 (4H, m), 7.76 (2H, d, J=8.9 Hz), 8.01 (1H, s). MS *m/z* (%) 341 (28), 340 (M^+, 100), 312 (15), 281 (16), 263 (16), 235 (21), 221 (25). Anal. Calcd for $C_{24}H_{20}O_2$: C, 84.68; H, 5.92%. Found: C, 84.36; H, 5.88%.

3.1.34. 3-Chloro-2,2-dimethyl-3-(*p*-tolylsulfinyl)propionitrile (5d). *Compound* **5d-L**. Colorless crystals, mp 62 °C (AcOEt–hexane); IR (KBr) 2973, 2939, 2243 (CN), 1082, 1046 (SO), 809, 501 cm^{-1}; ^1H NMR δ 1.41 (3H, s), 1.52 (3H, s), 2.44 (3H, s), 2.76, 3.12 (each 1H, d, J=16.8 Hz), 4.44 (1H, s), 7.34, 7.73 (each 2H, d, J=8.2 Hz). MS *m/z* (%) 269 (M^+, 9), 140 (100), 139 (56), 92 (43), 91 (22). Anal. Calcd for $C_{13}H_{16}ClNOS$: C, 57.88; H, 5.98; Cl, 13.14; N, 5.19; S, 11.88%. Found: C, 57.84; H, 5.88; Cl, 13.08; N, 5.11; S, 11.74%.

Compound **5d-P**. Colorless crystals, mp 136 °C (AcOEt–hexane); IR (KBr) 2980, 2946, 2239 (CN), 1087, 1054 (SO), 811, 515 cm^{-1}; ^1H NMR δ 1.48 (3H, s), 1.51 (3H, s), 2.44 (3H, s), 2.71, 2.76 (each 1H, d, J=16.8 Hz), 4.24 (1H, s), 7.36, 7.49 (each 2H, d, J=8.2 Hz). MS *m/z* (%) 269 (M^+, 9), 140 (100), 139 (54), 92 (44), 91 (17). Anal. Calcd for $C_{13}H_{16}ClNOS$: C, 57.88; H, 5.98; Cl, 13.14; N, 5.19; S, 11.88%. Found: C, 57.71; H, 5.85; Cl, 13.08; N, 5.05; S, 11.82%.

3.1.35. 2-Amino-3-(3-hydroxypropyl)-5,5-dimethylcyclopenta-1,3-diene-1-carbonitrile (7p). Colorless oil; IR (neat) 3361 (OH), 2930, 2173 (CN), 1652, 1565 cm^{-1}; ^1H NMR δ 1.23 (6H, s), 1.77–1.82 (2H, m), 2.31 (2H, t, J=7.3 Hz), 2.42 (1H, t, J=7.0 Hz), 3.69–3.73 (2H, m), 4.68 (2H, br s, NH), 6.12 (1H, s). MS *m/z* (%) 192 (M^+, 61), 177 (41), 159 (23), 147 (100), 133 (54), 132 (31), 131 (22). Calcd for $C_{11}H_{16}N_2O$: M, 192.1262. Found: *m/z* 192.1261.

3.1.36. 2-Amino-3-[3-(*tert*-butyldiphenylsilanyloxy)propyl]-5,5-dimethylcyclopenta-1,3-diene-1-carbonitrile (7q). Colorless oil; IR (neat) 3355 (NH), 3072, 2931, 2859, 2177 (CN), 1651, 1567, 1428, 1111 (OSi), 702 cm^{-1}; ^1H NHR δ 1.07 (9H, s), 1.20 (6H, s), 1.70–1.76 (2H, m), 2.29 (2H, t, J=6.7 Hz), 3.70 (2H, t, J=5.8 Hz), 4.59 (2H, br s, NH), 6.03 (1H, s), 7.38–7.46 (6H, m), 7.64–7.66 (4H, m). MS *m/z* (%) 430 (M^+, 14), 374 (24), 373 (100), 295 (17), 199 (35). Calcd for $C_{27}H_{34}N_2OSi$: M, 430.2441. Found: *m/z* 430.2434.

3.1.37. 3-(3,3-Dimethyl-5-oxocyclopent-1-enyl)propyl acetate (8p). Colorless oil; IR (neat) 2959, 2867, 1741 (CO), 1706 (CO), 1242 (COC), 1044, 756 cm^{-1}; ^1H NMR δ 1.20 (6H, s), 1.69–1.75 (2H, m), 2.05 (3H, s), 2.22 (2H, dt, J=7.6, 1.3 Hz), 2.28 (2H, s,), 4.07 (2H, t, J=6.6 Hz), 7.07 (1H, t, J=1.3 Hz). MS *m/z* (%) 210 (M^+, trace), 151 (16), 150 (100), 135 (95), 107 (44). Calcd for $C_{12}H_{18}O_3$: M, 210.1256. Found: *m/z* 210.1259.

3.1.38. 2-(3-Hydroxypropyl)-4,4-dimethyl-2-cyclopentenone (8q). To a solution of **8p** (12.9 mg; 0.061 mmol) in MeOH (3 ml) was added aq. K_2CO_3 (0.5 M, 0.4 ml) at room temperature and the reaction mixture was stirred for 40 min. The whole was extracted with $CHCl_3$. The product was isolated by silica gel column chromatography to give **8q** (10.2 mg; 99%) as a colorless oil; IR (neat) 3419 (OH), 2958, 2869, 1695 (CO), 1060 cm^{-1}; ^1H NMR δ 1.21 (6H, s), 1.80–1.85 (2H, m), 2.04 (1H, br s, OH), 2.26 (2H, t, J=7.3 Hz), 2.30 (2H, s), 3.59 (2H, br t, J=5.3 Hz), 7.10 (1H, s). MS *m/z* (%) 168 (M^+, 8), 150 (90), 135 (100), 125 (15), 122 (24), 112 (30), 109 (67), 107 (62). Calcd for $C_{10}H_{16}O_2$: M, 168.1148. Found: *m/z* 168.1133.

3.1.39. (*S*)-(R_S)-2-[Chloro(*p*-tolylsulfinyl)methyl]-2-methylhexanenitrile (16a). 16a-L/16a-P=17:4.

Compound **16a-L**. Colorless oil; IR (neat) 2959, 2872, 2243 (CN), 1462, 1055 (SO), 813 cm^{-1}; ^1H NMR δ 0.96 (3H, t,

J=7.0 Hz), 1.32–1.47 (4H, m), 1.39 (3H, s), 1.85–1.91 (1H, m), 1.97–2.03 (1H, m), 2.44 (3H, s), 2.64, 3.18 (each 1H, d, J=16.8 Hz), 4.55 (1H, s), 7.35, 7.74 (each 2H, d, J=8.0 Hz). MS *m/z* (%) 311 (M^+, 4), 142 (5), 141 (9), 140 (100), 139 (18), 123 (5). Calcd for $C_{16}H_{22}ClNOS$: M, 311.1111. Found: *m/z* 311.1115.

Compound **16a-P**. Colorless oil; IR (neat) 2933, 2864, 2238 (CN), 1089, 1060 (SO), 813, 514 cm^{-1}; ^1H NMR δ 0.97 (3H, t, J=7.0 Hz), 1.32–1.44 (4H, m), 1.40 (3H, s), 1.82–1.88 (1H, m), 1.92–1.98 (1H, m), 2.44 (3H, s), 2.79, 2.85 (each 1H, d, J=17.1 Hz), 4.35 (1H, s), 7.36, 7.48 (each 2H, d, J=8.3 Hz).

Racemic **16a-P**. Colorless crystals; mp 67–68 °C (AcOEt–hexane); IR (KBr) 2943, 2870, 2236 (CN), 1084, 1047 (SO), 816, 517 cm^{-1}; Anal. Calcd for $C_{16}H_{22}ClNOS$: C, 61.62; H, 7.11; Cl, 11.37; N, 4.49; S, 10.28%. Found: C, 61.63; H, 7.07; Cl, 11.24; N, 4.49; S, 10.09%.

3.1.40. (*R*)-(*R*$_S$)-2-[Chloro(*p*-tolylsulfinyl)methyl]-2-methylhexanenitrile (16b). 16b-L/16b-P=7:2.

Compound **16b-L**. Colorless oil; IR (neat) 2960, 2865, 2243 (CN), 1597, 1463, 1082, 1051 (SO), 813, 756 cm^{-1}; ^1H NMR δ 0.93 (3H, t, J=6.9 Hz), 1.20–1.39 (4H, m), 1.48 (3H, s), 1.71–1.80 (2H, m), 2.44 (3H, s), 3.00, 3.05 (each 1H, d, J=16.8 Hz), 4.42 (1H, s), 7.35, 7.73 (each 2H, d, J=8.0 Hz). MS *m/z* (%) 311 (M^+, 4), 142 (5), 141 (9), 140 (100), 139 (18), 124 (5), 123 (5). Calcd for $C_{16}H_{22}ClNOS$: M, 311.1110. Found: *m/z* 311.1120.

Compound **16b-P**. Colorless crystals; mp 120–121 °C (AcOEt–hexane); IR (KBr) 2940, 2872, 2240 (CN), 1463, 1087, 1050 (SO), 816, 518 cm^{-1}; ^1H NMR δ 0.96 (3H, t, J=7.2 Hz), 1.27–1.34 (2H, m), 1.37–1.43 (2H, m), 1.47 (3H, s), 1.78–1.84 (1H, m), 1.88–1.95 (1H, m), 2.44 (3H, s), 2.68, 2.81 (each 1H, d, J=17.1 Hz), 4.27 (1H, s), 7.36, 7.48 (each 2H, d, J=8.2 Hz). Anal. Calcd for $C_{16}H_{22}ClNOS$: C, 61.62; H, 7.11; Cl, 11.37; N, 4.49; S, 10.28%. Found: C, 61.57; H, 7.03; Cl, 11.31; N, 4.47; S, 10.15%.

Racemic **16b-P**. Colorless crystals; mp 94–95 °C (AcOEt–hexane).

3.1.41. (*R*)-2-Amino-5-butyl-3,5-dimethylcyclopenta-1,3-diene-1-carbonitrile (17a) and (*S*)-2-amino-5-butyl-3,5-dimethylcyclopenta-1,3-diene-1-carbonitrile (17b).

Colorless oil; IR (neat) 3446 (NH), 3359 (NH), 3242 (NH), 2959, 2929, 2862, 2175 (CN), 1652, 1568, 1456, 828 cm^{-1}; ^1H NMR δ 0.85 (3H, t, J=7.3 Hz), 1.07–1.12 (2H, m), 1.20 (3H, s), 1.22–1.28 (2H, m), 1.53–1.61 (2H, m), 1.87 (3H, d, J=1.6 Hz), 4.42 (2H, br s, NH), 6.07 (1H, q, J=1.6 Hz). MS *m/z* (%) 191 (5), 190 (M^+, 29), 147 (45), 134 (60), 133 (100), 118 (22). Calcd for $C_{12}H_{18}N_2$: M, 190.1469. Found: *m/z* 190.1469.

Compound **17a**. $[\alpha]_D^{27}=-122.1$ (c 2.0, acetone).

Compound **17b**. $[\alpha]_D^{27}=+119.4$ (c 1.11, acetone).

3.1.42. (*S*)-4-Butyl-2,4-dimethylcyclopent-2-enone (18a) and (*R*)-4-butyl-2,4-dimethylcyclopent-2-enone (18b).

Colorless oil; IR (neat) 2958, 2928, 1713 (CO), 1640, 1456, 1328 cm^{-1}; ^1H NMR δ 0.89 (3H, t, J=7.2 Hz), 1.16 (3H, s), 1.18–1.32 (4H, m), 1.38–1.50 (2H, m), 1.74 (3H, d, J=1.2 Hz), 2.14, 2.32 (each 1H, d, J=18.6 Hz), 7.05 (1H, q, J=1.2 Hz). MS *m/z* (%) 166 (M^+, 25), 123 (10), 110 (32), 109 (100). Calcd for $C_{11}H_{18}O$: M, 166.1356. Found: *m/z* 166.1356.

Compound **18a**. $[\alpha]_D^{30}=-46.7$ (c 0.88, acetone).

Compound **18b**. $[\alpha]_D^{30}=+43.4$ (c 1.55, acetone).

3.1.43. (*R*)-2-Amino-5-butyl-5-methyl-3-pentylcyclopenta-1,3-dienecarbonitrile (17c) and (*S*)-2-amino-5-butyl-5-methyl-3-pentyl-cyclopenta-1,3-dienecarbonitrile (17d).

Colorless oil; IR (neat) 3462 (NH), 3358 (NH), 3252 (NH), 2929, 2860, 2175 (CN), 1651, 1564, 1457, 1417, 1379 cm^{-1}; ^1H NMR δ 0.85 (3H, t, J=7.3 Hz), 0.90–0.92 (3H, m), 1.06–1.13 (2H, m), 1.21 (3H, s), 1.22–1.26 (2H, m), 1.21–1.35 (6H, m), 1.51–1.55 (2H, m), 2.14 (2H, t, J=7.6 Hz), 4.42 (2H, br s, NH), 6.04 (1H, s). MS *m/z* (%) 246 (M^+, 40), 203 (44), 190 (77), 189 (100), 165 (28), 133 (89), 132 (31). Calcd for $C_{16}H_{26}N_2$: M, 246.2094. Found: *m/z* 246.2097.

Compound **17c**. $[\alpha]_D^{27}=-64.2$ (c 0.65, acetone).

Compound **17d**. $[\alpha]_D^{27}=+63.9$ (c 1.14, acetone). Racemic compound is colorless crystals, low melting solid; IR (KBr) 3451 (NH), 3355 (NH), 3250 (NH), 2929, 2860, 2170 (CN), 1651, 1567, 1467, 1419, 1379 cm^{-1}.

3.1.44. (*R*)-2-Amino-5-butyl-3-isopropyl-5-methylcyclopenta-1,3-dienecarbonitrile (17e) and (*S*)-2-amino-5-butyl-3-isopropyl-5-methylcyclopenta-1,3-dienecarbonitrile (17f).

Colorless oil; IR (neat) 3445 (NH), 3359 (NH), 3249 (NH), 2962, 2929, 2175 (CN), 1652, 1615, 1558, 1417 cm^{-1}; ^1H NMR δ 0.85 (3H, t, J=7.3 Hz), 1.02–1.13 (2H, m), 1.15 (6H, d, J=7.0 Hz), 1.19–1.26 (2H, m), 1.20 (3H, s), 1.56–1.61 (2H, m), 2.42 (1H, septet, J=7.0 Hz), 4.45 (2H, br s, NH), 6.03 (1H, s). MS *m/z* (%) 219 (10), 218 (M^+, 44), 203 (35), 175 (60), 162 (68), 161 (100), 147 (55), 146 (57). Calcd for $C_{14}H_{22}N_2$: M, 218.1781. Found: *m/z* 218.1778.

Compound **17e**. $[\alpha]_D^{29}=-80.7$ (c 0.91, acetone).

Compound **17f**. $[\alpha]_D^{28}=+86.6$ (c 1.48, acetone). Racemic compound is colorless crystals; mp 66–67 °C (hexane); IR (KBr) 3440 (NH), 3354 (NH), 3251 (NH), 2963, 2928, 2164 (CN), 1671, 1648, 1560, 1419 cm^{-1}.

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Synthesis of novel *N*-methylated thiazole-based cyclic octa- and dodecapeptides

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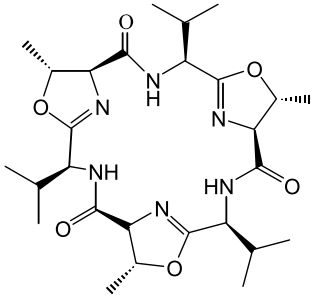
Abstract—Novel *N*-methylated valine-thiazole cyclic octa- and dodecapeptides are produced by cyclooligomerisation of a *N*-methylated-L-valine thiazole amino acid HCl in the presence of pentafluorophenyl diphenylphosphinate (FDPP).

1. Introduction

A large number of cytotoxic structures containing modified amino acids in the form of azole heterocycles have been isolated from marine organisms in recent years. Examples include the lissoclinums **1** and **2** from ascidians,[1] argyrin B (**3**)[2] and the apratoxins **4** and **5**.[3] The size and conformations of these macrocycles, and the heteroatoms and functional groups they accommodate, have suggested that they may exhibit novel metal ion binding and transport functions.[4] A number of other cyclic peptides are derived from *N*-methylated amino acids, and this substitution drastically alters the structural conformations they adopt, and hence their biological activity.

This feature is well illustrated by the differing biological activity shown by apratoxin A (**4**) and B (**5**), where **4** exhibits high levels of cytotoxicity against various cancer cell lines (IC_{50} values of 0.36 nM against LoVo cells),[5] whereas apratoxin B (**5**), having one less *N*-methylated amide residue, is two orders of magnitude less potent.

In earlier studies we have demonstrated the scope for cyclooligomerisation and metal templated synthesis of unusual cyclopeptidic structures from heterocyclic based amino acids[6,7] including a synthesis of a proline-thiazole cyclic tetramer[8] having structural features in common with the novel telomerase inhibitor telomestatin.[9] Several of these novel cyclopeptide isosteres show significant binding to the c-Myc quadruplex, which has emerged as an attractive target for anti-cancer therapeutic agents.[10] In continuation of our studies towards the synthesis of novel cyclopeptidic constructs acting on c-Myc, we have examined the cyclooligomerisation of the *N*-methyl valine-thiazole amino acid **10a**, in the synthesis of conformationally restrained *N*-methylated cyclopeptides, analogous to the apratoxins **4** and **5**.



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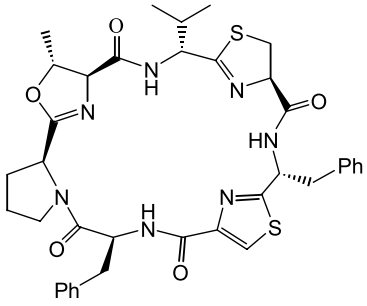

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Keywords: Dodecapeptides; Cyclooligomerisation; L-Valine thiazole.
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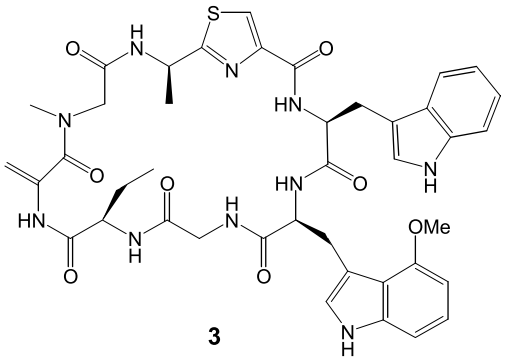

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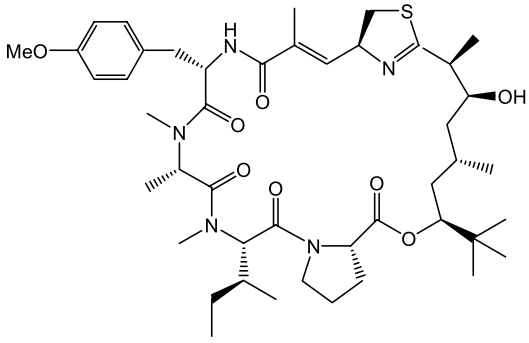

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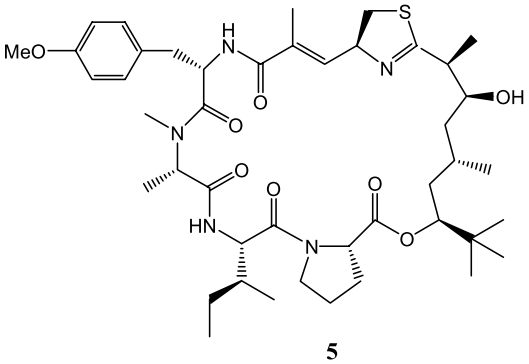

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2. Results and discussion

The known *N*-Boc protected L-valine thiazole amino acid ester **7**[11] was first synthesised starting from L-valine, following conversion to the Boc-protected thioamide **6** and a modified Hantzsch reaction with ethyl bromopyruvate. *N*-Methylation of **7**, to **8**, followed by saponification next gave the carboxylic acid **9**, which, after deprotection produced the *N*-methyl valine thiazole acid hydrochloride **10a** as colourless crystals (Scheme 1).

Treatment of the amino acid HCl **10a** with pentafluorophenyl diphenylphosphinate (FDPP) and *N*,*N*-diisopropylethylamine (DIPEA) in DMF for 3–8 days produced both the trimer **11** and the tetramer **12** in overall yields of 38–42%.

The optimum concentration for this cyclooligomerisation was found to be in the range of 10–80 mM. No reaction occurred at low concentrations (1–2 mM) whilst at higher concentrations (160 mM) yields were significantly lower. Unlike either the non *N*-methylated modified amino acids[6,7] or proline containing examples[8] we have studied previously, where the corresponding trimers are formed in preference to the tetramers (3:1), in the case of the *N*-methylated amino acid **10a**, the tetramer **12** is preferred over the trimer **11**, i.e. 3:2 to 9:1 (Table 1). Trace amounts of higher oligomers (pentamer and hexamer) were also observed by ESI mass spectrometry, but these compounds were not isolated or characterised.

Table 1

Entry[a]	Concentration (mM)	Yield (%)	Ratio (tetramer/trimer)
1	10	38	3:2
2	50	42	4:1
3	80	42	9:1
4	160	31	9:1
5[b]	50	51	4:1

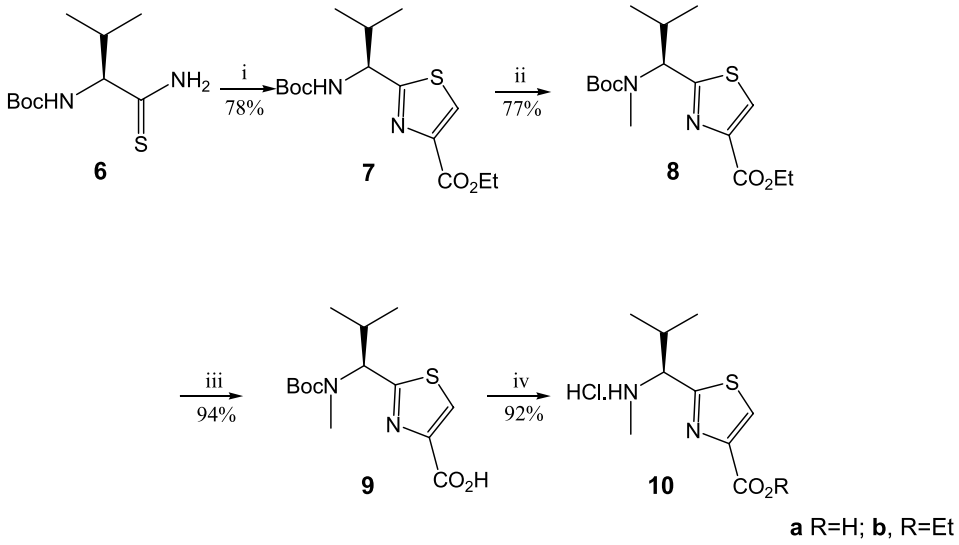
[a] Reactions were run at between 22 and 35 °C, with no change in yield or product distribution observed.
[b] Reaction carried out using pre-formed pentafluorophenol ester, with the reported yield over 3 steps (esterification, Boc deprotection and cyclooligomerisation).

The preference for the cyclic tetramer **12** in the cyclooligomerisation of **10a**, supports our initial presumption that *N*-methylation of an amino acid would result in greater steric requirements in the transition state between monomer and oligomer. This trend also increases with increasing concentration (Table 1).

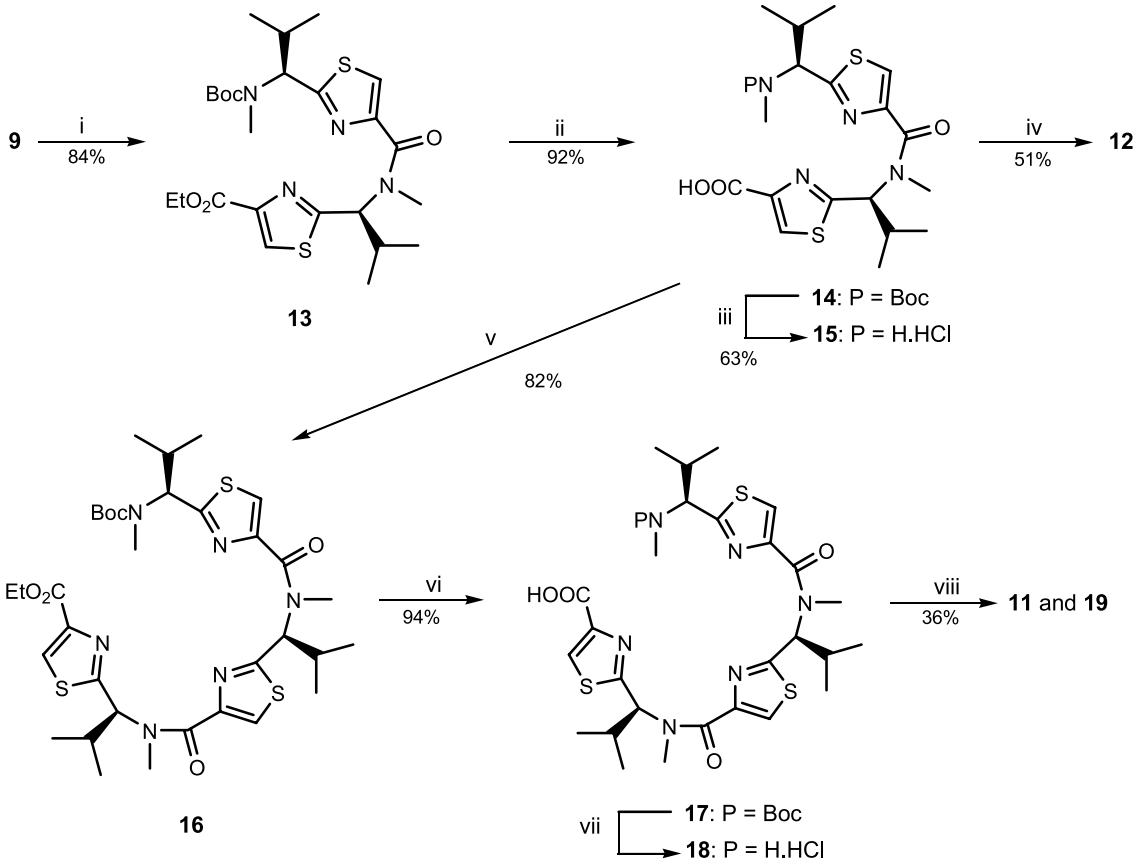
In order to further investigate the effects of *N*-methylation of amino acids in cyclopeptide formation, linear routes to the cyclopeptides **11** and **12** were also developed. Thus, coupling the carboxylic acid **9** with the ethyl ester of the amino acid **10a**, i.e. **10b** in the presence of 1-(3-dimethylaminopropyl-)-3-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxy benzotriazole (HOBt) first gave the *N*-methyl valine thiazole 'dimer' **13**. Saponification of **13** next gave the carboxylic acid **14**, which could be Boc-deprotected to the amino acid HCl salt **15**, and also subjected to a second coupling reaction with **10b** leading to the linear 'trimer' **16**. Cyclooligomerisation of the amino acid **15** in the presence of FDPP and DIPEA then gave the cyclic tetramer **12** as the sole product, in an agreeable 51% yield (Scheme 2).

In a separate sequence, saponification and *N*-Boc deprotection of **16** gave the corresponding amino acid **18**. When **18** was treated with FDPP and DIPEA it underwent cyclisation to the trimer **11** isolated in 7% yield, but the major product (29%) was the novel cyclic hexamer **19**. The structure and crystal conformation of **19** was established by X-ray crystallography (Fig. 1). The formation of the hexamer **19** from **18**, similar to the cyclooligomerisation of the monomer **10a** indicates a preference for linear *N*-methylated units to form longer chain oligomers prior to macrocyclisation over their corresponding non-methylated units.

In an identical sequence of deprotections and coupling

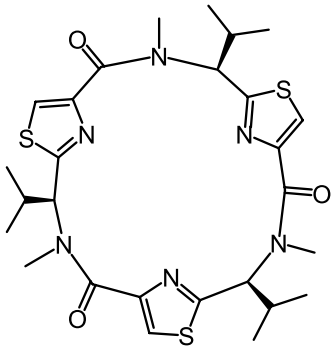


Scheme 1. Reagents: (i) $KHCO_3$, DME, ethyl bromopyruvate, −15 °C, then TFAA, collidine, −15 °C; (ii) NaH (1.3 eq), MeI (9 eq), DMF, 15 °C; (iii) NaOH, THF/H_2O (3:1); (iv) 4 M HCl in 1,4-dioxane.



Scheme 2. Reagents: (i) EDCI, HOBt, **10b**, NMM, DCM, 0 °C to RT, 40 h; (ii) NaOH, THF/H_2O (3:1), RT, 30 h; (iii) 4 M HCl in 1,4 dioxane, RT, 20 h; (iv) FDPP, DIPEA, DMF (50 mM), 35 °C, 8 d; (v) EDCI, HOBt, **10b**, NMM, 0 °C to RT, 48 h; (vi) NaOH, THF/H_2O (3:1), RT, 14 h; (vii) 4 M HCl in 1,4-dioxane, RT, 20 h; (viii) FDPP, DIPEA, DMF (7.5 mM), RT, 84 h, **11** (7%), **19** (29%).

reactions the valine-thiazole 'dimer' **13** was elaborated to **20** and then to the linear tetramer **21** (Scheme 3). Saponification of **21** followed by Boc deprotection next yielded the amino acid **22** which underwent macrocyclisation to the cyclic tetramer **12**.



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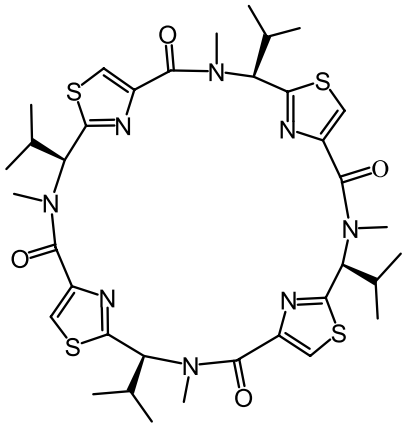

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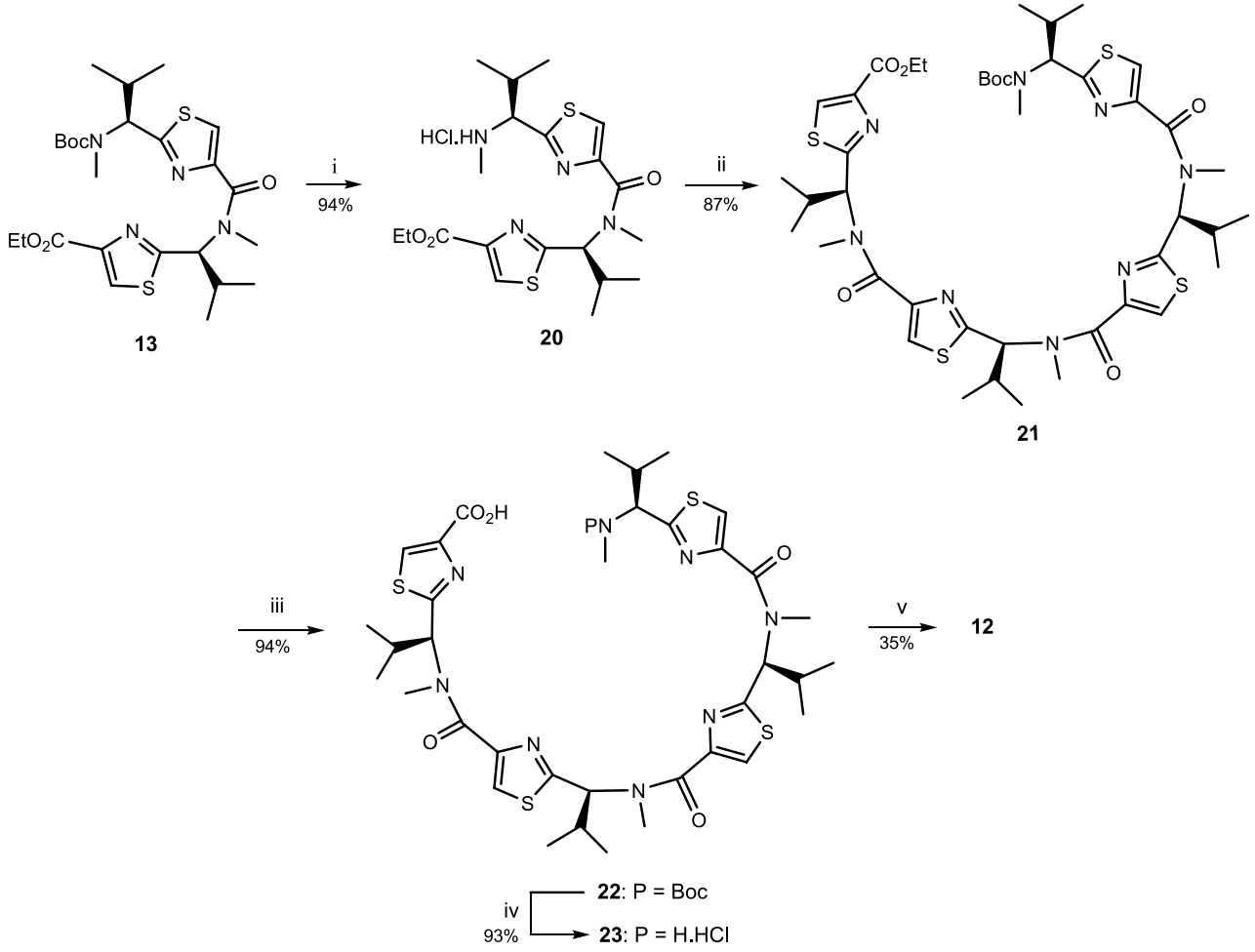
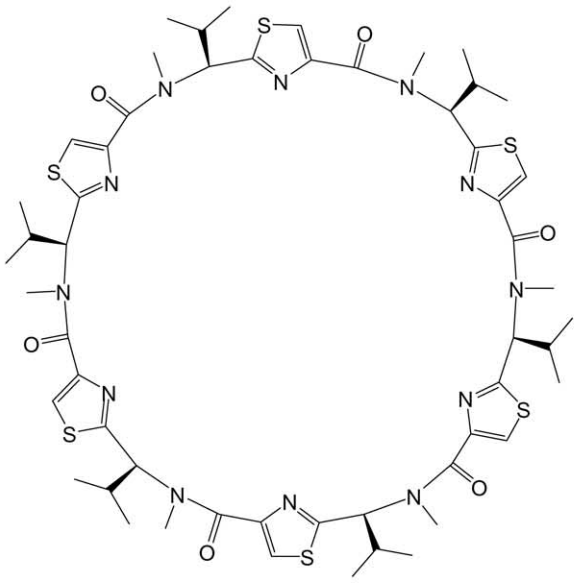
3. Conclusion

N-Methylated amino acids are commonly used in medicinal chemistry to adjust the conformations of peptides and to control their metabolic stability and prevent unfavourable hydrogen bonding observed in their N–H analogues.[12]



13 **20** **21**

Scheme 3. Reagents: (i) 4 M HCl in 1,4-dioxane, RT, 20 h; (ii) EDCI, HOBt, **15**, NMM, DCM, 0 °C to RT, 45 h; (iii) NaOH, THF/H_2O (3:1), RT, 24 h; (iv) 4 M HCl in 1,4-dioxane, RT, 20 h; (v) DPPA, DIPEA, DMF, RT, 5 days.



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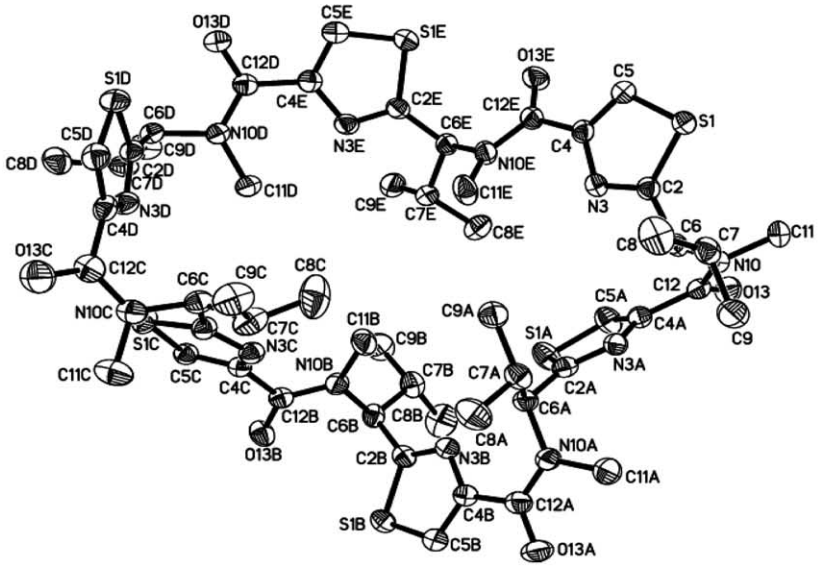

Figure 1. View of **19** showing atom labelling scheme, with atomic displacement parameters drawn at 50% probability level and hydrogen atoms and solvate molecules omitted for clarity.

The present study shows that the *N*-methylated valine thiazole amino acid **10a** has a propensity to undergo cyclooligomerisation to the cyclic tetramer **12**, rather than the corresponding trimer observed with the des-methyl analogue. In a separate study dimerisation of the linear hexapeptide **18** preferentially gave the novel dodecapeptide **19**, rather than the cyclic hexapeptide **11**.

4. Experimental

4.1. General details

For general details see Ref. 8.

4.1.1. (L)-Ethyl-2-[1-(*tert*-butoxycarbonylamino)-2-methylpropyl]-thiazole-carbanoate (7). The thiazole was prepared in 78% yield using the procedures described for the synthesis of the (D)-enantiomer in our total synthesis of (+)-nostocyclamide,[13] mp 119–120 °C (petrol–ether) (lit. (D)-enantiomer mp 118.5–119 °C); (Found: C, 54.8; H, 7.3; N, 8.5; Calc. for $C_{15}H_{24}N_2O_4S$: C, 54.9; H, 7.4; N, 8.5%); $[\alpha]_D^{22} = -44.1$ (*c* 1.26, $CHCl_3$) [lit. (D)-enantiomer $[\alpha]_D^{19} = 41.6$ (*c* 1.06, $CHCl_3$)].

4.1.2. (L)-Ethyl-2-[1-(*tert*-butoxycarbonyl-*N*-amino-methyl)-2-methylpropyl]-thiazole-4-carbonate (8). Sodium hydride (60% dispersion in oil, 0.048 g, 1.19 mmol) was added portionwise to a stirred solution of Boc-(L)-valine thiazole ester **7** (0.30 g, 0.91 mmol) and iodomethane (0.51 ml, 8.2 mmol) in DMF (3.6 ml) at −5 °C. The mixture was allowed to warm to 15 °C where

it was stirred for 72 h. The mixture was quenched with 10% aq. NH_4Cl (300 ml) and then extracted with EtOAc (3× 60 ml). The combined organic extracts were washed with sat. aq. $NaHCO_3$ (60 ml) and brine (60 ml) and then dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel using petrol–ethyl acetate (9:1) as eluent to give the *N*-methyl valine thiazole (0.24 g, 77%) as a colourless oil. $[\alpha]_D^{22}=-129.9$ (*c* 1.17, $CHCl_3$); ν_{max} ($CHCl_3$) 1722 and 1693 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) main rotamer, 0.93 (3H, d, $J=6.4$ Hz, $(CH_3)_2CH$), 1.00 (3H, d, $J=6.4$ Hz, $(CH_3)_2CH$), 1.39 (3H, t, $J=7.1$ Hz, CH_3CH_2), 1.46 (9H, s, $(CH_3)_3C$), 2.60–2.78 (1H, m, $CH(CH_3)_2$), 2.81 (3H, s, NCH_3), 4.40 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 4.85–5.11 (1H, m, $CHNCH_3$), 8.09 (s, CHS); δ_C(125.8 MHz, $CDCl_3$, $T=298$ K) main rotamer, 14.3 (q, CH_3), 19.3 (q, CH_3), 20.5 (q, CH_3), 29.2 (q, $(CH_3)_3C$), 29.5 (d, CH), 30.0 (q, NCH_3), 61.4 (t, CH_2), 62.9 (d, CH), 80.2 (s, $(CH_3)_3C$), 128.0 (d, CHS), 146.8 (s, NC=CH), 155.3 (s, N=CS), 161.5 (s, $CONCH_3$), 169.6 (s, CO_2Et); *m/z* (FAB) 343.1679 ($M+H^+$, $C_{16}H_{27}N_2O_4S$ requires 343.1692).

4.1.3. (L)-2-[1-(*tert*-Butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]-thiazole-4-carboxylic acid (9). Sodium hydroxide (0.69 g, 17.3 mmol) was added in one portion to a solution of the ester **8** (0.74 g, 2.16 mmol) in THF/water (16 ml; 3:1). The mixture was stirred at room temperature for 16 h, then cooled to −5 °C, acidified to pH 2 with 2 N HCl solution and extracted with DCM (2×40 ml). The combined DCM extracts were washed with brine (2× 30 ml) then dried ($MgSO_4$) and concentrated in vacuo to leave a residue which was triturated with ether. The solvent was removed under vacuum and the residue was dried under oil pump vacuum to leave the thiazole carboxylic acid (0.63 g, 94%) as a colourless foam; mp 116–117 °C (triturated with ether); $[\alpha]_D^{22}=-150.1$ (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 3427, 1761 and 1681 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) 3:2 mixture of rotamers, 0.94 (6H, d, $J=6.5$ Hz, 2×$(CH_3)_2CH$), 1.00 (6H, d, $J=6.1$ Hz, 2×$(CH_3)_2CH$), 1.47 and 1.52 (18H, 2×s, 2×$(CH_3)_3C$), 2.58–2.72 (2H, m, 2×$CH(CH_3)_2$), 2.80 and 2.83 (6H, 2×s, 2×NCH_3), 4.89 and 5.10 (2H, 2×d, $J=10.9$, 11.3 Hz, 2×$CHNCH_3$), 8.30 (2H, br, 2×CHS); δ_C(90.5 MHz, $CDCl_3$, $T=298$ K) 3:2 mixture of rotamers, 19.4 (q, CH_3), 19.7 (q, CH_3), 20.6 (q, 2×CH_3), 29.2 (q, 2×$(CH_3)_3C$), 29.1 (s, 2× NCH_3), 30.5 (d, $CH(CH_3)_2$), 32.0 (d, $CH(CH_3)_2$), 62.9 (d, $CHNCH_3$), 64.0 (d, $CHNCH_3$), 80.1 (s, $C(CH_3)_3$), 80.7 (s, $C(CH_3)_3$), 127.6 (s, CHS), 128.0 (s, CHS), 146.7 (s, 2×NC=CH), 155.3 (s, N=CS), 156.0 (s, N=CS), 161.4 (s, 2×CONMe), 169.6 (s, 2×CO_2H); *m/z* (FAB) 337.1184 ($M+Na^+$, $C_{14}H_{22}N_2O_4SNa$ requires 337.1197).

4.1.4. (L)-2-Amino-[1-(*N*-aminomethyl)-2-methylpropyl]-thiazole-4-carboxylic acid hydrochloride salt (10a). A solution of hydrochloric acid (4 M) in 1,4-dioxane (15 ml) was added to a stirred solution of the Boc-(L)-valine-thiazole acid **9** (1.77 g, 5.6 mmol) in 1,4-dioxane and the mixture was stirred at RT for 3 h. Toluene (3×40 ml) was added and the dioxane–toluene azeotrope was removed to leave the amine hydrochloride salt (1.33 g, 95%) which crystallised as colourless crystals; mp 233–234 °C (ethyl acetate–ethanol); $[\alpha]_D^{23}=-26.2$ (*c* 1.04, MeOH); ν_{max} (MeOH) 3814, 2304, and 2009 cm^{-1}; δ_H(360 MHz, CD_3OD, $T=298$ K) 1.00 (3H, d, $J=6.8$ Hz, $(CH_3)_2CH$), 1.16 (3H, d, $J=6.9$ Hz, $(CH_3)_2CH$), 2.50 (1H, hp, $J=6.7$ Hz, $CH(CH_3)_2$), 2.70 (3H, s, NCH_3), 4.73 (1H, d, $J=6.1$ Hz, $CHNCH_3$), 7.38–7.68 (1H, m, $NHCH_3$), 8.54 (1H, s, CHS); δ_C(125 MHz, CD_3OD, $T=298$ K) 17.2 (q, NCH_3), 19.1 (q, 2×CH_3), 32.4 (d, $CH(CH_3)_2$), 65.9 (d, $CHNCH_3$), 128.5 (d, CHS), 136.3 (s, NC=CH), 148.8 (s, N=CS), 163.5 (s, CO_2H); *m/z* (FAB) 215.0846 ($M+H^+$, $C_9H_{15}N_2O_2S$ requires 215.0854).

4.1.5. (L)-Ethyl-2-[1-(*N*-aminomethyl)-2-methlypropyl]-thiazole-4-carbanoate hydrochloride (10b). A solution of hydrochloric acid (4 M) in 1,4-dioxane (5.70 ml, 22.8 mmol) was added to a stirred solution of the Boc-(L)-valine thiazole ester **8** (1.56 g, 4.6 mmol) in 1,4-dioxane (5 ml) and the mixture was stirred at room temperature for 16 h. Toluene (3×3 ml) was added and the dioxane-toluene azeotrope was removed to leave a residue which was stirred in petrol–diethyl ether (1:1, 50 ml) for 1 h, then filtered and dried under a nitrogen filter to give the amine hydrochloride salt (1.23 g, 97%) as a colourless crystalline solid; mp 217–218 °C (ethyl acetate–dichloromethane); (Found: C, 47.3; H, 6.7; N, 9.8%; $C_{11}H_{19}N_2O_2SCl$ requires, C, 47.4; H, 6.9; N, 10.1%); $[\alpha]_D^{22}=-3.1$ (*c* 1.03, $CHCl_3$); ν_{max} ($CHCl_3$) 3125, 2971, 2678, 1726 and 1586 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) 1.03 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$), 1.31 (3H, d, $J=6.7$ Hz, $(CH_3)_2CH$), 1.42 (3H, t, $J=7.0$ Hz, CH_3CH_2), 1.69 (1H, bs, CHN), 2.67 (3H, s, CH_3N), 2.72–2.82 (1H, m, $CH(CH_3)_2$), 4.40–4.50 (1H, m, $CHNCH_3$), 4.45 (2H, q, $J=7.1$ Hz, OCH_2CH_3), 8.32 (s, CHS); δ_C(90.5 MHz, $CDCl_3$, $T=298$ K) 14.5 (q, CH_3), 18.9 (q, 2×CH_3), 20.3 (q, NCH_3), 32.1 (d, $CH(CH_3)_2$), 62.1 (t, OCH_2), 67.6 (d, $CHNCH_3$), 130.3 (s, CHS), 147.3 (s, NC=CH), 161.0 (s, N=CS), 163.5 (s, CO_2Et); *m/z* (FAB) 243.1156 ($M+H^+$, $C_{11}H_{19}N_2O_2S$ requires 243.1167).

4.1.6. Cyclic trimer (11) and cyclic tetramer (12) by cyclooligomerisation of the amine hydrochloride salt (10a). *N*,*N*-Diisopropylethylamine (63 μl, 0.36 mmol) and pentafluorophenyl diphenylphosphinate (FDPP) (138 mg, 0.36 mmol) were added to a solution of *N*-methyl-valine-thiazole hydrochloric acid salt **10a** (30.0 mg, 0.12 mmol) in DMF (1.5 ml, 80 mM) and the mixture was stirred at RT for 5 days. The mixture was quenched with sat. aq. K_2CO_3 (2 ml) and then concentrated in vacuo. The residue was dissolved in water (20 ml) and extracted with DCM (3× 20 ml). The combined organic extracts were washed with 10% aq. citric acid (30 ml), water (30 ml) and brine (30 ml) and then dried ($MgSO_4$). The filtrate was concentrated in vacuo to leave a residue which was purified by flash chromatography on silica gel using ethyl acetate–methanol (100:0)→(97:3) as eluent to give i) the cyclic-tri-(*S*),(*S*),(*S*)-valine-thiazole trimer **11** (0.9 mg, 4%). A small sample was repurified by HPLC (Water μ bondapak C18 column (4.6 mm I.D.×25 cm) using MeOH/H_2O (3:1) as solvent; flow rate 1 ml/min; R.I. detector) to afford the cyclic trimer as a colourless solid; mp 79–81 °C; $[\alpha]_D^{20}=-301.4$ (*c* 0.086, $CHCl_3$); δ_H(360 MHz, $CDCl_3$, $T=298$ K) 0.79–1.15 (18H, m, $(CH_3)_2CH$), 2.22–2.36 (3H, m, $CH(CH_3)_2$), 3.02–3.23 (9H, m, NCH_3), 4.93 and 5.64 (1H, 2×d, $J=9.6$ Hz, $CHNCH_3$), 7.03 (2H, d, $J=10.8$ Hz, $CHNCH_3$), 8.04 (1H, s, CHS), 8.08 (1H, s, CHS), 8.15 (1H, s, CHS); δ_C(90.5 MHz, $CDCl_3$, $T=298$ K) 20.1 (q, CH_3), 20.5 (q, CH_3), 30.0 (q, NCH_3), 32.3 (d, $CH(CH_3)_2$), 65.3 (d, $CHNCH_3$), 127.4 (d,

CHS), 150.0 (s, N–*C*=CH), 163.7 (s, N=CS), 168.7 (s, *C*ONCH$_3$); *m/z* (FAB) 589.2109 (M+H$^+$, $C_{27}H_{37}N_6O_3S_2$ requires 589.2089; and ii) the cyclic-tetra-(*S*),(*S*),(*S*),(*S*)-valine-thiazole tetramer **12** (8.9 mg, 38%) mp 177–179 °C (slow decomp); $[\alpha]_D^{23}=-309.1$ (*c* 0.92, $CHCl_3$); ν_{max} ($CHCl_3$) 1731 and 1621 cm^{-1}; δ_H(500 MHz, $CDCl_3$, *T*= 298 K) mixture of rotamers 0.60–1.40 (24H, m, (C*H*$_3$)$_2$CH), 2.54–2.60 (4H, m, (CH$_3$)$_2$C*H*), 2.78 and 2.82 (3H, 2×s, NCH$_3$), 2.94 (3H, s, NCH$_3$), 2.94 and 3.11 (3H, 2×s, NCH$_3$), 3.46 and 3.50 (3H, 2×s, NCH$_3$), 5.66–5.77 and 7.06 (2H, m and d, *J*=11.1 Hz, 2×C*H*NCH$_3$), 6.40 (2H, d, *J*=10.4 Hz, C*H*NCH$_3$), 7.94–8.00 (2H, m, CHS), 8.08 (1H, s, CHS), 8.14 (1H, s, CHS); δ_C(125 MHz, $CDCl_3$, *T*= 298 K) mixture of rotamers, 19.3 (q, CH$_3$), 19.5 (q, 2× CH$_3$), 19.8 (q, CH$_3$), 20.1 (q, CH$_3$), 20.3 (q, CH$_3$), 20.5 (q, CH$_3$), 21.1 (q, CH$_3$), 28.9 (q, NCH$_3$), 29.4 (q, 2×NCH$_3$), 30.3 (q, NCH$_3$), 31.4 (d, *C*H(CH$_3$)$_2$), 31.8 (d, *C*H(CH$_3$)$_2$), 32.9 (d, *C*H(CH$_3$)$_2$), 34.6 (d, *C*H(CH$_3$)$_2$), 59.8 (d, *C*HNCH$_3$), 60.5 (d, *C*HNCH$_3$), 61.2 (d, *C*HNCH$_3$), 64.4 (d, *C*HNCH$_3$), 125.0 (d, CHS), 126.3 (d, CHS), 126.7 (d, CHS), 129.0 (d, CHS), 149.7 (s, 2×N–*C*=CH), 150.2 (s, N–*C*=CH), 150.9 (s, N–*C*=CH), 163.6 (s, N=CS), 163.8 (s, N=CS), 163.9 (s, N=CS), 164.6 (s, N=CS), 165.9 (s, *C*ONCH$_3$), 166.3 (s, *C*ONCH$_3$), 167.0 (s, *C*ONCH$_3$), 168.7 (s, *C*ONCH$_3$); *m/z* (FAB) 785.2750 (M+H$^+$, $C_{36}H_{49}N_8O_4S_4$ requires 785.2759).

4.1.7. (L)-Ethyl-2-[1-(*tert*-butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_2$-thiazole-4-carbanoate (13). *N*-Methylmorpholine (0.24 ml, 2.25 mmol) was added dropwise to a solution of the Boc-(L)-*N*-methyl-valine-thiazole acid **9** (0.63 g, 2.0 mmol) in DCM (40 ml). The solution was cooled to 0 °C and then 1-hydroxybenzotriazole (0.30 g, 2.3 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.43 g, 2.3 mmol) were added in sequence. The solution was stirred at 0 °C for 10 min and then a pre-cooled solution of the amine hydrochloride salt **10b** (0.62 g, 2.2 mmol) in DMF (10 ml), followed by *N*-methylmorpholine (0.25 ml, 2.3 mmol) were added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, then allowed to warm to RT and stirred at this temperature for 40 h. The mixture was evaporated in vacuo and the residue was treated with 10% aq. citric acid (50 ml). The mixture was extracted with ethyl acetate (3×40 ml) and the combined organic extracts were washed sequentially with sat. aq. $NaHCO_3$ (3×40 ml), brine (2×40 ml) and water (2×50 ml), then dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by flash chromatography on silica gel using petrol–ethyl acetate (4:1) as eluent to give the dimer (0.90 g, 84%) as a sticky glassy solid, with no defined mp; (Found: C, 55.6; H, 7.1; N, 10.6; $C_{25}H_{38}N_4O_5S_2$ requires, C, 55.7; H, 7.1; N, 10.4%); $[\alpha]_D^{24}=-316.5$ (*c* 1.22, CHC_3); ν_{max} ($CHCl_3$) 1726, 1682, and 1619 cm^{-1}; δ_H(360 MHz, CD_3CN, *T*=335 K) 0.98 (6H, d, *J*=5.9 Hz, 2×(C*H*$_3$)$_2$CH), 1.03 (6H, d, *J*=6.4 Hz, 2×(C*H*$_3$)$_2$CH), 1.39 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.49 (9H, s, (C*H*$_3$)$_3$C), 2.70–2.78 (5H, m, 2×C*H*(CH$_3$)$_2$, 1× NCH$_3$), 2.95–3.01 (3H, bs, NCH$_3$), 4.38 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 5.09 (1H, s, C*H*NCH$_3$), 5.61–5.94 (1H, m, C*H*NCH$_3$), 7.90–8.00 (1H, bs, CHS), 8.25 (1H, s, CHS); δ_C(125.8 MHz, CD_3CN, *T*=298 K) main rotamer, 14.6 (q, CH$_3$), 19.6 (q, 2×CH$_3$), 20.6 (q, CH$_3$), 28.5 (q, (*C*H$_3$)$_3$C), 28.9 (q, NCH$_3$), 29.6 (d, *C*H(CH$_3$)$_2$), 30.1 (d, *C*H(CH$_3$)$_2$), 30.3 (q, NCH$_3$), 62.0 (t, O*C*H$_2$CH$_3$), 62.9 (d, *C*HNCH$_3$), 64.1 (d, *C*HNCH$_3$), 80.7 (s, *C*(CH$_3$)$_3$), 127.1 (d, CHS), 129.7 (d, CHS), 147.5 (s, N–*C*=CH), 150.8 (s, N–*C*=CH), 162.0 (s, N=CS), 164.5 (s, N=CS), 165.5 (s, *C*ONCH$_3$), 169.5 (N*C*O$_2^t$Bu), 170.1 (s, *C*O$_2$Et); *m/z* (FAB) 539.2356 (M+ H$^+$, $C_{25}H_{39}N_4O_5S_2$ requires 539.2362).

4.1.8. (L)-2-[1-(*tert*-Butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_2$-thiazole-4-carboxylic acid (14). Sodium hydroxide (0.62 g, 15.7 mmol) was added in one portion to a solution of the Boc-*N*-methylated-valine-thiazole dimer **13** (1.1 g, 2.0 mmol) in THF/water (20 ml; 3:1) and the mixture was stirred at RT for 30 h, then cooled to 0 °C and acidified to pH 2 with dilute 2 *N* HCl. The mixture was extracted with DCM (2×40 ml) and the combined organic extracts were then washed with brine (2×30 ml), dried ($MgSO_4$) and evaporated in vacuo. The oily residue was dissolved in ether and concentrated to leave the dimer carboxylic acid (0.92 g, 92%) as a colourless foam; mp 89–90 °C (triturated with ether); (Found: C, 53.9; H, 6.7; N, 10.9%; $C_{23}H_{34}N_4O_5S_2$ requires, C, 54.1; H, 6.7; N, 11.0%); $[\alpha]_D^{21}=-303.4$ (*c* 1.04, $CHCl_3$); ν_{max} ($CHCl_3$) 3437, 3124, 1762, 1682 and 1621 cm^{-1}; δ_H(360 MHz, CH_3CN, *T*=298 K) 3:2 mixture of rotamers, 0.75–1.00 (12H, m, 2×(C*H*$_3$)$_2$CH), 1.41 (9H, s, (CH$_3$)$_3$C), 2.65–2.73 (5H, m, 2×C*H*(CH$_3$)$_2$, 1×NCH$_3$), 2.91 and 3.08 (3H, 2×s, NCH$_3$), 4.92–5.21 (1H, m, C*H*NCH$_3$), 5.59 and 5.92 (1H, 2×d, *J*=10.6, 11.0 Hz, C*H*NCH$_3$), 7.87 and 8.05 (1H, 2×s, CHS), 8.30 (1H, s, CHS); δ_C(125 MHz, CD_3CN, *T*=298 K) main rotamer, 19.5 (q, 2×CH$_3$), 20.3 (q, CH$_3$), 20.6 (q, CH$_3$), 28.5 (q, (*C*H$_3$)$_3$C), 28.9 (q, NCH$_3$), 29.5 (q, NCH$_3$), 30.2 (d, *C*H(CH$_3$)$_2$), 33.1 (d, *C*H(CH$_3$)$_2$), 61.9 (d, *C*HNCH$_3$), 64.1 (d, *C*HNCH$_3$), 80.7 (s, *C*(CH$_3$)$_3$), 127.2 (d, CHS), 130.0 (d, CHS), 147.0 (s, N–*C*=CH), 150.7 (s, N–*C*=CH), 162.0 (s, N=CS), 164.2 (s, N=CS), 165.6 (s, *C*ONCH$_3$), 169.3 (s, *C*O$_2^t$Bu), 170.0 (s, CO$_2$H); *m/z* (FAB) 533.1877 (M+Na$^+$, $C_{23}H_{34}N_4O_5S_2Na$ requires 533.1868).

4.1.9. (L)-2-[1-(*N*-Aminomethyl)-2-methylpropyl]$_2$-thiazole-4-carboxylic acid hydrochloride salt (15). A solution of hydrochloric acid (4 M) in 1,4-dioxane (0.8 ml, 3.2 mmol) was added to a stirred solution of Boc-(L)-*N*-methyl-valine-thiazole dimeric carboxylic acid **14** (0.17 g, 0.323 mmol) in 1,4-dioxane (0.3 ml) and the mixture was stirred at RT for 36 h. Toluene (3×3 ml) was added and the dioxane–toluene azeotrope was removed to leave a residue which was washed with pentane to give the dimer hydrochloride salt (0.091 g, 63%) as a colourless crystalline solid; mp 156–158 °C (triturated with pentane); $[\alpha]_D^{19}=-102.1$ (*c* 1.07, MeOH); δ_H(360 MHz, CD_3OD, *T*=298 K) mixture of rotamers 0.73–1.13 (12H, m, 4×(C*H*$_3$)$_2$CH), 2.44–2.64 (1H, m, C*H*(CH$_3$)$_2$), 2.65 and 2.76 (3H, 2×s, NCH$_3$), 3.17 and 3.19 (3H, 2×s, NCH$_3$), 4.71 and 4.83 (1H, d, *J*=5.9 Hz, C*H*NCH$_3$), 5.28 and 5.59 (1H, d, *J*=11.1 Hz, C*H*NCH$_3$), 8.26 and 8.76 (1H, s, CHS), 8.39 and 8.59 (1H, s, CHS); δ_C(90.5 MHz, CD_3OD, *T*=298 K) mixture of rotamers 14.3 (q, CH$_3$), 14.4 (q, CH$_3$), 16.4 (q, CH$_3$), 16.6 (q, CH$_3$), 16.7 (q, CH$_3$), 16.9 (q, CH$_3$), 17.0 (q, CH$_3$), 17.4 (q, CH$_3$), 26.5 (q, NCH$_3$), 26.8 (d, *C*H(CH$_3$)$_2$), 29.5 (q, NCH$_3$), 29.6 (d, *C*H(CH$_3$)$_2$), 29.7 (d, *C*H(CH$_3$)$_2$), 30.0 (d, *C*H(CH$_3$)$_2$), 30.3 (q, NCH$_3$), 30.5 (q, NCH$_3$), 59.8 (d, *C*HNCH$_3$), 62.9 (d, *C*HNCH$_3$), 63.7 (d, *C*HNCH$_3$), 65.4 (d, *C*HNCH$_3$), 124.2 (d, CHS), 125.7 (d, CHS), 127.0 (d, CHS),

127.1 (d, CHS), 144.6 (s, N–*C*=CH), 145.3 (s, N–*C*=CH), 147.6 (s, N–*C*=CH), 148.5 (s, N–*C*=CH), 159.4 (s, N=CS), 159.8 (s, N=CS), 161.0 (s, N=CS), 161.2 (s, N=CS), 163.2 (s, *C*ONCH$_3$), 163.3 (s, *C*ONCH$_3$), 166.1 (s, CO$_2$H), 167.8 (s, CO$_2$H); *m/z* (FAB) 411.1544 (M+H$^+$, $C_{18}H_{27}N_4O_3S_2$ requires 411.1525).

4.1.10. Cyclic-tetra-(*S*),(*S*),(*S*),(*S*)-valine-thiazole (12) via dimer hydrochloride salt 15. *N*,*N*-Diisopropylethylamine (24 μl, 0.134 mmol) and pentafluorophenyl diphenylphosphinate (FDPP) (51.6 mg, 0.134 mmol) were added to a solution of *N*-methyl-valine-thiazole dimeric hydrochloric acid salt **15** (20.0 mg, 0.0447 mmol) in DMF (0.89 ml, 50 mM). The mixture was heated to 35 °C for 8 days, then quenched with sat. aq. K_2CO_3 (2 ml) and concentrated in vacuo. The residue was dissolved in water (20 ml) and extracted with DCM (3×20 ml). The combined organic extracts were washed successively with 10% aq. citric acid (30 ml), water (30 ml) and brine (30 ml), then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using ethyl acetate–methanol (100:0)→(97:3) as eluent to give the cyclic tetramer (8.9 mg, 51%) as a colourless solid whose spectroscopic data were identical to those reported previously.

4.1.11. (L)-Ethyl-2-[1-(*tert*-butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_3$-thiazole-4-carbanoate (16). *N*-Methylmorpholine (0.19 ml, 1.7 mmol) was added to a stirred solution of the Boc-*N*-methyl-valine-thiazole dimeric acid **14** (0.8 g, 1.6 mmol) in DCM (40 ml). The solution was cooled to 0 °C and 1-hydroxybenzotriazole (0.26 g, 1.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.36 g, 1.9 mmol) were added sequentially. A pre-cooled solution of the amine hydrochloric acid salt **10b** (0.48 g, 1.7 mmol) and *N*-methylmorpholine (0.20 ml, 1.9 mmol) in DCM (20 ml) was added dropwise via cannula over 5 min and the resulting mixture was stirred at 0 °C for 1 h and then at RT for 48 h. The mixture was evaporated under reduced pressure and the residue was quenched with 10% aq. citric acid (50 ml). The aqueous mixture was extracted with EtOAc (3×50 ml) and the combined organic extracts were washed with sat. aq. $NaHCO_3$ (2×40 ml) and brine (2×50 ml), then dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using petrol–ethyl acetate (1:1) as eluent to give the trimer ester (0.95 g, 82%) as a foam; mp 82–84 °C; (Found: C, 55.3; H, 6.9; N, 11.0%; Calc. for $C_{34}H_{50}N_6O_6S_3$; C, 55.6; H, 6.9; N, 11.4%); $[\alpha]_D^{20}=-349.2$ (*c* 1.0, $CHCl_3$); ν_{max} ($CHCl_3$) 1711, 1682 and 1621 cm^{-1}; δ_H(360 MHz, CD_3CN, $T=298$ K) mixture of rotamers, 0.89–1.09 (18H, m, 3×(C*H*$_3$)$_2$CH), 1.37 (3H, t, $J=7.0$ Hz, OC*H*$_2$CH$_3$), 1.45 (9H, s, (C*H*$_3$)$_3$C), 2.45–3.10 (12H, m, 3 × C*H*(CH$_3$)$_2$ and 3×NCH$_3$), 4.36 (q, $J=7.0$ Hz, OC*H*$_2$CH$_3$), 4.93–5.20 (1H, m, CHN), 5.58–5.70 (1H, m, CHN), 5.88–6.06 (1H, m, CHN), 7.85–8.10 (2H, m, 2×CHS), 8.06 (1H, bs, CHS), 8.23 (1H, bs, CHS); δ_C(125 MHz, CD_3CN, $T=298$ K) main rotamer, 14.6 (q, CH$_3$), 19.5 (q, 2×CH$_3$), 19.6 (q, CH$_3$), 20.3 (q, CH$_3$), 20.5 (q, CH$_3$), 20.7 (q, CH$_3$), 28.5 (q, (*C*H$_3$)$_3$C), 29.0 (s, NCH$_3$), 29.6 (s, NCH$_3$), 30.3 (s, NCH$_3$), 32.9 (d, *C*H(CH$_3$)$_2$), 33.0 (d, *C*H(CH$_3$)$_2$), 33.2 (d, *C*H(CH$_3$)$_2$), 62.0 (t, O*C*H$_2$CH$_3$), 65.1 (d, *C*HNCH$_3$), 65.3 (d, *C*HNCH$_3$), 66.2 (d, *C*HNCH$_3$), 80.6 (s, (*C*(CH$_3$)$_3$), 126.0 (d, CHS), 127.4 (d, CHS), 130.0 (d, CHS), 147.5 (s, N–*C*=CH), 150.8 (s, 2×N–*C*=CH), 161.9 (s, N=CS), 164.5 (s, N=CS), 165.4 (s, N=CS), 168.1 (s, *C*ONCH$_3$), 168.8 (s, *C*ONCH$_3$), 169.0 (s, CO$_2^t$Bu), 170.1 (s, CO$_2$Et); *m/z* (FAB) 735.3032 (M+H$^+$, $C_{34}H_{51}N_6O_6S_3$ requires 735.3032).

4.1.12. (L)-2-[1-(*tert*-Butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_3$-thiazole-4-carboxylic acid (17). Sodium hydroxide (0.40 g, 10.0 mmol) was added in one portion to a stirred solution of the Boc-(L)-valine-thiazole trimer ester **16** (0.92 g, 1.25 mmol) in THF/water (20 ml, 3:1) and the solution was stirred at RT for 14 h, then cooled to 0 °C and acidified to pH 2 with dilute 2 *N* HCl. The aqueous mixture was extracted with DCM (2×40 ml) and the combined organic extracts were then washed with brine (2×30 ml), dried ($MgSO_4$) and evaporated in vacuo. The residue was triturated with pentane to leave the trimer carboxylic acid (0.83 g, 94%) as colourless crystals; mp 112–113 °C (triturated with pentane); (Found: C, 54.4; H, 6.7; N, 11.5; $C_{32}H_{46}N_6O_6S_3$ requires, C, 54.4; H, 6.6; N, 11.9%); $[\alpha]_D^{21}=-376.5$ (*c* 1.02, $CHCl_3$); ν_{max} ($CHCl_3$) 3436, 3124, 1762, 1682 and 1621 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) mixture of rotamers, 0.86–1.08 (18H, m, 3×(C*H*$_3$)$_2$CH), 1.44 (9H, bs, (C*H*$_3$)$_3$C), 2.71–3.10 (12H, m, 3×C*H*(CH$_3$)$_2$ and 3×NCH$_3$), 4.90–5.18 (1H, m, CHN), 5.58–5.70 (1H, m, CHN), 5.88–6.06 (1H, m, CHN), 7.85–8.10 (2H, m, 2×CHS), 8.30 (1H, s, CHS); δ_C(125 MHz, $CDCl_3$, $T=298$ K) main rotamer, 14.3 (q, CH$_3$), 19.6 (q, CH$_3$), 20.4 (q, CH$_3$), 20.5 (q, CH$_3$), 20.6 (q, CH$_3$), 20.7 (q, CH$_3$), 22.5 (q, CH$_3$), 28.6 (s, (CH$_3$)$_3$*C*), 28.8 (q, NCH$_3$), 28.9 (q, NCH$_3$), 29.5 (q, NCH$_3$), 32.6 (d, *C*H(CH$_3$)$_2$), 33.01 (d, *C*H(CH$_3$)$_2$), 34.3 (d, *C*H(CH$_3$)$_2$), 61.2 (d, *C*HNCH$_3$), 61.9 (d, *C*HNCH$_3$), 64.1 (d, *C*HNCH$_3$), 80.6 (s, *C*(CH$_3$)$_3$), 126.7 (d, CHS), 127.7 (s, CHS), 129.5 (d, CHS), 145.9 (s, N–*C*=CH), 149.9 (s, N–*C*=CH), 150.2 (s, N–*C*=CH), 162.8 (s, N=C–S), 163.6 (s, N=C–S), 164.5 (s, N=C–S), 167.5 (s, *C*ONCH$_3$), 167.7 (s, *C*ONCH$_3$), 168.8 (s, CO$_2^t$Bu), 169.6 (s, CO$_2$H); *m/z* (FAB) 729.2550 (M+Na$^+$, $C_{32}H_{46}N_6O_6S_3Na$ requires 729.2538).

4.1.13. (L)-2-[1-(*N*-Aminomethyl)-2-methylpropyl]$_3$-thiazole-4-carboxylic acid hydrochloride salt (18). A solution of hydrochloric acid (4 M) in 1,4-dioxane (5.0 ml, 9.0 mmol) was added to a stirred solution of the trimer carboxylic acid **17** (1.0 g, 1.9 mmol) in 1,4-dioxane (3.0 ml) and the mixture was stirred at RT for 20 h. Toluene (4×20 ml) was added and the dioxane–toluene azeotrope was removed to leave a residue which was stirred in pentane for 1 h to give the trimer amine hydrochloride salt (0.86 g, 95%) as a pale green powder; mp 167–170 °C (triturated with pentane, slow decomp.); (Found: C, 49.3; H, 6.3; N, 12.3%; Calc, for $C_{27}H_{41}N_6O_5S_3Cl$ ($C_{27}H_{39}N_6O_4S_3Cl+H_2O$); C, 49.0; H, 6.3; N, 12.7%); $[\alpha]_D^{23}=-224.9$ (*c* 1.21, MeOH); ν_{max} ($CHCl_3$); 3125, 2967, 2876, 1709 and 1622 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) 1.5:1 mixture of rotamers, 0.84–1.24 (18H, m, 3×(C*H*$_3$)$_2$CH), 2.55–2.78 (6H, m, 3×C*H*(CH$_3$)$_2$ and 1×NCH$_3$), 3.00–3.40 (6H, m, 2×NCH$_3$), 4.33–4.50 (1H, m, C*H*NCH$_3$), 5.67–5.75 (2H, m, 2×C*H*NCH$_3$), 7.87–8.31 (3H, m, 3×CHS), 9.23–9.74 (1H, bs, *H*NCH$_3$), 10.09–10.49 (1H, bs, CO$_2$H); δ_C(125 MHz, $CDCl_3$, $T=298$ K) major conformer, 18.0 (q, CH$_3$), 19.7 (q, 2×CH$_3$), 20.1 (q, CH$_3$), 20.3 (q, CH$_3$),

20.4 (q, CH_3), 29.0 (q, NCH_3), 29.1 (q, NCH_3), 29.5 (q, NCH_3), 30.9 (d, $CH(CH_3)_2$), 31.9 (d, $CH(CH_3)_2$), 32.3 (d, $CH(CH_3)_2$), 65.4 (d, $CHNCH_3$), 66.2 (d, $CHNCH_3$), 66.5 (d, $CHNCH_3$), 126.6 (d, CHS), 127.1 (d, CHS), 128.6 (d, CHS), 146.3 (s, N–C=CH), 150.0 (s, N–C=CH), 151.6 (s, N–C=CH), 160.4 (s, N=C–S), 163.3 (s, N=C–S), 163.74 (s, N=C–S), 164.5 (s, $CONCH_3$), 166.4 (s, $CONCH_3$), 168.7 (s, CO_2H); *m/z* (FAB) 629.2004 ($M+Na^+$, $C_{27}H_{38}N_6O_4S_3Na$ requires 629.2014).

4.1.14. Cyclic-hexa-(*S*),(*S*),(*S*),(*S*),(*S*),(*S*)-valine-thiazole (19). *N*,*N*-Diisopropylethylamine (80 µl, 0.5 mmol) was added dropwise over 5 min to a stirred solution of the trimer amine hydrochloride salt **18** (0.10 g, 0.15 mmol) in DMF (20 ml, 7.5 mM). Pentafluorophenyl diphenylphosphinate (FDPP) (0.17 g, 0.45 mmol) was added in one portion and the mixture was stirred at RT for 84 h. The DMF was removed in vacuo and the residue was diluted with ethyl acetate (60 ml). The solution was washed successively with 2 M NaOH solution (3×40 ml), 2 N HCl solution (3×30 ml), brine (60 ml) and water (2×30 ml), then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using ethyl acetate–methanol (98:2) as eluent, and then by preparative chromatography on silica gel plates (Merck silica gel 60 F_{254} precoated aluminium backed plates) using ethyl acetate–methanol (98:2) as eluent to give: i) the cyclic trimer **11** (6.2 mg, 7%); and ii) the cyclic hexamer **19** (51.0 mg, 29%) which crystallised as colourless diamond shaped crystals; mp 195–196 °C (ethyl acetate–ether); $[\alpha]_D^{22}=-387.5$ (*c* 1.2, $CHCl_3$); ν_{max} ($CHCl_3$) 1622 cm^{-1}; δ_H(500 MHz, $CDCl_3$, $T=298$ K) mixture of rotamers, 0.47–1.19 (36H, m, $(CH_3)_2CH$), 2.40–3.32 (24H, m, 6×$CH(CH_3)_2$ and 6×NCH_3), 5.47–6.18 (6H, m, 6×$CHNCH_3$), 7.88–8.32 (6H, m, 6×CHS); δ_C(125 MHz, $CDCl_3$, $T=298$ K) mixture of rotamers, 19.4 (q, 2×CH_3), 19.5 (q, 2×CH_3), 19.6 (q, CH_3), 19.8 (q, CH_3), 20.2 (q, 2×CH_3), 20.3 (q, CH_3), 20.4 (q, CH_3), 20.5 (q, CH_3), 21.2 (q, CH_3), 28.6 (d, $CH(CH_3)_2$), 28.8 (d, $CH(CH_3)_2$), 28.9 (d, $CH(CH_3)_2$), 29.1 (d, $CH(CH_3)_2$), 29.2 (d, $CH(CH_3)_2$), 29.5 (d, $CH(CH_3)_2$), 29.9 (q, 2×NCH_3), 30.5 (q, NCH_3), 32.0 (q, NCH_3), 32.1 (q, NCH_3), 32.4 (q, NCH_3), 60.4 (d, $CHNCH_3$), 60.5 (d, $CHNCH_3$), 60.9 (d, $CHNCH_3$), 61.2 (d, $CHNCH_3$), 65.1 (d, $CHNCH_3$), 66.1 (d, $CHNCH_3$), 125.3 (d, CHS), 125.7 (d, CHS), 126.7 (d, CHS), 126.8 (d, CHS), 127.4 (d, CHS), 127.8 (d, CHS), 150.0 (s, N–C=CH), 150.1 (s, 3×N–C=CH), 150.2 (s, N–C=CH), 150.6 (s, N–C=CH), 163.6 (s, N=CS), 164.2 (s, N=CS), 164.7 (s, N=CS), 164.8 (s, N=CS), 164.9 (s, N=CS), 165.0 (s, N=CS), 166.4 (s, 2×$CONCH_3$), 166.6 (s, $CONCH_3$), 166.7 (s, $CONCH_3$), 167.5 (s, $CONCH_3$), 167.6 (s, $CONCH_3$); *m/z* (ESI) 1177.4071 ($M+H^+$, $C_{54}H_{73}N_{12}O_6S_6$ requires 1177.4100).

4.1.15. X-ray crystal structure determination for 19. X-ray diffraction data for the dodecacyclopeptide **19** were collected at 150 K on a Bruker SMART APEX CCD area detector diffractometer equipped with an Oxford Cryosystems open-flow nitrogen cryostat. The structure was solved by direct methods (SHELXS-97) and refined using full-matrix least squares refinement against F^2. All non-hydrogen atoms were refined with anisotropic atomic displacement parameters (adps) and H atoms with $U(H)_{iso}=1.2U_{eq}(C)$ and $U(H)_{iso}=1.5U_{eq}(C)$ for methyl groups. Hydrogen atoms were placed in geometrically calculated positions and refined as part of riding model, except those of methyl groups bound to an sp^2 hybridised N or C atom which were located from difference Fourier maps and refined as a rigid rotor.

A colourless pentagonal prism shaped crystal of dimensions $0.46\times0.36\times0.24$ mm^3 was selected and mounted in perfluoropolyether oil. The dodecacyclopeptide was found to crystallise in monoclinic space group $P2_1$ with $a=12.4620$ (1), $b=23.946$ (2), $c=13.7249$ (12) Å, $\beta=112.844$ (1)°, $V=3774.4$ (9) $Å^3$, $Z=2$, $D_{calcd}=1.230$ g/cm^3, $T=150$ K. 23294 reflections were measured, 14473 unique (Rint=0.021), 14452 of which were used in all calculations. The final $wR(F^2)$ was 0.104 for all data, $R_1(F)$ was 0.040 for 12512 observed data where $I>2\sigma(I)$. The Flack parameter refined to −0.02 (4) showed the absolute configuration assignment.

The crystals contain 2.5 molecules of ethyl acetate per molecule of **19**. The 0.5 molecule could not be modelled sensibly in terms of atomic sites and the electron density in this region was calculated and accounted for using SQUEEZE, within PLATON, and included in all calculations involving the unit cell contents.

Crystallographic data (excluding structure factors) for this structure have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 246955. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.1.16. (L)-Ethyl-2-[1-(*N*-aminomethyl)-2-methylpropyl]$_2$-thiazole-4-carbanoate hydrochloride salt (20). A solution of hydrochloric acid (4 M) in 1,4-dioxane (5.0 ml, 20.0 mmol) was added to a stirred solution of the the dimer ester **13** (1.0 g, 1.9 mmol) in 1,4-dioxane (3 ml) and the solution was stirred at RT for 20 h. Toluene (4×40 ml) was added and the dioxane–toluene azeotrope was removed to leave a residue which was washed with pentane to give the dimer amine hydrochloride salt (0.85 g, 94%) as a yellow powder; mp 135–137 °C (triturated with pentane); (Found: C, 48.8; H, 6.4; N, 11.0%; Calc. for $C_{20}H_{33}N_4O_4S_2Cl$ ($C_{20}H_{31}N_4O_3S_2Cl+H_2O$); C, 48.7; H, 6.8; N, 11.4%); $[\alpha]_D^{21}=-90.7$ (*c* 1.07, $CHCl_3$); ν_{max} ($CHCl_3$) 3683, 3124, 1725 and 1626 cm^{-1}; δ_H(360 MHz, $CDCl_3$, $T=298$ K) 2:3 mixture of rotamers, 0.77–1.31 (12H, m, $(CH_3)_2CH$), 1.38 and 1.39 (3H, 2×t, $J=7.0$ Hz, OCH_2CH_3), 2.49–2.84 (5H, m, 2×$CH(CH_3)_2$ and 1×NCH_3), 3.11 and 3.27 (3H, 2×s, NCH_3), 4.35 and 4.45 (2H, 2×q, $J=7.0$ Hz, OCH_2CH_3), 4.75 and 7.22 (1H, 2×m, $CHNCH_3$), 5.47–5.58 (1H, m, $CHNCH_3$), 8.07–8.18 (2H, m, CHS), 9.95 and 10.26 (1H, 2×s, $HNCH_3$); δ_C(360 MHz, $CDCl_3$, $T=298$ K) 2:3 mixture of rotamers, 14.5 (q, 2×CH_3), 17.0 (q, CH_3), 18.2 (q, CH_3), 19.6 (q, CH_3), 19.7 (q, CH_3), 20.0 (q, CH_3), 20.3 (q, 2×CH_3), 20.4 (q, CH_3), 28.9 (q, NCH_3), 29.0 (q, NCH_3), 30.5 (q, NCH_3), 31.5 (q, NCH_3), 31.8 (d, $CH(CH_3)_2$), 31.9 (d, $CH(CH_3)_2$), 32.7 (d, $CH(CH_3)_2$), 33.7 (d, $CH(CH_3)_2$), 61.4 (t, OCH_2CH_3), 62.0 (t, OCH_2CH_3), 66.2 (d, 2×$CHNCH_3$), 66.4 ($CHNCH_3$), 66.7 ($CHNCH_3$),

127.7 (d, CHS), 127.8 (d, CHS), 127.9 (d, CHS), 128.3 (d, CHS), 146.4 (s, N–C=CH), 146.9 (s, N–*C*=CH), 150.0 (s, N–*C*=CH), 151.2 (s, N–*C*=CH), 160.8 (s, N=CS), 161.2 (s, N=CS), 161.4 (s, N=CS), 161.5 (s, N=CS), 161.7 (s, *C*ONCH$_3$), 164.0 (s, *C*ONCH$_3$), 168.0 (s, CO$_2$Et), 169.4 (s, CO$_2$Et); *m/z* (FAB) 439.1829 (M+H$^+$, $C_{20}H_{31}N_4O_3S_2$ requires 439.1838).

4.1.17. Ethyl-(L)-2-[1-(*tert*-butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_4$-thiazole-4-carbanoate (21). 1-Hydroxybenzotriazole (HOBt) (0.24 g, 1.8 mmol) was added in one portion to a stirred solution of the dimer carboxylic acid **14** (0.78 g, 1.5 mmol) in DCM (50 ml) at 0 °C. 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (0.35 g, 1.80 mmol), followed by a solution of the dimeric free amine hydrochloric acid salt **20** (0.80 g, 1.70 mmol) in DCM (10 ml) and *N*-methylmorpholine (0.37 ml, 3.40 mmol) were then added sequentially. The mixture was stirred at 0 °C for 1 h then at RT for 45 h and quenched with 10% aq. citric acid (60 ml) and extracted with ethyl acetate (3×70 ml). The combined organic extracts were washed with sat. aq. NaHCO$_3$ (3×50 ml) and brine (60 ml), then dried (MgSO$_4$) and concentrated in vacuo. The yellow solid residue was purified by flash chromatography on silica gel using petrol–ethyl acetate (3:7) as eluent, then stirred in pentane (30 ml) for 2 h and filtered to give the tetramer ester (1.21 g, 87%) as a colourless semi-crystalline solid; mp 104–105 °C (triturated with pentane); $[\alpha]_D^{21}=-413.5$ (*c* 1.0, CHCl$_3$); ν_{max} (CHCl$_3$) 1711, 1683 and 1618 cm^{-1}; δ_H(360 MHz, CD$_3$CN, *T*=298 K) main rotamers, 0.87–1.09 (24H, m, 4×(C*H*$_3$)$_2$CH), 1.37 (3H, t, *J*=7.1 Hz, OCH$_2$C*H*$_3$), 1.44 (9H, s, (C*H*$_3$)$_3$C), 2.70–2.75 (4H, m, 4×C*H*(CH$_3$)$_2$), 2.91 (9H, bs, 3×NCH$_3$), 3.08 (3H, s, NCH$_3$), 4.36 (2H, q, *J*=7.1 Hz, OC*H*$_2$CH$_3$), 4.85–5.25 (1H, m, C*H*NCH$_3$), 5.57–5.70 (1H, m, C*H*NCH$_3$), 5.86–6.07 (2H, m, 2×C*H*NCH$_3$), 7.84–7.94 (1H, m, CHS), 8.00–8.11 (1H, m, CHS), 8.27 (1H, s, CHS); δ_C(125 MHz, CD$_3$CN, *T*=298 K) main rotamer, 14.6 (q, CH$_3$), 19.6 (q, CH$_3$), 20.4 (q, CH$_3$), 20.6 (q, CH$_3$), 20.7 (q, CH$_3$), 28.6 (q, (*C*H$_3$)$_3$C), 29.0 (q, 2×NCH$_3$), 29.5 (q, NCH$_3$), 29.6 (q, NCH$_3$), 30.3 (d, *C*H(CH$_3$)$_2$), 30.4 (d, 2×*C*H(CH$_3$)$_2$), 33.1 (d, *C*H(CH$_3$)$_2$), 61.7 (d, *C*HNCH$_3$), 61.8 (t, O*C*H$_2$CH$_3$), 65.1 (d, *C*HNCH$_3$), 65.2 (d, *C*HNCH$_3$), 65.3 (d, *C*HNCH$_3$), 125.5 (d, CHS), 126.9 (d, CHS), 127.4 (d, CHS), 129.7 (d, CHS), 147.5 (s, N–*C*=CH), 150.8 (s, N–*C*=CH), 150.8 (s, N–*C*=CH), 150.9 (s, N–*C*=CH), 162.0 (s, N=CS), 164.4 (s, N=CS), 164.5 (s, N=CS), 165.4 (s, N=CS), 168.3 (s, *C*ONCH$_3$), 168.8 (s, *C*ONCH$_3$), 169.1 (s, *C*ONCH$_3$), 169.6 (s, NCO$_2^t$Bu), 170.1 (s, CO$_2$Et); *m/z* (FAB) 931.3717 (M+H$^+$, $C_{43}H_{63}N_8O_7S_4$ requires 931.3703).

4.1.18. (L)-2-[1-(*tert*-Butoxycarbonyl-*N*-aminomethyl)-2-methylpropyl]$_4$-thiazole-4-carboxylic acid (22). Sodium hydroxide (0.4 g, 10.2 mmol) was added in one portion to a stirred solution of the tetramer ester **21** (1.1 g, 1.1 mmol) in THF/water (28 ml, 3:1) and the solution was stirred at RT for 24 h, then cooled to 0 °C and acidified to pH 2 with 2 *N* HCl. The mixture was extracted with DCM (3×50 ml) and the combined organic extracts were washed with brine (2×40 ml), dried (MgSO$_4$) and evaporated in vacuo. The foamy residue was triturated with pentane to give the tetramer carboxylic acid (0.96 g, 94%) as a colourless powder; mp 131–132 °C (triturated with pentane); (Found: C, 54.3; H, 6.5; N, 12.1%; Calc. for $C_{41}H_{58}N_8O_7S_4$; C, 54.5; H, 6.5; N, 12.4%); $[\alpha]_D^{21}=-557.2$ (*c* 1.06, CHCl$_3$); ν_{max} (CHCl$_3$) 3434, 3124, 1763, 1682 and 1621 cm^{-1}; δ_H(360 MHz, CDCl$_3$, *T*=298 K) mixture of rotamers, 0.86–1.33 (24H, m, 4×(C*H*$_3$)$_2$CH), 1.43–1.53 (9H, bs, (C*H*$_3$)$_3$C), 2.70–2.81 (10H, m, 4×C*H*(CH$_3$)$_2$ and 2×NCH$_3$), 2.94–3.00 (3H, m, 2×NCH$_3$), 3.13–3.31 (3H, m, NCH$_3$), 4.85–5.27 (1H, m, C*H*NCH$_3$), 5.60–5.77 (1H, m, C*H*NCH$_3$), 6.15–6.33 (2H, m, C*H*NCH$_3$), 7.95–8.31 (m, 4×CHS); δ_C(125 MHz, CDCl$_3$, *T*=298 K) main rotamer, 19.5 (q, CH$_3$), 20.6 (q, CH$_3$), 20.7 (q, CH$_3$), 22.5 (q, CH$_3$), 28.6 (q, (*C*H$_3$)$_2$C), 28.7 (q, NCH$_3$), 28.8 (q, NCH$_3$), 28.9 (q, 2×NCH$_3$), 29.0 (d, *C*H(CH$_3$)$_2$), 29.6 (d, *C*H(CH$_3$)$_2$), 30.5 (d, *C*H(CH$_3$)$_2$), 34.3 (d, *C*H(CH$_3$)$_2$), 61.1 (d, *C*HNCH$_3$), 61.9 (d, *C*HNCH$_3$), 64.5 (d, 2×*C*HNCH$_3$), 80.4 (s, *C*(CH$_3$)$_3$), 127.2 (d, CHS), 128.1 (d, CHS), 129.4 (d, CHS), 129.5 (d, CHS), 146.1 (s, N–*C*=CH), 146.3 (s, N–*C*=CH), 150.0 (s, N–*C*=CH), 150.1 (s, N–*C*=CH), 163.5 (s, N=CS), 163.6 (s, N=CS), 164.5 (s, N=CS), 164.6 (s, N=CS), 167.0 (s, *C*ONCH$_3$), 167.4 (s, *C*ONCH$_3$), 167.5 (s, *C*ONCH$_3$), 168.6 (s, NCO$_2^t$Bu), 169.3 (s, CO$_2$H); *m/z* (FAB) 903.3372 (M+H$^+$, $C_{41}H_{59}N_8O_7S_4$ requires 903.3390).

4.1.19. (L)-2-[1-(*N*-Aminomethyl)-2-methylpropyl]$_4$-thiazole-4-carboxylic acid hydrochloride salt (23). A solution of hydrochloric acid (4 M) in 1,4-dioxane (5.0 ml, 20.0 mmol) was added dropwise to a stirred solution of the tetramer carboxylic acid **22** (1.05 g, 1.16 mmol) in 1,4-dioxane (10 ml) and the solution was stirred at RT for 18 h. A further aliquot of 4 M HCl in 1,4-dioxane (5.0 ml, 20.0 mmol) was added and the mixture was stirred for an additional 2 h. Toluene (3×40 ml) was added and the toluene-dioxane azeotrope was removed in vacuo to leave the tetramer amine hydrochloride salt (0.90 g, 93%) as a light yellow powder; mp 162–163 °C; $[\alpha]_D^{23}=-382.6$ (*c* 1.05, CHCl$_3$); ν_{max} (CHCl$_3$) 3698, 3124, 1753, 1710 and 1622 cm^{-1}; δ_H(500 MHz, CDCl$_3$, *T*=298 K) mixture of rotamers, 0.87–1.30 (24H, m, 4×(C*H*$_3$)$_2$CH), 2.65–2.78 (7H, m, 4×C*H*(CH$_3$)$_2$ and 1×NCH$_3$), 2.96–3.01 (3H, m, 1×NCH$_3$), 3.09–3.31 (6H, m, 2×NCH$_3$), 5.58–5.86 (2H, m, 2×C*H*NCH$_3$), 6.03–6.39 (1H, m, C*H*NCH$_3$), 6.98–7.25 (1H, m, C*H*NCH$_3$), 7.97–8.30 (4H, m, 4×CHS); δ_C(125 MHz, CDCl$_3$, *T*=298 K) major conformer, 19.6 (q, CH$_3$), 19.7 (q, CH$_3$), 20.2 (q, CH$_3$), 20.4 (q, CH$_3$), 20.5 (q, 2×CH$_3$), 20.6 (q, 2×CH$_3$), 28.8 (q, NCH$_3$), 29.0 (q, 2×NCH$_3$) 29.8 (q, NCH$_3$), 31.8 (d, 2×*C*H(CH$_3$)$_2$), 32.6 (d, *C*H(CH$_3$)$_2$), 32.9 (d, *C*H(CH$_3$)$_2$), 61.0 (d, *C*HNCH$_3$), 64.4 (d, *C*HNCH$_3$), 65.0 (d, *C*HNCH$_3$), 66.4 (d, *C*HNCH$_3$), 126.3 (d, CHS), 127.0 (d, CHS), 128.0 (d, CHS), 129.4 (d, CHS), 146.5 (s, N–*C*=CH), 150.0 (s, N–*C*=CH), 150.1 (s, N–*C*=CH), 151.4 (s, N–*C*=CH), 160.3 (s, N=CS), 163.6 (s, N=CS), 163.8 (s, N=CS), 164.6 (s, N=CS), 166.6 (s, *C*ONCH$_3$), 166.8 (s, 2×*C*ONCH$_3$), 169.9 (s, CO$_2$H); *m/z* (FAB) 803.2842 (M+H$^+$, $C_{36}H_{51}N_8O_5S_4$ requires 803.2865).

4.1.20. Cyclic-tetra-(*S*),(*S*),(*S*),(*S*)-valine-thiazole (12). *N*,*N*-Diisopropylethylamine (120 µl, 0.7 mmol) and diphenylphosphoryl azide (DPPA) (0.15 ml, 0.7 mmol) were added in quick succession to a stirred solution of the tetramer amine hydrochloride salt **22** (0.20 g, 0.24 mmol) in DMF (90 ml, 2.6 mM) and the mixture was stirred at RT for

5 days. The DMF was removed in vacuo and the residue was diluted with water (20 ml) and extracted with chloroform (3×50 ml). The combined organic extracts were washed successively with a sat. aq. $NaHCO_3$ (3×40 ml), sat. aq. NH_4Cl (2×40 ml) and brine (60 ml), then dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using ethyl acetate–methanol (98:2) as eluent, and then by preparative chromatography on silica gel plates (Merck silica gel 60 F_{254} precoated aluminium backed plates) using chloroform–methanol (95:5) to give the cyclic tetramer (0.066 g, 35%) as a light yellow powder whose spectroscopic data were identical to those reported previously.

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Asymmetric synthesis using catalysts containing multiple stereogenic centres and a *trans*-1,2-diaminocyclohexane core; reversal of predominant enantioselectivity upon *N*-alkylation

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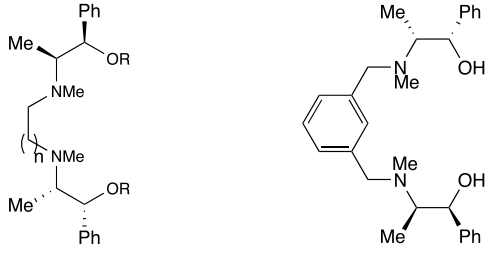
Abstract—*N*-Methylation of ligands containing a *trans*-1,2-diaminocyclohexane core and multiple stereogenic centres is shown to provide the product of the opposite configuration in significant enantiomeric excess, in the addition of diethylzinc to aldehydes. Some of the ligands were effective in an asymmetric Michael addition.

1. Introduction

Catalytic asymmetric formation of carbon–carbon bonds is a field of continuing importance in organic synthesis.[1] Ligands derived from a β-amino alcohol or a vicinal diamine are commonly found in catalysts, especially in the asymmetric addition of organometallic reagents to carbonyl compounds. In particular, the β-amino alcohol moiety has found extensive use as a ligand in the asymmetric addition of dialkylzincs to carbonyl compounds,[2–4] and mechanistic features have been thoroughly examined.[3] Catalysts incorporating a *trans*-1,2-diaminocyclohexane core have also found much use for asymmetric additions to carbonyl compounds.[5] For a ligand based upon either a β-amino alcohol or a vicinal diamine, the co-ordination geometry is reasonably well understood, leading in a number of cases to plausible models for the catalytic processes. In contrast, catalysts prepared from ligands that contain multiple stereocentres have been studied much less. Representative catalysts **1**[6] and **2**[7] (Fig. 1) were constructed from two ephedrine units linked, respectively, by an alkyl or alkylarylalkyl chain. In the addition of diethylzinc to benzaldehyde, ligands **1a** and **2** afforded (*R*)-1-phenylpropan-1-ol in 32 and 85% ee, respectively;[6] ligand **2** afforded the (*S*)-enantiomer in 80% ee.[7] Additional possibilities for intramolecular coordination of related compounds could widen the scope of catalytic asymmetric processes.



1a n=1 R=Li
1b n=2 R=H

2

Figure 1.

Recently, our research has shown that catalysts with up to four co-ordinating sites and at least as many possible coordinating atoms permit asymmetric hydrogenation of carbonyl compounds; moreover, in several instances, *N*-benzylation of the terminal amino groups resulted in reversal of the absolute configuration of the major product.[8] In our search for new catalysts for asymmetric carbon–carbon bond formation that contain multiple co-ordinating sites and stereogenic centres, a catalyst containing both a *trans*-1,2-diaminocyclohexane subunit and β-amino alcohol moiety was shown to be effective in the asymmetric addition of diethylzinc to aromatic aldehydes.[9] These ligands possess an extended array of up to six chiral centres. The preparation, further reactions and reversal, upon *N*-methylation, of the predominant enantioselection induced by such catalysts is here described.

The unadorned ligands **4** and **5** incorporating bis(β-

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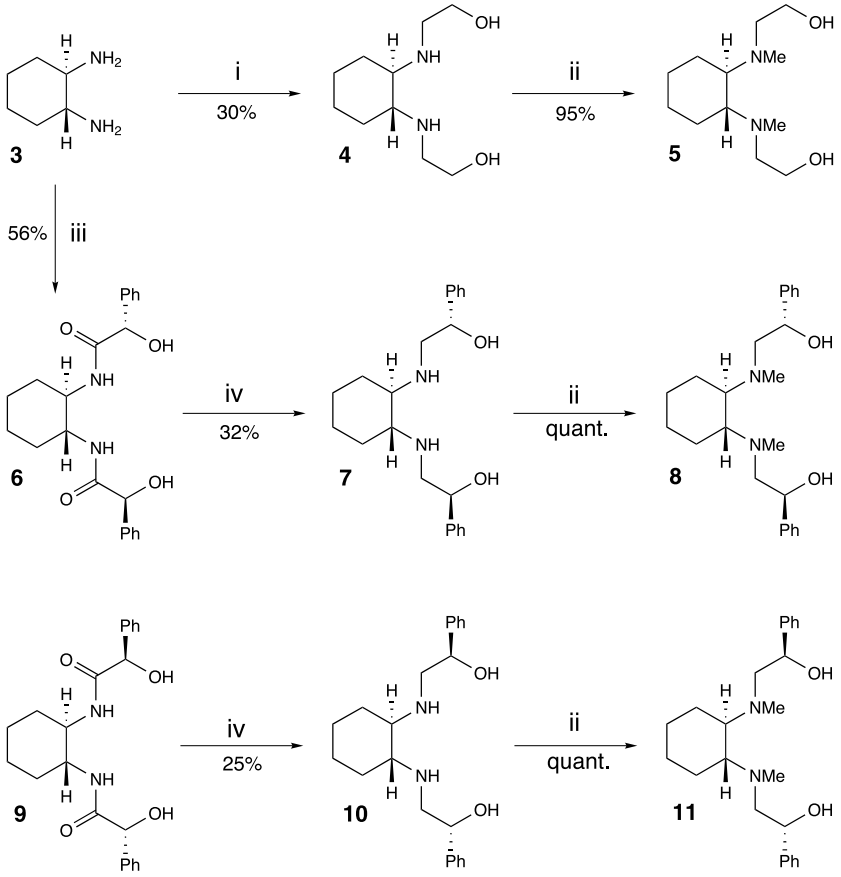
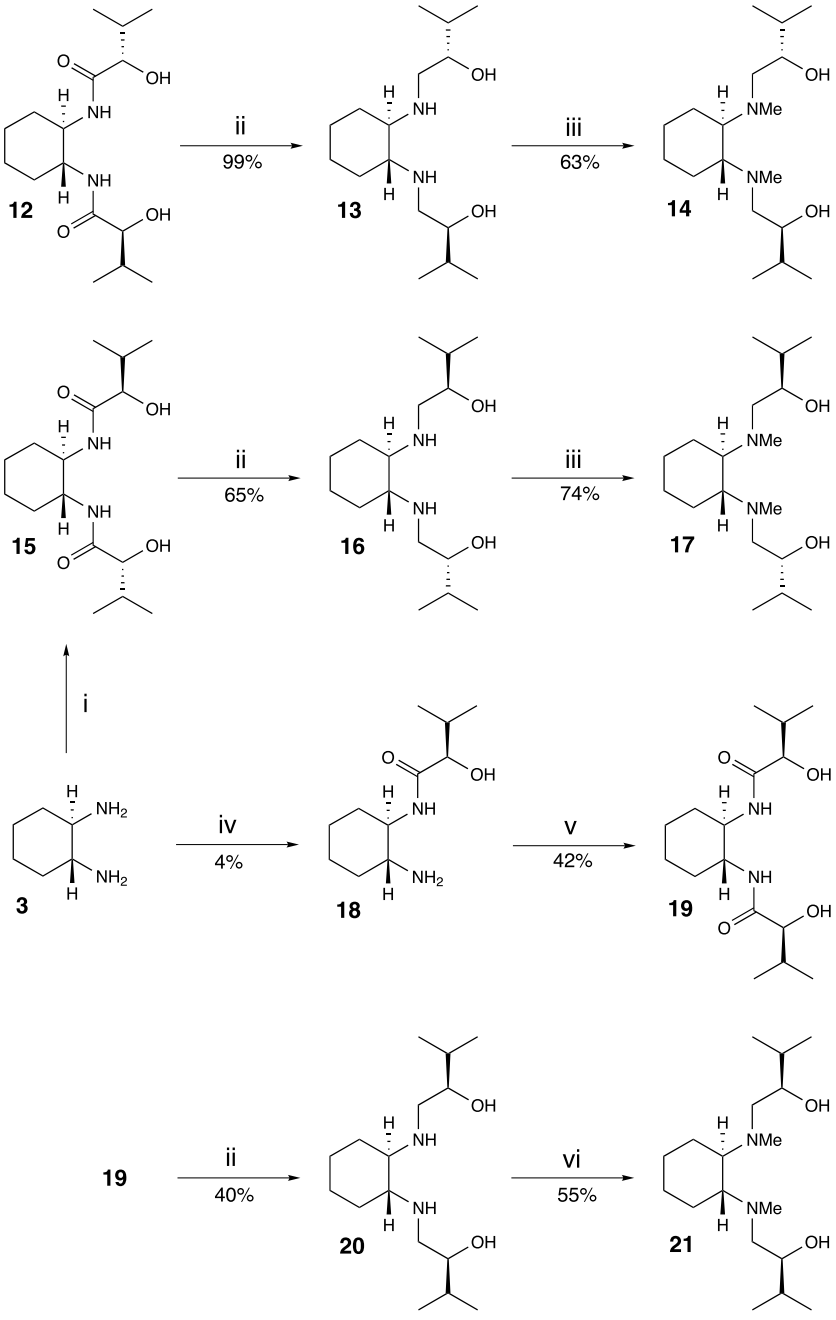
aminoalcohol) moieties were prepared according to Scheme 1. (1*R*,2*R*)-(−)-1,2-Diaminocyclohexane **3**[10] was dialkylated with 2-bromoethanol (water, reflux, 12 h) to give diol **4** (30%).[11] *N*,*N*′-Dimethylation of diol **4** to give the tertiary amino diol **5** (95%) was achieved using formaldehyde and formic acid in an Eschweiler–Clarke procedure,[12] but modified by addition of the hydrogen donor sodium formate.[13] The introduction of additional chiral centres on the β-aminoalcohol unit was found to be achieved satisfactorily by acylation followed by reduction. Activation of the requisite enantiomer of mandelic acid with dicyclohexylcarbodiimide (DCC) in the presence of *N*-hydroxysuccinimide followed by addition of the diamine **3** afforded ligands **6** and **9** in respective yields of 56% and 50%.[14] Reduction of amides **6** and **9** with $Me_2S\cdot BH_3$ gave the secondary amines **7** (32%) and **10** (25%) respectively.[15] Those amines were also subjected to Eschweiler–Clarke *N*,*N*′-dimethylation in the above manner to give the corresponding tertiary amines **8** and **11**[16] in quantitative yields.

To provide a contrast to the planarity of the phenyl substituents in the ligands **6**–**11**, isopropyl-substituted systems were also prepared (Scheme 2). Ligands **12** and **15**, (89% and 92%, respectively) were prepared by activation of the requisite enantiomer of 2-hydroxy-3-methylbutyric acid with carbonyldiimidazole in the presence of 1-hydroxybenzotriazole, followed by addition of the diamine **3**. Reduction of amides **12** and **15** gave the secondary amines **13** (99%) and **16** (65%) respectively.[15] Those amines were also subjected to Eschweiler–Clarke *N*,*N*′-dimethylation in the manner described above to give the corresponding tertiary amines **14** (63%) and **17** (74%). Since each of the above ligands possesses C_2 symmetry, it was of interest to prepare ligands with a *trans*-diaminocyclohexane core that are not C_2-symmetric, because of the presence of *N*-substituents of opposite configuration to each other. A stepwise synthesis was required and proceeded by reaction of diamine **3** with (*R*)-(−)-2-hydroxy-3-methylbutyric acid activated by carbonyldiimidazole in the presence of 1-hydroxybenzotriazole to give the amide **18** followed by subsequent reaction with (*S*)-(+)-2-hydroxy-3-methylbutyric acid and carbonyldiimidazole in the presence of 1-hydroxybenzotriazole to give the diamide **19** (42%). Reduction of **19** with $Me_2S\cdot BH_3$ afforded the diamine **20** (40%) which underwent *N*,*N*′-dimethylation with formaldehyde and formic acid to give the tetraamine **21** in 55% yield.

Lastly, amino alcohols containing six chiral centres were obtained by heating diamine **3** with cyclohexene oxide to give diamino diol **22** (30%) which was also reacted with formaldehyde and formic acid in the presence of sodium formate to give quantitatively the corresponding tertiary diamino diol **23**.[9] The relative configuration of each stereocentre in diamino diol **22** was established by X-ray



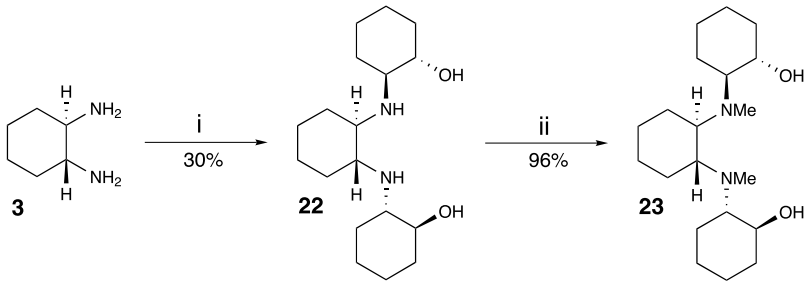
Scheme 1. Reagents and conditions. (i) 2-Bromoethanol (2 mol equiv), reflux in water; (ii) 37% HCHO (20 mol equiv), 96% HCOOH (53 equiv), HCOONa (10 mol%); (iii) (*S*)-(+)-mandelic acid (2.2 mol equiv), DCC (2.2 mol equiv), *N*-hydroxysuccinimide (2.2 mol equiv), THF; (iv) $Me_2S\cdot BH_3$ (6 mol equiv), $Et_2O\cdot BF_3$ (14 mol equiv), THF.



Scheme 2. Reagents and conditions. (i) (*R*)-(−)-2-Hydroxy-3-methylbutyric acid (2.2 mol equiv), carbonyldiimidazole (1.5 mol equiv), 1-hydroxybenzotriazole (0.14 mol equiv), THF; (ii) $Me_2S{\cdot}BH_3$ (5.5 mol equiv), $Et_2O{\cdot}BF_3$ (4 mol equiv), THF; (iii) 37% HCHO, 90% HCOOH, HCOONa (10 mol%); (iv) (*R*)-(−)-2-hydroxy-3-methylbutyric acid (0.5 mol equiv), carbonyldiimidazole (0.86 mol equiv), 1-hydroxybenzotriazole (0.1 mol equiv), THF; (v) (*S*)-(+)-2-hydroxy-3-methylbutyric acid (2.2 mol equiv), carbonyldiimidazole (1.5 mol equiv), 1-hydroxybenzotriazole (0.35 mol equiv), THF (vi) 37% HCHO, 90% HCOOH.

crystallography performed on the racemic modification.[17] A single diastereoisomer was also obtained from the reaction of (1*R*,2*R*)-(−)-1,2-diaminocyclohexane with cyclohexene oxide, as had been found in a previous study using the racemic diamine.[17] Such directed stereochemical control is presumably assisted by hydrogen bonding networks and has features in common with adducts formed from the co-crystallisation of enantiopure 1,2-diaminocyclohexane with cyclohexane-1,2-diols (Scheme 3).[18]

Some of the new ligands were evaluated as catalysts by investigating the addition of diethylzinc to aldehydes.[2,19] This is considered as a yardstick for the efficiency and enantioselectivity of a catalyst, since the rate of the reaction in the absence of a catalyst is low but markedly increased in the presence of a suitable catalyst.[3,20] The unadorned ligands as catalysts **4** and **5** did not provide 1-phenylpropan-1-ol in either acceptable yield or enantiomeric excess (Table 1). However, all of the catalysts studied containing appended stereogenic centres (compounds **7**, **8**, **10**, **11**, **22** and **23**) showed appreciable catalysis and in some cases afforded the secondary alcohols in high ee, showing that



Scheme 3. Reagents and conditions. (i) Cyclohexene oxide (3 mol equiv), EtOH, reflux; (ii) 37% HCHO, 96% HCOOH, HCOONa.

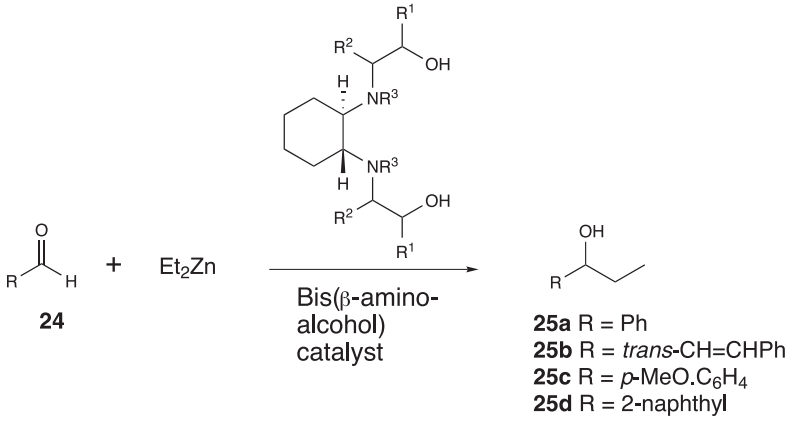
Table 1. Reaction of aldehydes with diethylzinc in toluene[a]

Entry	Ligand	Aldehyde	Temperature (°C)	Yield (%)[b]	ee (%)[c]	Configuration
1	**4**	PhCHO	−30	30	8	(*S*)
2	**5**	PhCHO	−30	0	—	—
3	**7**	PhCHO	−30	40	23	(*R*)
4	**8**	PhCHO	−30	55	54	(*S*)
5	**10**	PhCHO	−30	42	45	(*S*)
6	**11**	PhCHO	−30	51	16	(*R*)
7	**22**	PhCHO	−30	50	80	(*R*)
8	**23**	PhCHO	−30	25	92	(*S*)
9	**22**	PhCHO	0	99	64	(*R*)
10	**23**	PhCHO	0	68	75	(*S*)
11	**22**	PhCH=CHCHO	−30	41	72	(*R*)
12	**22**	*p*-MeO·C_6H_4CHO	−30	74	56	(*R*)
13	**23**	*p*-MeO·C_6H_4CHO	−30	18	52	(*S*)
14	**22**	2-Naphthaldehyde	0	95	60	(*R*)

[a] In the presence of the *trans*-1,2-diaminocyclohexane ligand (10 mol%), and 2.2 equiv of diethylzinc. Reactions were maintained at −30 or 0 °C for 4 h, then allowed to warm to 20 °C over a further 12 h.
[b] Yields were determined by ^{1}H NMR spectrometry.
[c] Enantiomeric excesses and absolute configurations of the alcohols were determined using a Chiralcel OD column.[24]

ligands with multiple stereogenic centres can indeed participate as catalysts in asymmetric carbon–carbon bond formation.

In all pairs of compounds studied (i.e., the secondary amines and their corresponding *N*-methylated derivatives), a reversal was observed in the configuration of the major enantiomer. The configuration at the carbinol carbon atom has a pronounced effect upon the asymmetric induction, and where it is (*R*), as for pairs **7** and **8** (Table 1, entries 3 and 4), and for pairs **22** and **23** (entries 7 and 8, 9 and 10, 12 and 13) the *N*-methylated derivative favours induction of the (*S*)-enantiomer, as compared with the corresponding secondary amine ligand. Conversely, for pair **10** and **11**, which possess the (*S*)-configuration at the carbinol carbon atom, the *N*-methylated derivative **11** favours induction of the (*R*)-enantiomer (entries 5 and 6). In previous work, *N*,*N*-dimethylation led to reversal of enantioselectivity but in only low ee's using secondary amine ligands.[21,22] Accordingly, it is noteworthy that the secondary amine catalyst **22** affords 80% ee (Table 1, entry 7). While the *N*-methylated catalysts **8**, **11** and **23** all give greater amounts of (*S*)-1-phenylpropan-1-ol, the effect is greatest with ligand **23**, containing six stereogenic centres. Using **23** and 2-naphthaldehyde, the aryl alcohol was not detected, presumably because of steric hindrance of approach to the



Scheme 4.

catalyst. Using a *trans*-1,2-diaminocyclohexane as part of a salen ligand, ee's of 30–70% were obtained for the addition of diethylzinc to benzaldehyde;[23] ligands such as **22** compare favourably, and show that systems based on a *trans*-1,2-diaminocyclohexane but with additional chirality can deliver significantly high ee's in the enantioselective addition to carbonyl compounds (Scheme 4).

The absolute configurations obtained with catalysts **22** and **23** might be accounted for by a catalyst with a pocket defined by the flanking wall of the aminocyclohexanol ring, and the basal plane that includes two zinc and two oxygen atoms. Interaction of the carbonyl group of the aldehyde with the zinc atom coordinated to the diamine unit, prior to alkyl transfer from the other zinc atom (presumed to be bound to the two oxygen atoms) would be consistent with previous models.[19,25] For ligand **22**, the bulk at nitrogen is sufficiently small to allow the aryl ring to reside nearby, leading to the attack of the aldehyde on its *Re*-face. Conversely, for **23**, the bulk of the *N*-methyl group is deemed to hinder location of the aryl group as above, so leading to *Si*-face addition and predominantly the (*S*)-1-arylpropan-1-ol.

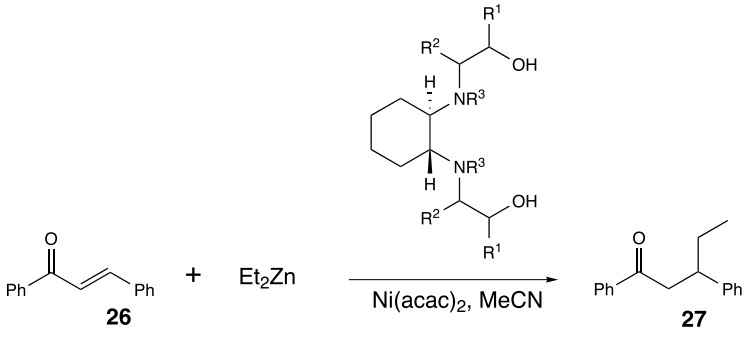
In view of the use of tetradentate amino alcohols as ligands in the asymmetric Michael addition[26] of diethylzinc to chalcone, the efficacy of some of the diamino diol ligands was briefly examined (Scheme 5). Ligand **8** (Table 2) was found to be significantly better than **14**, again showing that the stereogenic centre at the carbinol carbon atom plays a major role. In the isopropyl substituted series, ligand **14** (corresponding to **8**) gave a somewhat higher ee than the diastereoisomer **17**, but no asymmetric induction was observed using ligand **21**, containing opposite stereochemistries at the carbinol position. Again, a (modest) reversal in the configuration of the major enantiomer was observed for both the phenyl-substituted series (**8** and **11**), and the isopropyl series (**14** and **17**), indicating that similar complexation features regarding secondary and tertiary (*N*-methylated) amine ligands are likely to operate for Michael additions as well as for 1,2-additions to carbonyl compounds.

These results show that introduction of new chiral centres at the β-amino alcohol carbon atoms of the diamino diol **4** can lead to improved ee's, and that catalysts with multiple stereogenic centres can lead to significant asymmetric induction in carbon–carbon bond-forming reactions. A cyclohexane backbone, as in **22** and **23**, gave the highest ee's of those catalysts studied, as well as providing the products of the opposite configuration in high enantiomeric excess, simply by *N*,*N*′-dimethylation of the ligand.[27]

2. Experimental

2.1. General

Melting points were determined on a microscope hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Perkin–Elmer PE-983 spectrophotometer. Optical rotations were measured at 20 °C. Unless otherwise stated, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300 instrument operating at 300 and 75 MHz, respectively; chemical shifts are reported in δ (ppm) relative to the internal reference (tetramethylsilane or deuteriochloroform). Thin-layer chromatography was performed on Merck 0.2 mm aluminium-backed silica gel 60 F_{254} plates and visualized using alkaline $KMnO_4$ spray or by ultraviolet light. Flash column chromatography was performed using Merck 0.040–0.063 mm, 230–400 mesh silica gel. Microanalytical data were obtained on a Perkin–Elmer 2400 CHN



Scheme 5.

Table 2. Reaction of chalcone with diethylzinc in toluene[a]

Entry	Ligand	Yield (%)[b]	ee (%)[c]	Configuration
1	**8**	72	37	(*R*)
2	**11**	68	10	(*S*)
3	**14**	63	13	(*R*)
4	**17**	70	8	(*S*)
5	**21**	61	0	—

[a] Reactions were conducted at −30 °C with 16 mol% of $Ni(acac)_2$ and 16 mol% of ligand.
[b] Yields were determined by ^{1}H NMR spectrometry.
[c] Absolute configurations of the conjugate ketone were determined by HPLC analysis using a Chiralcel OD column.[24]

elemental analyser. Mass spectra were obtained on a VG7070H mass spectrometer with Finigan Incos II. All solvents were reagent grade and, where necessary, were purified and dried by standard methods. Evaporation refers to the removal of solvent under reduced pressure.

The following compounds were prepared according to literature procedures: (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane;[10] (1*S*,2*S*)-(+)-*trans*-1,2-diaminocyclohexane; (*R*)-(−)-2-hydroxy-3-methylbutyric acid;[28] (*S*)-(+)-2-hydroxy-3-methylbutyric acid;[28] (1*R*,2*R*)-(−)-*N*,*N*′-bis-(1-hydroxyethyl)-*trans*-diaminocyclohexane.[29]

2.1.1. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(1-hydroxyethyl)-*trans*-diaminocyclohexane (5). (1*R*,2*R*)-(−)-*N*,*N*′-Bis-(1-hydroxyethyl)-*trans*-diaminocyclohexane (0.40 g, 2.0 mmol) was dissolved in formaldehyde (3.3 mL, 37% w/v, 41 mmol,) and formic acid (4.2 mL, 96% v/v, 107 mmol) and the resulting solution heated to 90 °C. Sodium formate (14 mg, 0.20 mmol) was then added and the mixture was kept stirring at 90 °C for 16 h. The solution was then was cooled to room temperature and made alkaline, with cooling, to pH 12 with aqueous sodium hydroxide (2 M). The mixture was extracted with diethyl ether (3×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give amine **5** (0.43 g, 95%) as a clear oil; $[\alpha]_D=-32.8$ ($c=0.01$, $CHCl_3$); IR (film) 3628 (br), 2886, 1123 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.63 (2H, br, OH), 3.68 (4H, m, CH_2OH), 3.58 (2H, m, C*H*N), 2.84 (4H, m, CH_2N), 2.41 (6H, s, Me), 2.07–1.20 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 64.4 (*C*H_2OH), 53.3 (*C*H_2N), 40.7 (*C*HN), 35.9 (Me), 23.5 (*C*H_2CHN), 21.6 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{12}H_{27}N_2O_2$ (MH^+) 231.2073, found 231.2081.

2.1.2. (1*R*,2*R*)-(+)-*N*,*N*′-Bis(α-hydroxy-(*S*)-phenyl)-acetamido-*trans*-1,2-diaminocyclohexane (6). L-Mandelic acid (11.7 g, 77 mmol) and *N*-hydroxysuccinimide (8.86 g, 77 mmol) were added to a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.0 g, 35 mmol) in THF (100 mL) and the resulting mixture was stirred for 30 min at 20 °C. To this solution was added 1,3-dicyclohexylcarbodiimide (15.9 g, 77 mmol) in portions over 10 min and the resulting mixture was stirred for 48 h at 20 °C. Saturated aqueous sodium hydrogen carbonate (50 mL) was then added and the aqueous layer was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid that was purified by flash column chromatography (7:3 ethyl acetate/petroleum ether). Any residual urea by-product is removed in the first few fractions and is visible by its precipitation within the fraction solvent. Evaporation of the required fractions gave a white solid that was recrystallized from the elution solvent to give amide **6** (7.4 g, 56%) as white plates, mp 158–160 °C; $[\alpha]_D=+28.7$ ($c=1$, $CHCl_3$) cm^{-1}; IR ($CHCl_3$) 3185 (br), 1645, 1535, 1060 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.22 (10H, m, phenyl), 6.38 (2H, br, NH), 4.47 (2H, s, C*H*OH), 3.67 (2H, br, OH), 3.52 (2H, m, C*H*N), 1.80–1.10 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 173.3 (C=O), 140.0 (*ipso*-phenyl), 129.2 (*o*-phenyl), 129.0 (*m*-phenyl), 127.1 (*p*-phenyl), 74.2 (*C*HOH), 54.2 (*C*HN), 34.3 (*C*H_2CHN), 25.3 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{22}H_{26}N_2O_4$ (M^+) 382.1893, found 382.1889.

2.1.3. (1*R*,2*R*)-(+)-*N*,*N*′-Bis(ethan-(1-(*R*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (7). To an oven-dried, 25 mL pear-shaped flask with an inlet capped with a septum and containing a stirrer bar (1 cm length) was attached a 4′ Vigreux column. At the top of the column was placed a distillation arm with a small condenser. Between the condenser and a 10 mL receiver flask was an outlet connected to nitrogen through a mercury bubbler. The whole system was flushed with nitrogen and the pear-shaped flask was charged with a solution of amide **6** (0.235 g, 0.62 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.312 mL, 8.61 mmol); the mixture was then heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.84 mL, 2 M, 3.69 mmol) was then added carefully over 15 min. The liberated dimethyl sulfide and ether were distilled and collected. After 18 h at reflux, the remaining solution was allowed to cool to room temperature and the solvent carefully removed by connecting the outlet for nitrogen to a vacuum pump. The residual amine–boron trifluoride complex was cooled to 0 °C and hydrochloric acid (10 mL, 6 M) was added dropwise for the first few mL; CAUTION: the initial reaction is very vigorous! The acidified solution was heated at reflux for 1 h to ensure complete hydrolysis. The solution was then allowed to cool to 20 °C and the non-basic components removed by extraction with diethyl ether (3× 15 mL). The aqueous layer was made alkaline by addition of aqueous sodium hydroxide (6 M, CAUTION) to pH 12 and was then extracted with diethyl ether (3×15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated to give a clear oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **7** (71 mg, 32%) as a clear oil; $[\alpha]_D=+1.87$ ($c=1.55$, $CHCl_3$); IR (film) 3618 (br), 3149, 1645, 1580 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.48 (10H, m, phenyl), 4.97 (2H, m, C*H*OH), 3.48 (2H, br, CHO*H*), 3.22 (2H, m, C*H*NH), 2.70 (4H, m, CH_2NH), 2.15–1.25 (8H, m, CH_2CH_2CHNH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.9 (*ipso*-phenyl), 128.7 (*o*-phenyl), 127.8 (*m*-phenyl), 126.3 (*p*-phenyl), 74.7 (C*H*OH), 64.3 (*C*H_2NH), 56.5 (*C*HNH), 33.4 (CH_2CHNH), 25.6 (CH_2CH$_2$CHNH). HRMS (EI): calcd for $C_{22}H_{31}N_2O_2$ (MH^+) 355.2377, found 355.2386.

2.1.4. (*R*,*R*)-(+)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*R*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (8). Amino alcohol **7** (0.25 g, 0.65 mmol) was dissolved in aqueous 37% formaldehyde (1.2 mL, 15 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1.5 mL, 35 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was then cooled to 20 °C and made alkaline (pH 12) by addition of aqueous sodium hydroxide (2 M) with constant cooling. The aqueous layer was extracted with diethyl ether (2×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **8** (0.26 g, quantitative) as a clear oil; $[\alpha]_D=-27.7$ ($c=0.76$, $CHCl_3$); IR (film) 3520 (br), 3061, 1645, 1511 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35 (10H, m, phenyl), 5.71 (2H, br, OH), 4.79 (2H, m, C*H*OH), 2.85

(2H, m, C*H*N), 2.43 (4H, m, CH_2N), 2.17 (6H, s, CH_3), 1.75–1.05 (8H, m, CH_2CH_2CHN)); ^{13}C NMR ($CDCl_3$) δ 143.8 (*ipso*-phenyl), 128.6 (*o*-phenyl), 127.4 (*m*-phenyl), 126.4 (*p*-phenyl), 70.6 (*C*HOH), 63.2 (*C*H_2N and *C*HN), 37.4 (*C*H_3), 25.9 (*C*H_2CHN), 24.8 (*C*H_2CH$_2$CHN). HRMS (EI): calcd for $C_{24}H_{35}N_2O_2$ (MH^+) 383.2699, found 383.2692.

2.1.5. (1*R*,2*R*)-(+)-*N*,*N*′-(α-Hydroxy-(*R*)-phenyl)-acetamido-*trans*-1,2-diaminocyclohexane (9). D-Mandelic acid (11.7 g, 77 mmol) and *N*-hydroxysuccinimide (8.86 g, 77 mmol) were added to a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.0 g, 35 mmol) in THF (100 mL) and the resulting mixture stirred for 30 min at 20 °C. To this solution was added 1,3-dicyclohexylcarbodiimide (15.9 g, 77 mmol) in portions over 10 min and the resulting mixture was stirred for 48 h at 20 °C. The mixture was worked up as described for **6**, and after column chromatography, evaporation of the required fractions gave a white solid which was recrystallized from ethyl acetate. The white plates so obtained were filtered and dried under reduced pressure to give amide **9** (6.5 g, 50%) as plates, mp 173–174 °C; $[\alpha]_D = +17.6$ ($c=1$, $CHCl_3$); ($CHCl_3$) 3184, 1645, 1534, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.12 (10H, m, aryl), 4.88 (2H, br, NH), 4.72 (2H, s, C*H*OH), 3.48 (2H, m, C*H*N), 1.65–1.00 (8H, m, CH_2CH_2CHN); ^{13}C NMR ($CDCl_3$) δ 174.1 (C=O), 139.6 (*ipso*-phenyl), 129.0 (*o*-phenyl), 128.7 (*m*-phenyl), 127.1 (*p*-phenyl), 74.4 (*C*HOH), 53.6 (*C*HN), 32.4 (*C*H_2CHN), 25.0 (*C*H_2CH$_2$-CHN); IR (KBr pellet) 3355, 2944, 2832, 1657 cm^{-1}; FAB-MS *m*/*z* 383 (MH^+, 100%). HRMS (EI): calcd for $C_{22}H_{26}N_2O_4$ (M^+) 382.1893, found 382.1897.

2.1.6. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*S*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (10). The procedure described for amine **7** was followed using a solution of amide **9** (0.404 g, 1.06 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.153 mL, 4.22 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added carefully over 15 min. The subsequent steps, work-up and isolation as described for amine **7** gave an oil that was purified by flash column chromatography (1:19 methanol/chloroform) to give amine **10** (94 mg, 25%) as a clear oil that solidified on cooling to 4 °C; $[\alpha]_D = -96.6$ ($c=0.5$, $CHCl_3$); IR (film) 3626, 3090, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.30 (10H, m, phenyl), 4.76 (2H, m, C*H*OH), 3.00–2.60 (6H, m, CH_2NH and C*H*NH), 2.25 (2H, m, NH), 2.05–1.20 (8H, m, CH_2CH_2CHNH); ^{13}C NMR ($CDCl_3$) δ 143.1 (*ipso*-phenyl), 128.8 (*o*-phenyl), 127.9 (*m*-phenyl), 126.4 (*p*-phenyl), 72.6 (*C*HOH), 60.8 (*C*H_2NH), 54.4 (*C*HNH), 32.5 (*C*H_2CHNH), 25.5 (*C*H_2CH$_2$CHNH). HRMS (EI): calcd for $C_{22}H_{30}N_2O_2$ (MH^+) 355.2377, found, 355.2386.

2.1.7. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*S*)-phenyl)-1-ol)-*trans*-1,2-diaminocyclohexane (11). Amino alcohol **10** (30 mg, 0.085 mmol) was dissolved in aqueous 37% formaldehyde (1.4 mL, 19 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1.8 mL, 42 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **11** (31 mg, quantitative) as a clear oil; $[\alpha]_D = -111.6$ ($c=0.57$, $CHCl_3$); IR (film) 3567, 2988, 1511, 1168 cm^{-1}; ^{1}H NMR ($CHCl_3$) δ 7.31 (10H, m, phenyl), 7.51 (2H, br, OH), 4.83 (2H, m, C*H*OH), 2.75 (2H, m, C*H*NH), 2.50–2.30 (10H, m, NCH_3, NCH_2, C*H*N), 2.02–1.80 (4H, CH_2CHN), 1.10 (4H, m, CH_2CH$_2$CHN); ^{13}C NMR ($CDCl_3$) δ 143.3 (*ipso*-phenyl), 128.9 (*o*-phenyl), 127.9 (*m*-phenyl), 126.6 (*p*-phenyl), 72.2 (*C*HOH), 65.0 (*C*H_2N), 60.5 (*C*HN), 42.0 (N*C*H_3), 26.0 (CH_2CHN), 23.8 (CH_2CH$_2$CHN). FAB-MS *m*/*z* 383 (MH^+, 100%), 232 (17%). HRMS (EI): calcd for $C_{24}H_{35}N_2O_2$ (MH^+) 383.2701, found 383.2699.

2.1.8. (1*R*,2*R*)-(+)-*N*,*N*′-Bis-(1-hydroxy-1-(*S*)-isopropyl-acetamido)-*trans*-1,2-diaminocyclohexane (12). A solution of carbonyldiimidazole (3.14 g, 19.4 mmol) in dry THF (10 mL) was added to a stirred solution of (*S*)-(+)-2-hydroxy-3-methylbutyric acid (2.0 g, 17.0 mmol) and 1-hydroxybenzotriazole (0.23 g, 1.7 mmol) in freshly distilled THF (60 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. A solution of (1*R*,2*R*)-(−)-*trans*-diaminocyclohexane (0.88 g, 0.77 mmol) in dry THF (2 mL) was then added dropwise. The mixture was stirred at 20 °C for 24 h, then hydrochloric acid (50 mL, 1 M) as added. The aqueous layer was extracted with diethyl ether (3×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid which was purified by flash column chromatography (4:1 ethyl acetate/40–60 °C petroleum ether). Evaporation of the appropriate fractions gave a white solid that was recrystallized from isopropanol to give amide **12** as white needles (2.16 g, 89%), mp 197–198 °C; $[\alpha]_D = +32.2$ ($c=1$, MeOH); IR ($CHCl_3$) 3592, 2859, 1602 cm^{-1}; ^{1}H NMR (CD_3OD) δ 3.75 (2H, d, $J=3.5$ Hz, C*H*OH), 3.68 (2H, m, C*H*N), 2.01 (2H, m, CH_3CHCH_3), 2.00–1.75 (4H, m, CH_2CHN), 1.35 (4H, m, CH_2CH$_2$CHN), 0.97 (6H, d, $J=7.0$ Hz, CH_3CHCH$_3$), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR (CH_3OD) δ 177.2 (C=O), 77.6 (*C*HOH), 54.2 (*C*HN), 33.7 (CH_3CHCH_3), 33.5 (*C*H_2CHN), 26.1 (*C*H_2-CH$_2$CHN), 20.1 (*C*H_3CHCH$_3$), 17.2 (CH_3CH*C*H_3); FAB-MS *m*/*z* 315 (MH^+, 100%), 215 (21%), 141 (23%), 98 (42%). Anal. calcd for $C_{16}H_{30}N_2O_4$: C, 61.10; H, 9.62; N, 8.91. Found: C, 61.09; H, 9.74; N, 8.85.

2.1.9. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (13). The procedure described for amine **7** was followed using a solution of amide **12** (0.10 g, 0.32 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.16 mL, 1.27 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (3 mL, 2 M, 3.18 mmol) was then added carefully over a period of 15 min. The subsequent steps, work-up and isolation as described for amine **7** gave an oil that was purified by flash column chromatography (1:49 methanol/chloroform) to give amine **13** (90 mg, 99%) as a clear oil; $[\alpha]_D = -7.2$; ($c=0.31$, $CHCl_3$); IR (film) 3202, 1556, 1383 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.91 (2H, br, OH), 3.32 (2H, m, C*H*OH), 2.88 (4H, m, CH_2NH), 2.16 (2H, m, C*H*NH), 2.00–1.15 (8H, m, CH_2CH$_2$CHNH), 1.53 (2H, m, CH_3CHCH_3), 0.87 (6H, d, $J=7.0$ Hz, CH_3CHCH$_3$), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 76.7 (*C*HOH), 63.8 (*C*H_2NH), 51.6 (*C*HNH), 32.8 (CH_3CHCH_3), 30.4 (*C*H_2CHNH), 25.5 (*C*H_2CH$_2$CHNH), 19.1

(CH_3CHCH_3), 18.7 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2710.

2.1.10. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (14). Amino alcohol **13** (29 mg, 0.10 mmol) was dissolved in aqueous 37% formaldehyde (2.8 mL, 27 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (2.0 mL, 35 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **14** (20 mg, 63%) as a clear oil; $[\alpha]_D=-42.8$ ($c=1$, $CHCl_3$); IR (film) 3119, 1503, 1204 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.29 (2H, m, C*H*OH), 2.68 (2H, m, C*H*HN), 2.44 (2H, m, C*H*N), 2.26 (2H, m, CH*H*N), 2.23 (6H, s, NCH_3), 1.77–1.10 (8H, m, CH_2CH_2-CHN), 1.55 (2H, m, CH_3CHCH_3), 0.97 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.89 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 72.1 (*C*HOH), 65.9 (CH_2N), 59.2 (*C*HN), 35.5 (NCH_3), 32.4 (CH_3CHCH_3), 25.5 (CH_2CHN), 24.9 (CH_2CH_2CHN), 18.8 (CH_3CHCH_3), 18.4 (CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3009.

2.1.11. (1*R*,2*R*)-(+)-*N*,*N*′-Bis-(1-hydroxy-1-(*R*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (15). A solution of carbonyldiimidazole (3.14 g, 19.4 mmol) in dry THF was added to a stirred solution of (*R*)-(−)-2-hydroxy-3-methylbutyric acid (3.42 g, 29.0 mol) and 1-hydroxybenzotriazole (0.46 g, 2.7 mmol) in freshly distilled THF (70 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. A solution of (1*R*,2*R*)-(−)-*trans*-diaminocyclohexane (1.50 g, 13.1 mmol) in dry THF (5 mL) was then added dropwise. The mixture was stirred at 20 °C for 24 h followed by work-up and flash column chromatography as described for **12**. Evaporation of the appropriate fractions gave a white solid that was recrystallized from ethanol to give amide **15** as white needles (3.78 g, 92%), mp 210–212 °C; $[\alpha]_D=+51.7$ ($c=1$, MeOH); IR ($CHCl_3$) 3616, 2864, 1619 cm^{-1}; ^1H NMR (CD_3OD) δ 3.84 (2H, d, $J=3.5$ Hz, C*H*OH), 3.75 (2H, m, *C*HN), 2.15 (2H, m, CH_3CHCH_3), 2.00–1.40 (8H, m, CH_2CH_2CHN), 1.03 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.87 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$) δ 177.0 (C=O), 77.2 (*C*HOH), 54.1 (*C*HN), 33.8 (CH_3CHCH_3), 33.3 (CH_2CHN), 26.2 (CH_2CH_2CHN), 20.1 (CH_3CHCH_3), 16.5 (CH_3CHCH_3). Anal. calcd for $C_{16}H_{30}N_2O_4$: C, 61.10; H, 9.62; N, 8.91. Found: C, 61.14; H, 9.74; N, 8.82.

2.1.12. (1*R*,2*R*)-(−)-*N*,*N*′-Bis(ethan-(1-(*S*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (16). The procedure described for amine **7** was followed using a solution of amide **15** (0.134 g, 0.43 mmol) in dry THF (5 mL). To this solution was added boron trifluoride etherate (0.22 mL, 1.71 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added *carefully* over 15 min. The subsequent steps, work-up and isolation as described for amine **7** (chromatography not required) gave amine **16** (79 mg, 65%) as a clear oil; $[\alpha]_D=-29.8$ ($c=0.04$, $CHCl_3$); IR (film) 3369, 3200, 1565, 1382 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.26 (2H, m, C*H*OH), 2.51 (4H, m, CH_2NH), 2.11 (2H, m, C*H*NH), 1.99–1.08 (8H, m, CH_2CH_2CHNH), 1.54 (2H, m, CH_3CHCH_3), 0.88 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.83 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 74.8 (*C*HOH), 60.9 (CH_2NH), 49.9 (*C*HNH), 32.6 (CH_3CHCH_3), 32.4 (CH_2CHNH), 25.5 (CH_2CH_2CHNH), 19.0 (CH_3CHCH_3), 18.6 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2696.

2.1.13. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*,*N*′-bis(ethan-(1-(*S*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (17). Amino alcohol **16** (46 mg, 0.16 mmol) was dissolved in aqueous 37% formaldehyde (2.8 mL, 27 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (3.6 mL, 63 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was worked up and purified as described for amine **8** to give amine **17** (36 mg, 74%) as a clear oil; $[\alpha]_D=-67.3$ ($c=1.8$, $CHCl_3$); IR (film) 3602, 3128, 1512, 1206 cm^{-1}; ^1H NMR ($CHCl_3$, 500 MHz) δ 3.39 (2H, m, C*H*OH), 2.40–2.29 (6H, m, CH_2N and CHN), 2.14 (6H, s, CH_3N), 1.97–1.80 (4H, m, C*H*HC*H*HCHN), 1.55 (2H, m, CH_3CHCH_3), 1.12 (4H, m, CH*H*CH*H*CHN), 0.89 (6H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.85 (6H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 73.6 (*C*HOH), 64.8 (CH_2N), 54.8 (*C*HN), 32.3 (CH_3CHCH_3), 31.2 (NCH_3), 25.8 (CH_2CHN), 23.3 (CH_2CH_2CHN), 18.8 (CH_3CHCH_3), 18.5 (CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3016.

2.1.14. (1*R*,2*R*)-(+)-*N*-(α-Hydroxy-(*R*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (18). Carbonyldiimidazole (3.10 g, **19** mmol) was added in portions to a stirred solution of (*R*)-(−)-2-hydroxy-3-methylbutyric acid (1.30 g, 11 mmol) and 1-hydroxybenzotriazole (0.30 g, 2.2 mmol) in anhydrous THF (45 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1 h. After this time, a solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (2.50 g, 22 mmol) in anhydrous tetrahydrofuran (5 mL) was added dropwise over 15 min. The mixture was stirred at 20 °C for 16 h followed by evaporation of the solvent and acidification of the residue with hydrochloric acid (1 M) to pH 2. The aqueous layer was washed with ethyl acetate (3×30 mL) and the combined organic layers discarded. The remaining aqueous layer was then made alkaline to pH 11 with aqueous sodium hydroxide (1 M) and extracted with ethyl acetate (3× 30 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a white solid which was recrystallized from isopropanol to give **18** as white plates (0.14 g, 4%), mp 127–128 °C; $[\alpha]_D=+83.3$ ($c=0.5$, $CHCl_3$); IR (film) 3520 (br), 1683, 1469, 1183 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.64 (1H, m, NH), 3.96 (1H, d, $J=4.0$ Hz, C*H*OH), 3.64 (1H, m, *C*HNHCO), 2.99 (3H, br, OH and NH_2), 2.49 (1H, m, *C*HNH$_2$), 2.13 (1H, m, CH_3CHCH_3), 1.95–1.35 (8H, m, CH_2CH_2CHN), 1.04 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.89 (3H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.5 (C=O), 76.3 (*C*HOH), 55.4 (*C*HNH), 54.3 (*C*HNH$_2$), 35.7 (CH_2-CHNHCO), 32.7 (CH_2CHNH_2), 31.6 (CH_3CHCH_3), 25.0 (CH_2CHN), 24.9 (CH_2CH_2CHN), 19.3 (CH_3CHCH_3), 15.8 (CH_3CHCH_3). FAB-MS *m*/*z* 215 (MH^+, 100%). HRMS (EI): calcd for $C_{11}H_{23}N_2O_2$ (MH^+) 215.1760, found 215.1761.

2.1.15. (1*R*,2*R*)-(+)-*N*-(α-Hydroxy-(*R*)-isopropylacetamido)-*N*′-(α-hydroxy-(*S*)-isopropylacetamido)-*trans*-1,2-diaminocyclohexane (19). A solution of 1,1′-carbonyldiimidazole (36 mg, 0.22 mmol) in dry tetrahydrofuran (2 mL) was added via a pressure-equilibrating dropping funnel to a solution of (*S*)-(+)-2-hydroxy-3-methylbutyric acid (26 mg, 0.22 mmol) and 1-hydroxybenzotriazole hydrate (30 mg, 0.22 mmol) in dry tetrahydrofuran (10 mL) under an inert atmosphere at 20 °C, and the mixture was stirred for 1.5 h. A solution of amide **18** (40 mg, 0.19 mmol) in dry THF (2 mL) was then added dropwise via a gas-tight syringe and the resulting solution stirred for 16 h under an inert atmosphere at 20 °C. The solution was then acidified with hydrochloric acid (20 mL, 1 M) and the aqueous layer extracted with ethyl acetate (3× 20 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated to give an off-white solid that was purified *via* flash chromatography (4:1 ethyl acetate/40–60 °C petroleum ether) to give amide **19** as a white solid (25 mg, 42%), mp 182 °C; $[\alpha]_D = +5.3$ ($c=0.5$, MeOH); IR ($CHCl_3$) 3601 (br), 1689, 1694, 1465 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (1H, br, CHN*H*), 7.02 (1H, br, CHN*H*), 3.92 (1H, d, $J=4.5$ Hz, C*H*OH), 3.77 (1H, d, $J=4.5$ Hz, C*H*OH), 3.75 (2H, m, C*H*NH), 2.12 (1H, m, CH_3CHCH_3), 1.91 (1H, m, CH_3CHCH_3), 1.89–1.35 (8H, m, CH_2CH_2CHN), 0.99 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.92 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.79 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.77 (3H, d, $J=7.0$ Hz, CH_3CHCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8 (C=O), 174.6 (C=O), 76.7 (*C*HOH), 76.0 (*C*HOH), 53.2 (*C*HNH), 52.7 (*C*HNH), 32.3 (CH_2CHNH), 32.2 (CH_2CHNH), 31.8 (CH_3CHCH_3), 31.4 (CH_3CHCH_3), 24.8 (CH_2CH_2CHN), 24.7 (CH_2CH_2CHN), 19.7 (CH_3CHCH_3), 19.4 (CH_3CHCH_3), 16.2 (CH_3CHCH_3), 15.8 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{31}N_2O_4$ (MH^+) 315.2284, found 315.2273.

2.1.16. (1*R*,2*R*)-(−)-*N*-(Ethan-(1-(*S*)-isopropyl)-1-ol)-*N*′-(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diamino-cyclohexane (20). The procedure described for amine **7** was followed using a solution of amide **19** (22 mg, 0.07 mmol) in dry THF (2 mL). To this solution was added boron trifluoride etherate (0.04 mL, 0.27 mmol) and the solution was heated to reflux until it became clear. Borane–dimethyl sulfide complex in THF (1.17 mL, 2 M, 2.33 mmol) was then added *carefully* over 15 min. The subsequent steps, work-up and isolation as described for amine **7** (chromatography not required) gave amine **20** (8 mg, 40%) as a clear oil; $[\alpha]_D = -35.2$ ($c=0.4$, $CHCl_3$); IR (film) 3321 (br), 1566, 1213 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.27 (2H, m, C*H*OH), 2.85–2.60 (2H, m, CH_2NH), 2.50–2.25 (2H, m, CH_2NH), 2.10 (2H, m, C*H*NH), 1.56 (2H, m, CH_3CHCH_3), 2.00–1.15 (8H, m, CH_2CH_2CHNH), 0.90–0.82 (12H, m, CH_3CHCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 76.3 (*C*HOH), 74.8 (*C*HOH), 61.4 (CH_2NH), 59.7 (CH_2NH), 51.1 (*C*HNH), 49.8 (*C*HNH), 32.6 (CH_2CHNH), 32.3 (CH_2CHNH), 31.3 (CH_3CHCH_3), 31.2 (CH_3CHCH_3), 25.4 (CH_2CH_2CHNH), 19.1 (CH_3CHCH_3), 19.0 (CH_3CHCH_3), 18.7 (CH_3CHCH_3), 18.6 (CH_3CHCH_3). HRMS (EI): calcd for $C_{16}H_{35}N_2O_2$ (MH^+) 287.2699, found 287.2694.

2.1.17. (1*R*,2*R*)-(−)-*N*,*N*′-Dimethyl-*N*-(ethan-(1-(*S*)-isopropyl)-1-ol)-*N*′-(ethan-(1-(*R*)-isopropyl)-1-ol)-*trans*-1,2-diaminocyclohexane (21). Amino alcohol **20** (50 mg, 0.17 mmol) was dissolved in aqueous 37% formaldehyde (1.0 mL, 9.6 mmol) and the resulting solution stirred at 20 °C for 10 min. Aqueous 90% formic acid (1 mL, 17.5 mmol) was then added and the mixture was stirred and heated at 90 °C for 24 h. The mixture was allowed to cool to 20 °C and made alkaline (pH 12) by addition of sodium hydroxide (2 M) with constant cooling. The aqueous layer was extracted with diethyl ether (2×25 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give amine **21** (30 mg, 55%) as a clear oil; $[\alpha]_D = -18.2$ ($c=0.15$, $CHCl_3$); IR (film) 3482 (br), 1399, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 3.40 (2H, m, C*H*OH), 2.50–2.25 (6H, m, CH_2N and C*H*N), 2.15 (6H, s, CH_3N), 1.95–1.25 (8H, m, CH_2CH_2CHNH), 1.60 (2H, m, CH_3CHCH_3), 0.90 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.88 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.87 (3H, d, $J=7.0$ Hz, CH_3CHCH_3), 0.85 (3H, d, $J=7.0$ Hz, CH_3CHCH_3). HRMS (EI): calcd for $C_{18}H_{39}N_2O_2$ (MH^+) 315.3012, found 315.3025.

2.1.18. (1*R*,2*R*)-*N*,*N*′-Bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane (22). To a stirred solution of (1*R*,2*R*)-(−)-*trans*-1,2-diaminocyclohexane (4.80 g, 42.0 mmol) in anhydrous ethanol (100 mL) under an inert atmosphere at 20 °C was added cyclohexene oxide (17.3 mL, 171 mmol) *via* a pressure-equilibrated dropping funnel over a period of 20 min. Upon complete addition, the mixture was heated at reflux for 16 h. After this time, the pale yellow solution was allowed to cool to 20 °C whereupon the solvent was evaporated to give a brown oil that was acidified to pH 2 with 2 M hydrochloric acid and the aqueous layer extracted with chloroform (2×50 mL) which was discarded. The aqueous layer was then basified to pH 11 with 2 M aqueous sodium hydroxide and the aqueous layer was again extracted with chloroform (2×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and evaporated. The resulting yellow-orange oil was subjected to purification by flash column chromatography, initially with methanol/chloroform (1: 4 v/v), then followed by methanol/chloroform (1:19 v/v) to give a clear oil that was dissolved in hot petroleum ether (40–60 °C). On allowing to cool, small glassy needles deposited which were isolated and recrystallised from cyclohexane to give **22** (3.90 g, 30%), as small glassy needles, mp 129–130 °C; $[\alpha]_D = +11.2$ (*c* 1, $CHCl_3$); IR (film) ν_{max} 3126, 2926, 2854, 1446, 1369, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 600 MHz) δ 7.63 (2H, br, OH), 3.49 (2H, m, C_1HOH), 2.43 (2H, m, $C_{1'}HNH$), 2.29 (2H, m, C_2HNH), 2.01 (2H, m), 1.91 (2H, m), 1.67 (6H, m), 1.64 (2H, m), 1.30–1.18 (10H, m), 0.99 (2H, m), 0.65 (2H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 77.46, 65.58, 65.44, 35.25, 33.19, 32.57, 25.59, 25.46, 24.33. HRMS calcd for $C_{18}H_{35}N_2O_2$ (MH^+) 311.2699. Found: 311.2699. FAB MS (%) 311 (MH^+, 100), 196 (52), 115 (42). Anal. calcd for $C_{18}H_{34}N_2O_2$ C, 69.62; H, 11.04; N, 9.03. Found: C, 69.42; H, 11.14; N, 8.93.

2.1.19. (1*R*,2*R*)-*N*,*N*′-Dimethyl-*N*,*N*′-bis((3*S*,4*S*)-4-hydroxycyclohexyl)-*trans*-1,2-diaminocyclohexane (23). Diamine **22** (0.556 g, 1.80 mmol) was dissolved in formaldehyde (37% by wt., 4.0 mmol, 6.0 mL) and formic acid (96% v/v, 0.22 mol, 7.8 mL), and the resulting solution heated to 90 °C. Sodium formate (7.40 mmol, 0.50 g) was then added in one portion and the resulting solution was

stirred at 90 °C for 16 h. After this time, the solution was cooled to 20 °C and then basified, with cooling, to pH 12 with 2 M aqueous sodium hydroxide. The aqueous layer was washed with diethyl ether (3×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated under reduced pressure to give a clear oil (0.58 g, 95%) that required no further purification; $[\alpha]_D = +42.2$ (*c* 0.53, $CHCl_3$); IR (film) ν_{max} 3401, 1454, 1204, 1061 cm^{-1}; ^1H NMR δ ($CDCl_3$, 300 MHz) δ 3.23 (2H, m, C_1HOH), 2.45 (2H, m, $C_{1'}HNH$), 2.30 (2H, m, C_2HNH), 2.09 (6H, s, CH_3), 2.02 (2H, m), 1.86 (2H, m), 1.75–1.63 (8H, m), 1.64–1.18 (12H, m); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 72.59, 67.77, 66.55, 34.00, 29.31, 28.78, 27.80, 26.57, 26.33, 24.87. HRMS calcd for $C_{20}H_{38}N_2O_2$ (MH^+) 339.3012. Found: 339.3009. FAB MS (%) 339 (MH^+, 100), 210 (22), 112 (19).

2.1.20. (*R*)- or (*S*)-1-Phenylpropan-1-ol (25a). *Representative procedure*. Ligand **22** (0.06 g, 0.20 mmol, 10 mol%) was dissolved with stirring in freshly distilled toluene (9 mL) under an atmosphere of nitrogen at 20 °C. Freshly distilled benzaldehyde (0.20 mL, 2.0 mmol) was then injected by syringe and the resulting solution stirred for 15 min. The mixture was then cooled to −30 °C (cooling bath) and a solution of diethylzinc in toluene (3.5 mL, 1.1 M, 4 mmol) was injected by syringe, ensuring that the tip of the needle was below the surface of the solution. The mixture was stirred at −30 °C for 16 h. Aqueous hydrochloric acid (10 mL, 1 M) was then added slowly (CAUTION: vigorous reaction). The aqueous layer was extracted with diethyl ether (2×20 mL) and the combined organic layers were dried ($MgSO_4$), filtered and evaporated to give a turbid oil that was purified by flash column chromatography (3:17 ethyl acetate: 40–60 °C petroleum ether) to give **25a** (0.135 mg, 50%) as a clear oil; ^1H NMR ($CDCl_3$) δ 7.32 (5H, m, phenyl), 4.56 (1H, t, $J=7.5$ Hz, C*H*OH), 2.43 (1H, br, OH), 1.78 (2H, m, CH_2), 1.43 (3H, t, $J=7.5$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (99:1 *i*-PrOH/hexane; 1 mL min^{-1} t_R 20 min, t_S 29 min).

2.1.21. (*R*)- or (*S*)-1-Phenylpent-1-en-3-ol (25b). ^1H NMR ($CDCl_3$) δ 7.12 (5H, m, aryl), 6.40 (1H, d, $J=16.0$ Hz, aryl–C*H*=CH), 5.92 (1H, dd, $J=16.0$, 7.0 Hz, aryl–CH=C*H*), 4.08 (1H, m, C*H*OH), 1.80 (1H, br, OH), 1.51 (2H, m, CH_2), 0.82 (3H, t, $J=7.5$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (5:95 *i*-PrOH/hexane, 1 mL min^{-1}; t_R 12 min, t_S 19 min).

2.1.22. (*R*)- or (*S*)-1-*p*-Methoxyphenylpropan-1-ol (25c). ^1H NMR ($CDCl_3$) δ 7.15–6.80 (4H, m, aryl), 4.71 (1H, t, $J=$ 7.0 Hz, C*H*OH), 3.79 (3H, s, CH_3), 2.48 (1H, br, OH), 1.85 (2H, m, CH_2), 0.92 (3H, t, $J=7.0$ Hz, CH_3). ee was determined on a Chiralcel OD column (2.5: 97.5 *i*-PrOH/hexane; 0.7 mL min^{-1}; t_R 33 min, t_S 40 min).

2.1.23. (*R*)- or (*S*)-1-(α-Naphthyl)-1-propanol (25d). ^1H NMR ($CDCl_3$) δ 7.72 (7H, m, aryl), 5.35 (1H, t, $J=7.0$ Hz, C*H*OH), 2.31 (1H, br, OH), 1.99 (2H, m, CH_2), 1.02 (3H, t, $J=7.0$ Hz, CH_3). Enantiomeric excess was determined on a Chiralcel OD column (4:96 *i*-PrOH/hexane, 0.5 mL min^{-1}; t_R 31 min, t_S 27 min).

2.1.24. (*R*)- or (*S*)-Ethylchalcone 27. *Typical procedure*. Amino alcohol **8** (30.6 mg, 0.08 mmol, 8 mol%) and nickel acetonylacetonate (18 mg, 0.07 mmol, 7 mol%) in freshly distilled acetonitrile (2 mL) were heated at reflux under an atmosphere of nitrogen with stirring for 1 h. The solution was allowed to cool to 20 °C and a solution of chalcone (208 mg, 1.0 mmol) in freshly distilled acetonitrile (5 mL) was added. The mixture was cooled to −35 °C (cooling bath) and a solution of diethylzinc in toluene (1.36 mL, 1.1 M, 1.5 mmol) was added cautiously whereupon an immediate colour change from green to dark brown occurred. After stirring at −30 °C for 16 h, the solution was poured into hydrochloric acid (15 mL, 3 M) and the aqueous layer extracted with dichloromethane (3×20 mL). The combined organic layers were shaken with brine (25 mL) and then dried ($MgSO_4$), filtered and evaporated to give crude **27** which was purified by flash column chromatography; ^1H NMR ($CDCl_3$) δ 7.93 (2H, m, *o*-aryl ketone), 7.52 (3H, m, *m* and *p*-aryl ketone), 7.25 (5H, m, *phenyl*-alkyl), 3.31 (3H, m, C(O)CH_2CH), 1.75 (2H, m, CH_2CH_3), 0.88 (3H, t, $J=7.0$ Hz, CH_2CH_3). Enantiomeric excess was determined on a Chiralcel OD column (0.2: 99.8, *i*-PrOH/hexane, 1 mL min^{-1}; t_R 23 min, t_S 18 min).

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An improved synthesis of piperazino-piperidine based CCR5 antagonists with flexible variation on pharmacophore sites

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Abstract—An improved and efficient synthetic route towards piperidino-piperazine based CCR5 antagonists was developed. The new approach was flexible for introducing various substituents in the pharmacophore sites via Grignard reagent addition and reductive amination. L-Amino acids were used as a chiral pool to introduce and then induce the desired stereochemistries, meanwhile rendering the variable substitution. The efficient construction of the piperazino-piperidine nucleus was achieved in a highly convergent manner with a key building block of N^1-Boc-4-substituent-4-aminopiperidine, exhibiting significant advantages in terms of concise synthetic route and environmental-friendly reagents over the previously described stepwise synthesis, in which a modified Strecker reaction was involved with highly toxic reagents such as diethylaluminum cyanide.

1. Introduction

Human immunodeficiency virus type 1 (HIV-1) is the etiological agent of acquired immunodeficiency syndrome (AIDS). Currently HIV-1 reverse transcriptase and protease inhibitors are available for the treatment of AIDS, and the highly active antiretroviral therapy has been very effective in bringing down the viral load; however, emergence of multi-drug resistant viral strains and intolerance to available agents can complicate the response to the treatment. Recently, CCR5, a co-receptor essential for HIV-1 recognition and entry into $CD4^+$ macrophages and T-cells[1] but not essential for human functions[2] has emerged as a highly validated target for antiviral therapy.[3] The blockade of viral entry with small molecules targeting the CCR5 co-receptor could represent a new class of anti HIV-1 agent.[3,4] A proof of concept for this approach has been provided by Sch-C and Sch-D, two CCR5 antagonists as HIV-1 entry inhibitors under clinical trials (Fig. 1).[5]

Among an impressive number of structurally diverse, small-molecule CCR5 inhibitors reported so far,[4–11] piperidine- and piperazine-based compounds disclosed by Schering–Plough Research Institute are an attractive and promising class of potent CCR5 antagonists, as exemplified by compounds in Figure 1. The SAR investigation in the two series has disclosed that the 1-*N*-substituents and 2(*S*)-substituents in the piperazine ring as well as the 4-substitution at the phenyl group are important pharmacophore elements determining the potency and selectivity.[6–8] The methyl group at the 4-position of the piperidine ring enhanced the binding potency by 3–7 fold relative to its des-methylation counterparts. However, the three important sites in the pharmacophore were inaccessible through previously reported synthetic methodology, and the introduction of the methyl group at the 4-position of the piperidine ring involved a highly toxic reagent of diethylaluminum cyanide.[6,7]

To enable further structural optimization and pharmacological study of the promising piperazine-core compounds, we sought a facile and practical synthesis of the structurally diverse piperazino-piperidine analogs. In this paper, we report a versatile synthetic approach which provides potential for the variation of the pharmacophore elements without using highly toxic and flammable reagent such as diethylaluminum cyanide employed by the Schering–Plough's modified Strecker reaction.

2. Results and discussion

As part of our program to further refine compounds in the piperazino-piperidine family for improved potency and higher selectivity, we developed a concise and convenient

Keywords: Piperazino-piperidine nucleus; CCR5 antagonist; Reductive amination; Chiral pool; 4-Substituent-4-aminopiperidine.
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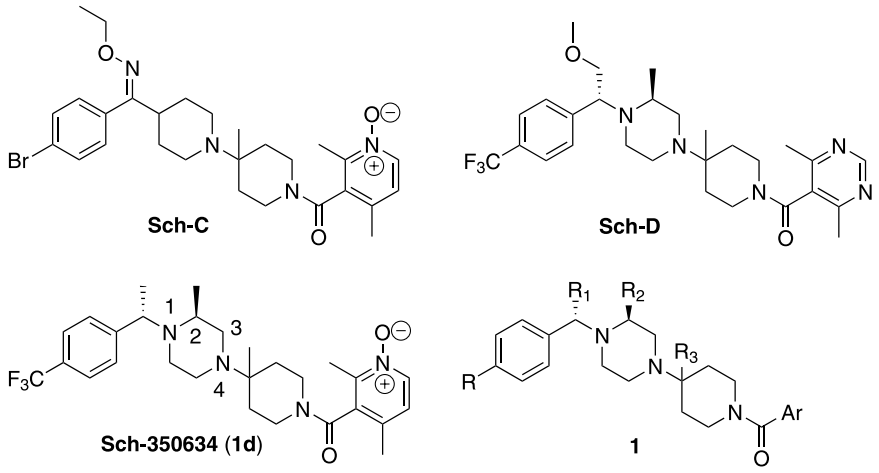
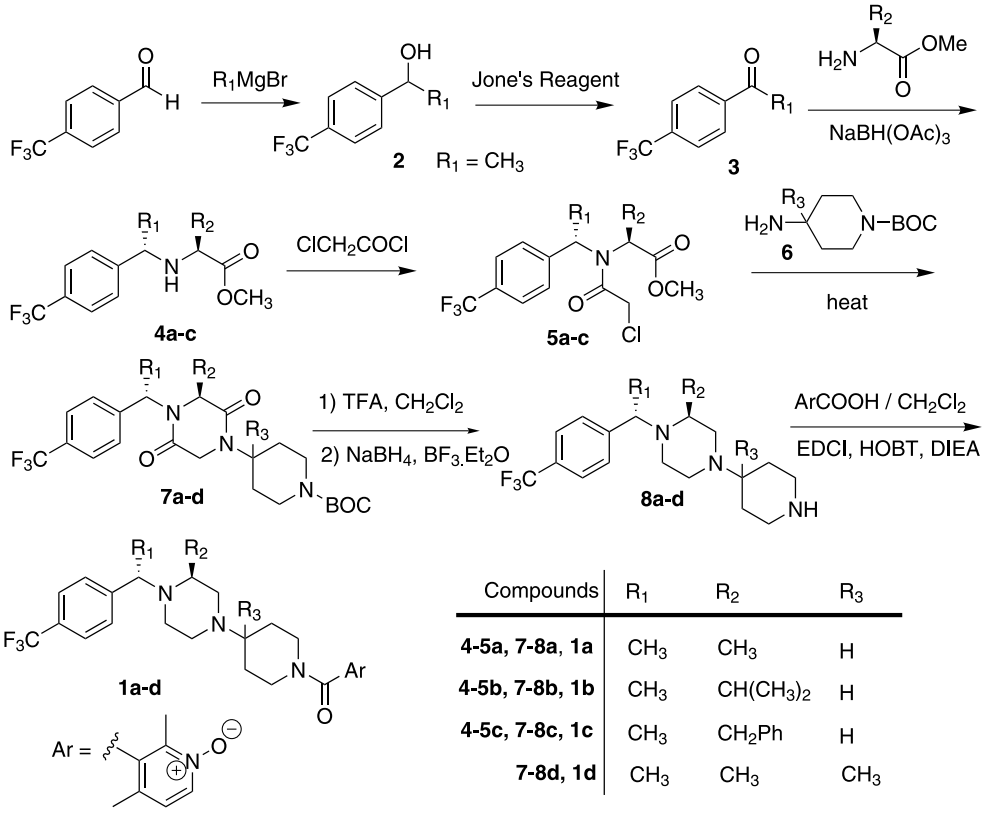


Figure 1. Piperidine- and piperazine-based CCR5 antagonists.

synthetic approach (Scheme 1) to afford structurally diverse piperidino-piperazine containing compounds typified by the general structure of **1**, in which the 1-*N*-substituents and 2(*S*)-substituents in the piperazine ring as well as the group at the 4-position of the piperidine can be varied readily. Our improved methodology provides a general access to a variety of piperazino-piperidine amide analogs for further pharmacological study as HIV-1 entry inhibitors.

Following an early finding that the chirality of piperazine 2-substituent requires (*S*)-configuration for effective CCR5 binding,[7] we envisioned that this stereochemistry could be introduced using natural amino acids as a chiral pool, which also renders the structural variation of 2-substituent. Accordingly, the adjacent asymmetric center of the 1-*N*-substituent (*S*-configuration is preferred) could be installed via asymmetric induction by the reductive amination of the aryl methyl ketone with the L-amino acid. Our experiments showed that the asymmetric induction effect is dependent on the structure of the side chain of L-amino acid. Under our reaction conditions, the dr value [the diastereomeric ratio of (1*S*,2*S*) over (1*R*,2*S*)] varied in the range of 50–72% with the 2*S*-methyl group being the best one. The resulting diastereoisomers were easily separated by flash silica gel chromatography (for **4b**, its following chloroacetylated products were more easy to separate by column chromatography). The stereochemistry of the synthetic **4a** was determined by the comparison of ^{1}H NMR data with the



Compounds	R_1	R_2	R_3
4-5a, 7-8a, 1a	CH_3	CH_3	H
4-5b, 7-8b, 1b	CH_3	$CH(CH_3)_2$	H
4-5c, 7-8c, 1c	CH_3	CH_2Ph	H
7-8d, 1d	CH_3	CH_3	CH_3

Scheme 1. A general procedure to synthesize various piperazino-piperidine based CCR5 antagonists.

literature.[12] The less polar diastereomer was found to be (1*S*,2*S*)-configured, and the more polar counterpart was the (1*R*,2*S*)-configured. The configuration of the resulting diastereoisomers [(1*S*,2*S*)-**4** and (1*R*,2*S*)-**4**] was further confirmed in the case of compound **4c**, by synthesizing an authentic sample according to the literature method,[6] which was identified to correspond to the less polar fraction of the diastereomer pair generated by the reductive amination. Therefore, the established guideline could be applied to the determination of the absolute configuration of the 1*N*-substituent of the piperazine ring produced by the asymmetric induction of the adjacent L-amino acid.

The general synthetic method for the preparation of structurally diverse piperidino-piperazine amides is depicted in Scheme 1. Nucleophilic addition of alkylmagnesium reagent to commercially available 4-trifluoromethylbenzaldehyde followed by Jone's oxidation afforded ketone **3**, possessing the various R_1 substituents. Reductive amination of the ketone **3** with various L-amino acid produced diastereoisomers which were easily separated by flash silica gel chromatography to afford the desired (1*S*,2*S*)-amine **4**, introducing a variable group of R_2. The secondary amine was then reacted with 2-chloroacetyl chloride to yield the corresponding (2-chloroacetyl)-amino-acetic acid methyl ester **5**, which was converted to the desired aryl diketopiperazino-piperidine **7** by treatment with 4-substituent-4-amino-piperidine-1-*N*-Boc **6**, allowing the introduction of an alkyl or aryl group (R_3) at the 4-position of the piperidine. The key building blocks **6** were conveniently prepared according to our recently developed efficient methodology employing isonipecotate as a starting material and Curtius rearrangement as a key step.[13] Boc removal of **7** with trifluoroacetic acid followed by reduction with $NaBH_4$ in the presence of boron trifluoride etherate gave the aryl piperazino-piperidine analogs **8**. The coupling of the resulting free amine with the desired aromatic acids proceeded under standard conditions to furnish the desired products **1**.

Notably, our approach employed the 4-substituent-4-amino-piperidine-1-*N*-Boc **6** as a building block to construct the piperazino-piperidine scaffold in a highly convergent manner. The reactivity was affected by the substituent at the 4-position of the 4-amino-piperidine. When N^1-Boc-4-aminopiperidine **6a** is used, the cyclization was readily accomplished in one step with high yield (compounds **7a**–**c**), while the mono-substituted intermediate was isolated and continued the intramolecular lactamization in a different reaction condition (with refluxing toluene and catalytic 2-pyridinol)[14] when N^1-Boc-4-methyl-4-amino-piperidine **6b** is used (compound **7d**). In both cases, no racemization was observed. Our developed methodology is devoid of using highly toxic and flammable reagent such as diethylaluminum cyanide employed by the Schering–Plough's modified Strecker reaction, and provides potential for convenient introduction of various substituents at the important 4-position of the piperidine ring.

Using this improved methodology, we efficiently synthesized a series of piperazino-piperidine amide analogs **1a**–**d** with a variety of 2-substituents on the piperazine ring. The concise synthesis of compound **1d** (Sch-350634), a potent and orally active CCR5 antagonist as HIV-1 entry inhibitor developed by Schering–Plough Research Institute, was accomplished in excellent yield using ^1N-Boc-4-methyl-4-aminopiperidine as a smart building block. Compared to previously reported procedure, the newly developed methodology provides us with a facile and practical access to structurally diverse piperazino-piperidine compounds for the elaboration of effective inhibitors of HIV-1 cell entry.

3. Conclusions

In summary, we developed an improved and efficient procedure to prepare various piperidino-piperazine based CCR5 antagonists. Starting from commercially available 4-substituted-benzaldehyde, the nucleophilic addition of the Grignard reagent followed by Jone's oxidation afforded the aryl alkyl ketone. Reductive amination of the aryl alkyl ketone with L-amino acid introduced the desired chirality and the substitution at the 2(*S*)-position of the piperazine ring. Subsequently the efficient and concise synthesis of the piperazino-piperidine nucleus was achieved in a highly convergent manner with a key building block of ^1N-Boc-4-substituted-4-amino-piperidine, devoid of using highly toxic reagents employed by previously described stepwise synthetic approach. The improved methodology was versatile and flexible for introducing various substituents in the key positions of the pharmacophore, thus potentially benefits the SAR studies of piperazino-piperidine compounds as HIV-1 entry inhibitors.

4. Experimental

4.1. General

All reactions were performed under nitrogen atmosphere with flame-dried glassware. Solvents were distilled and dried according to standard procedures. ^{1}H NMR spectra were recorded on a Varian 300-MHz or 400-MHz spectrometer. ^{13}C NMR spectra were recorded on a Varian Mercury VX 400-MHz spectrometer. Melting points (uncorrected) were determined on a Buchi-510 capillary apparatus. Specific rotations (uncorrected) were determined in a Perkin–Elmer 241 polarimeter. Elemental analysis were determined to be within $\pm 0.4\%$ of the theoretical values for elements C, H and N. IR spectra were recorded on a DTGS spectrometer in KBr pellets. Low and high-resolution mass spectra were determined on Finnigan MAT-95 mass spectrometer. TLC was performed on 0.25 mm HSGF 254 silica gel plates. All final products were characterized by NMR, IR, MS and elemental analysis or high resolution mass spectra.

4.1.1. 1-(4-Trifluoromethyl-phenyl)-ethanol (2).[15] Magnesium turnings (0.631 g, 25.0 mmol) were placed into a dry three-neck flask, equipped with an addition funnel and condenser. Anhydrous ether (10 mL) was added to cover the turnings. To initiate the reaction, about 2 mL of a solution of CH_3I (1.6 mL, 25.0 mmol) and 16.0 mL of anhydrous ether were added. After formation of bubbles at the surface of the turnings, the remaining CH_3I–ether solution was added

dropwise (at a ratio to maintain a moderate reflux). After the addition, the mixture was stirred at room temperature for 45 min. To the above ethereal Grignard reagent (11.0 mL), α,α,α-trifluro-*p*-tolualdehyde (1.68 mL, 12.26 mmol) in 15.0 mL of anhydrous ether was added with constant agitation at 0 °C under N_2. The mixture was refluxed for 1.5 h, then poured into a cold aqueous ammonium chloride solution. The aqueous layer was extracted with Et_2O, the combined Et_2O extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine, then dried over Na_2SO_4- and evaporated under vacuum. The residue was purified by chromatography using petroleum ether/ether = 10:1 to afford compound **2** (3.145 g, 100%) as yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, *J* = 8.2 Hz); 7.48 (d, 2H, *J* = 8.1 Hz); 4.96 (q, 1H, *J* = 6.4 Hz); 2.03 (s, 1H); 1.50 (d, 1H, *J* = 6.4 Hz).

4.1.2. 1-(4-Trifluoromethyl-phenyl)-ethanone (3).[16] A solution of CrO_3 (26.72 g, 267.2 mmol) in 23.0 mL of concentrated sulfuric acid was diluted with water to a volume of 100 mL to afford 2.672 N Jone's reagent. To a solution of compound **2** (3.314 g, 17.25 mmol) in 50 mL of acetone at 0 °C was added Jone's reagent (13.11 mL) dropwise with stirring. The resulting orange solution was stirred at 0 °C for 0.5 h. The cooling bath was removed and 2-propanol was added dropwise, whereupon a green precipitate formed immediately. The mixture was stirred at room temperature for 20 min and filtered through celite. The flask and the celite pad was washed with acetone and the solvent was removed, the yellow oil was purified by flash chromatography on silica gel eluted with petroleum ether/ether = 10:1 to obtain compound **3** (2.588 g, 82.2%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.07 (d, 2H, *J* = 8.0 Hz); 7.60 (d, 2H, *J* = 8.0 Hz); 2.67 (s, 3H).

4.1.3. 2-[1-(4-Trifluoromethyl-phenyl)-ethylamino]-propionic acid methyl ester (4a). To the solution of L-alanine methyl ester hydrochloride (1.023 g, 6.41 mmol) in dry 1,2-dichloroethane (15 mL) was added Et_3N (1.117 mL, 6.41 mmol). After stirring at room temperature for 0.5 h, 4′-(trifluoromethyl)acetophenone (1.0 g, 5.34 mmol) was added, then the reaction mixture was treated with sodium triacetoxyborohydride (2.266 g, 10.69 mmol) and HOAc (0.61 mL, 10.69 mmol). The mixture was stirred at room temperature for 22 h. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4. The solvent was removed under vacuum. The residue was purified by chromatography using petroleum ether/ether = 10:1 to give compound **4a** (0.788 g, yield 54.2%) as colorless oil. $[\alpha]_D^{20} = -113.6$ (*c* = 0.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.1 Hz); 7.45 (d, 2H, *J* = 8.1 Hz); 3.80 (q, 1H, *J* = 6.6 Hz); 3.72 (s, 3H); 3.06 (q, 1H, *J* = 7.0 Hz); 1.38 (d, 3H, *J* = 6.6 Hz); 1.25 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 176.42, 149.25, 129.64, 126.98 (×2), 125.19 (×2), 122.79, 56.25, 54.13, 51.42, 24.92, 19.43. IR (KBr) ν: 3334, 2975, 1737, 1619, 1452, 1419, 1324, 1203, 1164, 1124, 1066, 1016, 844 cm^{-1}. EI-MS (*m*/*z*, %): 274 ($M^+ - 1$, 1.0); 260 (7.0); 216 (100.0); 173 (99.0); 153 (37.0).

The (1*R*, 2*S*) isomer is colorless oil, yield 17.0%. $[\alpha]_D^{20} = +9.5$ (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, *J* = 8.1 Hz); 7.44 (d, 2H, *J* = 8.1 Hz); 3.87 (q, 1H, *J* = 6.6 Hz); 3.61 (s, 3H); 3.34 (q, 1H, *J* = 6.9 Hz); 1.93 (br, 1H); 1.36 (d, 3H, *J* = 6.6 Hz); 1.29 (d, 3H, *J* = 7.0 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.50, 148.97, 129.21, 126.95(×2), 125.23(×2), 125.19, 55.41, 53.81, 51.48, 22.95, 18.46. IR (KBr) ν: 3330, 2977, 1739, 1619, 1454, 1326, 1201, 1162, 1124, 1068, 1016, 844 cm^{-1}.

4.1.4. 3-Methyl-2-[1-(4-trifluoromethyl-phenyl)-ethylamino]-butyric acid methyl ester (4b). The solution of L-valine methyl ester hydrochloride (1.10 g, 6.57 mmol) in dry 1,2-dichloroethane (25.0 mL) was treated with sequential 4′-(trifluoromethyl)-acetophenone (1.12 g, 5.98 mmol) and sodium triacetoxyborohydride (1.77 g, 8.37 mmol) in a similar way to the preparation of **4a**. The residue was purified by chromatography using petroleum ether/EtOAc = 10:1 as eluent to give compound **4b** (0.91 g, yield 50.0%) as colorless oil (mixture of two diastereoisomers). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57–7.42 (m, 9.44H); 3.75 (q, 1.36H, *J* = 6.5 Hz); 3.71 (s, 3H); 3.67 (q, 1H, *J* = 6.6 Hz); 3.57 (s, 4.08H); 3.06 (d, 1.36H, *J* = 6.2 Hz); 2.70 (d, 1H, *J* = 6.2 Hz); 1.92–1.79 (m, 4.72H); 1.32 (d, 1H, *J* = 6.5 Hz); 1.31 (d, 1.36H, *J* = 6.6 Hz); 0.94 (d, 4.08H, *J* = 6.7 Hz); 0.93 (d, 4.08H, *J* = 6.7 Hz); 0.91 (d, 3H, *J* = 6.7 Hz); 0.87 (d, 3H, *J* = 6.7 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.90, 175.20, 149.50, 149.10, 129.25, 127.32, 127.18, 125.29, 64.79, 56.74, 56.64, 51.2, 51.33, 31.65, 25.43, 22.61, 19.42, 19.03, 18.63, 18.38. IR (KBr) ν: 3446, 2996, 1735, 1619, 1469, 1419, 1324, 1199, 1162, 1126, 1066, 1018, 844, 781, 609 cm^{-1}. EI-MS (*m*/*z*, %): 302 ($M^+ - 1$); 260 (20.0); 228 (8.0); 173 (100.0); 153 (37.0).

4.1.5. 3-Phenyl-2-[1-(4-trifluoromethyl-phenyl)-ethylamino]-propionic acid methyl ester (4c). The solution of L-phenylalanine methyl ester hydrochloride (2.588 g, 12.0 mmol) in 30.0 mL of dry 1,2-dichloroethane was treated with 4′-(trifluoromethyl) -acetophenone (1.871 g, 10.0 mmol) and sodium triacetoxyborohydride (3.179 g, 15.0 mmol) in a similar way to the preparation of **4a**. The purification from chromatography using petroleum ether/EtOAc (12:1) gives compound **4c** (1.342 g, yield 37%) as glassy solid. $[\alpha]_D^{20} = -49.7$ (*c* = 1.6, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 2H, *J* = 8.0 Hz); 7.31–7.26 (m, 3H); 7.17 (d, 2H, *J* = 8.0 Hz); 7.12–7.10 (m, 2H); 3.74 (q, 1H, *J* = 6.4 Hz); 3.68 (s, 3H); 3.19 (dd, 1H, *J* = 8.0, 6.0 Hz); 2.93 (dd, 1H, *J* = 13.2, 5.6 Hz); 2.81 (dd, 1H, *J* = 13.2, 8.0 Hz); 1.92 (br, 1H); 1.29 (d, 3H, *J* = 6.4 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 175.42, 149.03, 137.32, 129.33 (×3), 128.26 (×2), 127.03 (×2), 126.65 (×2), 125.26, 122.38, 60.49, 56.35, 51.69, 40.09, 25.22. EI-MS (*m*/*z*, %): 351 (M^+, 0.1); 332 (1.0); 292 (18.0); 260 (66.0); 173 (100.0). IR (KBr): 3346, 2928 (m), 1736, 1618, 1327, 1140, 1067, 702 cm^{-1}.

The (1*R*,2*S*) isomer, colorless oil in yield of 30%. $[\alpha]_D^{20} = +44.3$ (*c* = 0.7, $CDCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (d, 2H, *J* = 8.1 Hz); 7.40 (d, 2H, *J* = 8.1 Hz); 7.31–7.15 (m, 5H); 3.79 (q, 1H, *J* = 6.5 Hz); 3.52 (t, 1H, *J* = 6.7 Hz); 2.95 (d, 2H, *J* = 6.7 Hz); 1.90 (br, 1H); 1.28 (d, 2H, *J* = 6.6 Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 174.20, 148.60, 137.00, 129.31, 129.17, 128.43, 128.27 (×2), 127.24 (×2), 127.05, 126.79, 125.38, 122.80, 60.59, 56.32, 51.62, 39.38,

23.00. EI-MS (*m/z*, %): 332 (M^+-19, 2.0); 292 (19.0); 260 (85.0); 173 (100.0); 153 (11.0); 91 (8.0).

4.1.6. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-propionic acid methyl ester (5a). The secondary amine **4a** (0.479 g, 1.74 mmol) was dissolved in 1,2-dichloroethane (15.0 mL), chloroacetyl chloride (2.78 mL, 34.8 mmol) was added to the above solution at room temperature. The mixture was stirred under refluxing for 3 h. Both the solvent and chloroacetyl chloride was removed under vacuum. The remaining yellow syrup was purified by chromatography using petroleum ether/EtOAc (3.5:1) to give compound **5a** (0.589 g, yield 96.0%) as glassy solid. $[\alpha]_D^{20}=-105$ ($c=0.6$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.70–7.60 (m, 4H); 5.28 (q, 1H, $J=7.2$ Hz); 4.19 (q_{AB}, 2H, $J=12.4$ Hz); 3.57 (s, 3H); 3.49 (q, 1H, $J=7.2$ Hz); 1.77 (d, 3H, $J=7.2$ Hz); 1.56 (d, 3H, $J=7.2$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 170.30, 165.30, 142.24, 130.31, 128.23 (×2), 125.31 (×2), 122.53, 56.03, 52.60, 52.12, 41.45, 18.76, 15.93. EI-MS (*m/z*, %): 353 ($M^+ +2$, 0.3); 351 (M^+, 1.0); 274 (28.0); 266 (12.0); 264 (36.0); 173 (100.0); 153 (14.0). IR (KBr): 3467, 3037, 2958, 1741, 1633, 1437, 1329, 1240, 1121, 1068, 841, 613 cm^{-1}.

4.1.7. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-3-methyl-butyric acid methyl ester (5b). Compound **5b** was prepared from **4b** according to the same procedure as **5a**. The residue was chromatographed using petroleum ether/EtOAc=7:1 to separate the diastereoisomers (0.797 g, total yield 84.0%, each isomer in yield of ~42%). The less polar isomer **5b** is colorless oil. $[\alpha]_D^{20}=-84.4$ ($c=2.4$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.39 (m, 4H); 5.31 (br, 1H); 4.29–3.81 (m, 3H); 3.39 (s, 3H); 2.55–2.38 (m, 1H); 1.76 (d, 3H, $J=6.6$ Hz); 1.02 (d, 6H, $J=6.3$ Hz). EI-MS (*m/z*, %): 381 ($M^+ +2$, 2.0); 379 (M^+, 6.0); 362 (3.0); 360 (9.0); 322 (1.3); 320 (3.9); 264 (20.0); 173 (100.0). IR (KBr): 3450 2989, 2974, 2881, 1734, 1714, 1651, 1452 (m), 1335, 1165, 1121, 1273, 1120, 849, 613 cm^{-1}. HRMS (EI) calcd for $C_{17}H_{21}ClF_3NO_3$ 379.1162, found 379.1157.

The more polar isomer: $[\alpha]_D^{20}=-23.5$ ($c=1.1$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.66–7.57 (m, 4H); 5.33–5.31 (m, 1H); 4.34–4.13 (m, 2H); 3.80–3.72 (m, 3H); 3.40–3.37 (m, 1H); 2.42–2.25 (m, 1H); 1.71–1.63 (brd, 3H); 0.98–0.20 (m, 6H). EI-MS (*m/z*, %): 381 ($M^+ +2$, 3.0); 379 (M^+, 9.0); 362 (4.0); 360 (12.0); 322 (2.0); 320 (6.0); 264 (30.0); 173 (100.0).

4.1.8. 2-{(2-Chloro-acetyl)-[1-(4-trifluoromethyl-phenyl)-ethyl]-amino}-3-phenyl-propionic acid methyl ester (5c). Compound **5c** was prepared analogously to **5a**. The purification by chromatography using petroleum ether/EtOAc=6:1 afforded compound **5c** (0.553 g, yield 90.0%) as glassy solid. $[\alpha]_D^{20}=-72.6$ ($c=0.8$, $CDCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, $J=8.2$ Hz); 7.45 (d, 2H, $J=8.1$ Hz); 7.36–7.21 (m, 5H); 5.10 (q, 1H, $J=7.0$ Hz); 4.28–4.13 (m, 2H); 3.70–3.67 (m, 1H); 3.58–3.53 (m, 1H); 3.51 (s, 3H); 1.12 (d, 3H, $J=7.0$ Hz). EI-MS (*m/z*, %): 429 ($M^+ +2$, 2.0); 427 (M^+, 6.0); 410 (1.0); 408 (3.0); 350 (12.0); 336 (6.0); 292 (14.0); 260 (39.0); 196 (16.0); 173 (40.0); 162 (100.0); 91 (20.0). IR (film): 2953 (m), 1740, 1653, 1456 (m), 1327, 1167, 1122, 1070, 847, 754, 704 cm^{-1}.

4.1.9. 4-{3-Methyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7a). The compound **5a** (0.8 g, 2.28 mmol), N^1-Boc-4-aminopiperidine **6a** (0.5 g, 2.5 mmol) and Et_3N (0.35 mL) in CH_3OH (10 mL) were refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc=1:1 to give compound **7a** (0.644 g, yield 59%) as white solid. $[\alpha]_D^{20}=-42.0$ ($c=1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, $J=8.2$ Hz); 7.35 (d, 2H, $J=8.3$ Hz); 5.83 (q, 1H, $J=7.1$ Hz); 4.47–4.41 (m, 1H); 4.24–4.21 (m, 2H); 3.90 (s, 2H); 3.75 (q, 1H, $J=7.1$ Hz); 2.78–2.75 (m, 2H); 1.65 (d, 3H, $J=7.1$ Hz); 1.70–1.48 (m, 4H); 1.47 (d, 3H, $J=7.1$ Hz); 1.46 (s, 9H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 167.69, 164.82, 154.46, 143.40, 130.24, 127.21 (×2), 125.88, 125.20, 122.50, 79.95, 53.51, 51.57, 50.67, 45.04, 42.94 (×2), 28.59 (×2), 28.38 (×3), 19.45, 17.64. EI-MS (*m/z*, %): 484 ($M^+ +1$, 1.0); 483 (M^+, 7.0); 427 (24.0); 410 (20.0); 301 (13.0); 173 (12.0); 82 (100). IR (KBr): 3431, 2982, 1676, 1659, 1443, 1327, 1142 cm^{-1}.

4.1.10. 4-{3-Isopropyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7b). The compound **5b** (0.527 g, 1.39 mmol), N^1-Boc-4-aminopiperidine **6a** (0.2 g, 1.67 mmol) and DIPEA (0.44 mL, 2.51 mmol) in CH_3CN (10 mL) were refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc=1:1 to give the compound **7b** as white solid in yield of 42.3%. $[\alpha]_D^{20}=-16.8$ ($c=1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, 2H, $J=8.0$ Hz); 7.37 (d, 2H, $J=8.0$ Hz); 5.57–5.51 (m, 1H); 4.53–4.45 (m, 1H); 4.18 (brs, 2H); 3.95 (d, 1H, $J=17.6$ Hz); 3.82 (d, 1H, $J=17.6$ Hz); 3.56 (d, 1H, $J=7.2$ Hz); 2.21–2.12 (m, 1H); 1.85–1.71 (m, 2H); 1.65 (d, 3H, $J=7.2$ Hz); 1.59–1.48 (m, 4H); 1.46 (s, 9H); 1.04 (d, 3H, $J=6.8$ Hz); 0.96 (d, 3H, $J=6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.01, 164.44, 154.46, 143.51, 130.12, 127.46 (×2), 125.81, 125.77, 122.57, 79.90, 64.01, 54.28, 50.72, 45.68, 33.99, 28.81 (×2), 28.34 (×3), 28.08 (×2), 20.42, 18.14, 16.86. EI-MS *m/z*: 511 (M^+).

The more polar isomer (1*R*,2*S*)-**5b** was analogously converted to the corresponding (1*R*,2*S*)-**7b** as white solid in yield of 48%. $[\alpha]_D^{20}=+55.1$ ($c=5.1$, EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ 7.55 (d, 2H, $J=8.4$ Hz); 7.49 (d, 2H, $J=8.4$ Hz); 5.35 (br, 1H); 4.56–4.44 (m, 1H); 4.18 (brs, 1H); 3.91 (d, 1H, $J=17.2$ Hz); 3.89 (d, 1H, $J=4.0$ Hz); 3.74 (d, 1H, $J=17.2$ Hz); 2.74 (br, 2H); 1.70 (d, 3H, $J=7.2$ Hz); 1.53 (br, 4H); 1.49 (s, 9H); 0.87 (d, 3H, $J=6.8$ Hz); 0.79 (d, 3H, $J=6.8$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.91, 164.35, 154.37, 143.43, 130.04, 127.65, 127.39, 125.73, 125.12, 122.41, 79.81, 63.93, 54.20, 50.64, 45.60, 33.92, 28.75 (×2), 28.26 (×3), 28.01 (×2), 20.34, 18.07, 16.88. IR (KBr): 3315, 2974, 2247, 1662, 1126, 1072, 1016, 922, 733 cm^{-1}. EI-MS (*m/z*, %): 511 (M^+), 455 (26.0); 438 (18.0); 369 (8.0); 173 (25.0); 82 (100); 57 (50.00). HREI-MS calcd for $C_{26}H_{36}F_3N_3O_4$ 511.2658, found 511.2668.

4.1.11. 4-{3-Benzyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7c). The compound **7c** was prepared from **5c** and **6a** according to the same procedure as **7b**. The residue was purified by chromatography using petroleum ether/EtOAc = 1:1 to give compound **7c** (0.436 g, yield 83%) as white foam. $[\alpha]_D^{20} = -42.0$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.62 (d, 2H, $J = 8.3$ Hz); 7.40 (d, 2H, $J = 8.0$ Hz); 7.33–7.29 (m, 3H); 7.15 (d, 2H, $J = 6.8$ Hz); 5.92 (q, 1H, $J = 7.4$ Hz); 4.45–4.38 (m, 1H); 4.15–4.09 (m, 2H); 4.03 (t, 1H, $J = 4.2$ Hz); 3.32 (d, 1H, $J = 17.1$ Hz); 3.27 (dd, 1H, $J = 13.9$, 3.6 Hz); 3.12 (dd, 1H, $J = 14.0$, 4.7 Hz); 2.74–2.67 (m, 2H); 2.12 (d, 1H, $J = 16.8$ Hz); 1.85 (d, 1H, $J = 7.2$ Hz); 1.46–1.37 (m, 3H); 1.43 (s, 9H); 1.10–1.06 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 165.85, 165.66, 154.31, 143.41, 134.56, 130.45, 130.12 (×2), 128.77 (×2), 127.88, 127.45 (×2), 125.88, 125.09, 122.39, 79.8, 58.82, 52.59, 50.52, 44.37, 42.78, 39.87 (×2), 28.26 (×3), 27.96 (×2), 18.26. EI-MS (*m*/*z*, %): 559 (M^+, 2.0), 503 (9.0), 486 (5.0), 459 (10.0), 368 (6.0), 285 (4.0), 173 (58.0), 91 (20.0), 82 (100.0). IR (KBr): 3442, 2978, 2933, 1691, 1662, 1427, 1327, 1167, 1124, 1072 cm^{-1}. HREI-MS calcd for $C_{30}H_{36}F_3N_3O_4$ 559.2658, found 559.2671.

4.1.12. 4-Methyl-4-{3-methyl-2,5-dioxo-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidine-1-carboxylic acid *tert*-butyl ester (7d). Compound **5c** (0.221 g, 0.63 mmol), N^1-Boc-4-amino-4-methyl-piperidine **6b** (0.148 g, 0.69 mmol) in CH_3CN (5.0 mL) was refluxed overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using petroleum ether/EtOAc 1:1 as eluent to give the mono-substituted intermediate (0.265 g, yield 80.0%) as colorless oil. $[\alpha]_D^{20} = +80$ ($c = 1.65$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (AB, 2H, $J_{AB} = 8.3$ Hz); 7.60 (AB, 2H, $J_{AB} = 8.3$ Hz); 5.19 (q, 1H, $J = 6.9$ Hz); 3.56 (s, 3H); 3.52–3.40 (m, 7H); 1.97 (br, 1H, D_2O exchangeable); 1.71 (d, 3H, $J = 6.9$ Hz); 1.55 (d, 3H, $J = 6.9$ Hz); 1.49–1.47 (m, 2H); 1.44 (s, 9H); 1.08 (s, 3H). EI-MS (*m*/*z*, %): 529 (M^+, 3.0); 428 (6.0); 301 (23.0); 256 (21.0); 188 (56.0); 171 (100.0); 127 (62.0).

The mono-substituted intermediate (0.309 g, 0.58 mmol) and 2-hydroxy-pyridine (0.05 g, 0.43 mmol) were dissolved in dry toluene (1.5 mL) and stirred at 90 °C for 6 h. After removing the solvent, the residue was purified by chromatography using PE/EtOAc (1:1) as eluent to give compound **7d** as white solid (0.244 g, yield 84%). $[\alpha]_D^{20} = -16.3$ ($c = 1.2$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, 2H, $J = 8.0$ Hz); 7.36 (d, 2H, $J = 8.0$ Hz); 5.82 (q, 1H, $J = 7.2$ Hz); 4.06 (d, 1H, $J = 12.8$ Hz); 3.91 (d, 1H, $J = 12.8$ Hz); 3.64 (q, 1H, $J = 7.2$ Hz); 3.59–3.48 (m, 2H); 3.26–3.11 (m, 2H); 2.44–2.39 (m, 1H); 2.26–2.21 (m, 1H); 1.79–1.68 (m, 2H); 1.66–1.62 (m, 3H); 1.48 (d, 3H, $J = 7.2$ Hz); 1.47 (s, 9H); 1.36 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 169.51, 164.75, 154.58, 143.47, 130.38, 128.16 (×2), 125.60, 125.15, 122.32, 79.69, 58.85, 54.83, 50.64, 46.48 (×2), 40.13, 35.43, 35.20, 28.32 (×3), 21.77, 18.06, 15.93. EI-MS (*m*/*z*, %): 497 (M^+); 441 (56.0); 424 (11.0); 301 (23.0); 173 (18.0); 96 (100); 57 (43.0). IR (KBr): 3400, 2980, 2862, 1684, 1653, 1414, 1327, 1140, 1173 cm^{-1}.

4.1.13. 2-Methyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8a). The compound **7a** (0.242 g, 0.5 mmol) was dissolved in methylene chloride (2.5 mL) and trifluoroacetic acid (5 mL) was added. The mixture was stirred at room temperature for 2 h. After removing the solvent and trifluoroacetic acid under reduced pressure, 2 N NaOH was added and extractive work up with EtOAc. The organic layer was washed with saturated $NaHCO_3$, brine and dried over Na_2SO_4. The solvent was removed under vacuum to give (*S*)-4-((*S*)-1-(4-trifluoromethyl)phenyl)- ethyl-3-methyl)-1-(piperidin-4-yl)piperazine-2,5-dione, which was used directly for next step without purification.

The crude diketopiperzaine (0.192 g, 0.5 mmol) prepared above was dissolved in dimethoxy ethane (5 mL) and sodium borohydride (0.189 g, 5.0 mmol), boron trifluoride etherate (0.38 mL, 3.0 mmol) were added to the solution. The mixture was stirred under reflux for 3 h and then cooled to 0 °C. Methanol (6 mL) and concentrated hydrogen chloride (3.6 mL) were added successively to the mixture and stirred for 15 min at room temperature, then refluxed for 45 min. The mixture was concentrated, and basified with 6 N sodium hydroxide, then extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum to give the compound **8a** as glassy solid. Used for next step without further purification.

4.1.14. 2-Isopropyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8b). The preparation of **8b** is similar to that of **8a**.

4.1.15. 2-Benzyl-4-piperidin-4-yl-1-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazine (8c). The preparation of **8c** is also similar to that of **8a**.

4.1.16. 2-Methyl-4-(4-methyl-piperidin-4-yl)-1-[1-(4-trifluoromethyl-phenyl)-ethyl] -piperazine (8d). Prepared analogously to **8a**. Used directly for next step without further purification.

4.1.17. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-{3-methyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1a).[17] The crude piperidine **8a** (0.178 g, 0.5 mmol) was dissolved in methylene chloride (2 mL) and treated with 2,4-dimethylnicotinic acid-*N*-oxide (0.1 g, 0.6 mmol), EDCI (0.144 g, 0.75 mmol), HOBT (0.101 g, 0.75 mmol) and DIPEA (0.175 mL). The mixture was stirred at room temperature overnight and the solvent was removed under reduced pressure. The residue was purified by chromatography using CH_2Cl_2/CH_3OH (30:1) to give the compound **1a** (0.1 g, 37.0% overall yield of three steps) as white foam. $[\alpha]_D^{20} = +12.1$ ($c = 1.0$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J = 6.3$ Hz); 7.58–7.51 (m, 4H); 7.00 (dd, 1H, $J = 6.3$, 3.6 Hz); 4.76 (brt, 1H); 4.11 (brs, 1H); 3.55 (brd, 1H); 3.04–2.75 (m, 4H); 2.58–2.56 (m, 1H); 2.44 (d, 3H, $J = 19.5$ Hz); 2.31–2.22 (m, 5H); 2.15 (d, 3H, $J = 19.5$ Hz); 2.04–2.00 (m, 1H); 1.80–1.76 (m, 2H); 1.54–1.48 (m, 1H); 1.29 (d, 3H, $J = 6.6$ Hz); 1.14 (dd, 3H, $J = 6.0$, 1.5 Hz). ESI-MS (*m*/*z*, %): 505 ($M^+ + 1$, 100). EI-MS (*m*/*z*, %): 504 (M^+, 0.85); 487 (40.0); 426 (51.0); 314 (41.0); 246 (44.0); 173 (31.0); 134 (100). HREI-MS calcd for $C_{27}H_{35}N_4O_2F_3$: 504.2712, found, 504.2719.

4.1.18. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-{3-isopropyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1b). Prepared from the crude piperidine **8b** in a similar manner to **1a**. Chromatography purification using CH_2Cl_2/CH_3OH (30:1) afforded **1b** as white foam in an overall yield of 68.0%. $[\alpha]_D^{20}=-15.6$ ($c=0.70$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 2H, $J=6.8$ Hz); 7.57 (m, 4H); 7.01 (dd, 1H, $J_1=4.0$ Hz, $J_2=6.8$ Hz); 4.78 (m, 1H); 4.34 (q, 1H, $J=6.8$ Hz); 3.39 (m, 1H); 3.02–2.82 (m, 3H); 2.72–2.53 (m, 2H); 2.44 (d, 3H, $J=25.2$ Hz); 2.38–2.33 (m, 1H) 2.15–2.05 (m, 3H); 2.25 (d, 3H, $J=25.2$ Hz); 2.10–1.99 (m, 2H); 1.57–1.45 (m, 1H); 1.30 (d, 3H, $J=6.8$ Hz); 1.26–1.24 (m, 2H); 0.97 (m, 6H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.63, 148.52, 145.08, 138.41, 134.70, 132.88, 132.67, 128.67, 127.85 (×2), 124.87 (×3), 61.77, 61.10, 52.83, 48.86, 45.60, 44.12, 40.69, 29.64, 29.00, 27.80, 26.14, 19.93, 18.34, 15.92, 15.39, 14.95. ESI-MS (*m/z*, %): 533 ($M^+ +1$, 100%).

Similarly the diastereoisomer (1*R*,2*S*)-**1b** was synthesized from (1*R*,2*S*)-**8b** in yield of 66.0% as white foam. $[\alpha]_D^{20}=+17.9$ ($c=0.7$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.17 (d, 2H, $J=6.0$ Hz); 7.55 (d, 2H, $J=7.8$ Hz); 7.34 (d, 2H, $J=7.8$ Hz); 7.00 (d, 1H, $J=6.0$ Hz); 4.80–4.70 (m, 1H); 4.31 (q, 1H, $J=6.0$ Hz); 3.40–3.34 (m, 1H); 3.02–2.80 (m, 3H); 2.69–2.61 (m, 2H); 2.51–2.49 (m, 1H); 2.43 (d, 3H, $J=18.0$ Hz); 2.34–2.20 (m, 4H); 2.23 (d, 3H, $J=18.0$ Hz); 2.10–1.99 (m, 2H); 1.81–1.74 (m, 1H); 1.47–1.38 (m, 2H), 1.38 (d, 3H, $J=6.0$ Hz); 1.00–0.96 (m, 3H); 0.92 (d, 3H, $J=6.9$ Hz). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.60, 145.90, 145.01, 138.36, 134.67, 132.74, 128.96, 128.13 (×2), 125.48, 124.93, 124.78, 122.78, 61.60, 60.29, 54.62, 47.54, 45.40, 44.55, 40.54, 29.60, 28.40, 27.20, 26.24, 19.80, 18.29, 17.14, 15.34, 14.90. IR (film): 3421, 2960, 2869, 1639, 1450, 1326, 1122 cm^{-1}. ESI-MS (*m/z*, %): 533 ($M^+ +1$, 100%). HR-ESIMS calcd for $C_{29}H_{39}O_2N_4F_3+H$: 533.3103, found: 533.3098.

4.1.19. (4-{3-Benzyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-(2,4-dimethyl-1-oxy-pyridin-3-yl)-methanone (1c). Prepared from the crude piperidine **8c** analogously to **1a**. The residue was purified by chromatography using CH_2Cl_2/CH_3OH (30:1) to give the compound **1c** (0.305 g, three steps in yield of 54.0%) as white foam. $[\alpha]_D^{20}=+6.1$ ($c=0.9$, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, 1H, $J=6.4$ Hz); 7.57 (d, 2H, $J=8.0$ Hz); 7.52 (d, 2H, $J=8.4$ Hz); 7.34–7.29 (m, 2H); 7.25–7.17 (m, 3H); 7.18 (t, 2H, $J=7.6$ Hz); 4.77 (t, 1H, $J=13.6$ Hz); 3.98–3.96 (m, 1H); 3.36 (d, 1H, $J=9.6$ Hz); 3.26–3.24 (m,1H); 3.02–2.80 (m, 4H); 2.51–2.32 (m, 7H); 2.42 (d, 3H, $J=22.4$ Hz); 2.22 (d, 3H, $J=24.4$ Hz); 1.97–1.92 (m, 1H); 1.84 (s, 1H); 1.74–1.71 (m, 1H); 1.41 (d, 3H, $J=6.4$ Hz); 1.46–1.40 (m, 1H). ^{13}C NMR (400 MHz, $CDCl_3$): δ 164.57, 149.97, 144.99, 140.11, 138.34, 134.69, 132.78, 129.08 (×2), 128.78, 128.41 (×2), 127.59 (×2), 125.96, 125.53, 125.17, 124.93, 124.77, 122.82, 61.27, 58.67, 56.68, 49.63, 45.57, 45.03, 40.74, 29.50, 28.44, 27.90, 18.27, 15.30, 14.88. IR (KBr): 3423, 2926 (m), 1637, 1450, 1325, 1283, 1161, 1121, 1067, 845, 744, 702 cm^{-1}. ESI-MS (*m/z*, %): 581 ($M^+ +1$, 100%). HREI-MS calcd for $C_{33}H_{39}N_4O_2F_3+H$: 581.3103, found 581.3110.

4.1.20. (2,4-Dimethyl-1-oxy-pyridin-3-yl)-(4-methyl-4-{3-methyl-4-[1-(4-trifluoromethyl-phenyl)-ethyl]-piperazin-1-yl}-piperidin-1-yl)-methanone (1d).[6,7] Compound **1d** was synthesized from the crude piperidine **8d** analogously to **1a**. The residue was purified by chromatography ($CH_2Cl_2/CH_3OH=30:1$) to give compound **1d** (0.085 g, three steps in 64% yield) as white gum. $[\alpha]_D^{20}=+9.1$ ($c=0.9$, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, 1H, $J=6.6$ Hz); 7.58–7.50 (m, 4H); 7.00 (d, 1H, $J=6.9$ Hz); 4.22 (brt, 1H); 3.98 (brs, 1H); 3.45–3.36 (m, 2H); 3.01–2.96 (m, 2H); 2.67–2.57 (m, 1H); 2.46 (d, 3H, $J=9.9$ Hz); 2.41–2.24 (m, 4H); 2.26 (d, 3H, $J=9.0$ Hz); 2.03–1.95 (brt, 1H); 1.76–1.70 (m, 2H); 1.46–1.34 (m, 3H); 1.29 (d, 3H, $J=6.9$ Hz); 1.14 (d, 3H, $J=6.3$ Hz); 0.93 (s, 3H). ESI-MS (*m/z*, %): 519 ($M^+ +H$, 100.0), 541 ($M^+ +Na$, 37.0).

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The trimethylsilyl xylyl (TIX) ether: a useful protecting group for alcohols

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Abstract—A new protecting group for alcohols, the *p*-trimethylsilyl xylyl (TIX) group has been developed. The TIX group is used to protect various alcohols under acidic as well as basic conditions. The protected ethers thus formed had noteworthy chemoselectivity upon deprotection in the presence of other benzyl ethers and commonly used protecting groups. The stability of the TIX group towards various reagents has also been examined.

1. Introduction

Protection and deprotection are inevitable requirements of a lengthy synthetic sequence leading to natural products, fine chemical intermediates, or important industrial or pharmaceutical organic materials. Protecting groups exist for various functional moieties and have their own pattern of chemoselectivity during deprotection. In molecules with multiple, discrete, simultaneous protections, a careful strategy exists for specific removal and modification of the exposed functionality. Thus, elaborately protected, highly functional templates can serve as total synthetic intermediates. In addition, such templates bound to solid support can lead to diversity upon chemoselective deprotection of various functional groups with subsequent elaboration of the liberated functional group. To date, a remarkable variety of protecting groups have been reported and their preparation, attachment and deprotection strategies under a variety of conditions have been summarized nicely.[1]

Among hydroxyl protecting groups, benzyl ethers are highly robust and are often employed so that they can be removed at later stages in a synthetic sequence. Thus, benzyl ethers are often employed as 'long-term' protecting groups carried through multiple steps in a synthetic sequence. On the other hand, substituted benzyl ethers are deliberately less stable, can be cleaved easily, and are employed as temporary protecting groups that can be removed conveniently at earlier stages of the synthesis when more delicate functionality is present.

A number of esoterically substituted benzyl ethers have been reported in the literature including methoxy, nitro, halo, cyano, azido benzyl ethers, etc.[1,2] Among these, the *p*-methoxy benzyl (PMB) group has found frequent application in natural product synthesis, and can be removed oxidatively in a selective manner.[3] However, the sensitivity of this group to acid[4] severely restricts its synthetic utility. Recently, *p*-substituted benzyl ethers with acetoxy, SEM and halo substituents have been reported.[5] Although these groups offer some advantages, the cleavage conditions are incompatible with either base-sensitive or acid-sensitive groups or functionalities. The development of a benzyl protecting group that is stable to both acidic and basic conditions is certainly a useful addition to the existing substituted benzyl ethers.

In this direction, we envisioned a new protecting group, the trimethylsilyl xylyl ether (TIX), which can be attached to a hydroxyl group efficiently and selectively removed in the presence of other groups under mild conditions. Furthermore, as one procedural iteration involves a polymer-supported reagent during preparation of the reagent **2** for protection, it can also be beneficially applied to solution-phase parallel chemistry using solid-phase reagents during generation of parallel libraries.

Keywords: Trimethylsilyl xylyl; Protecting groups; Ethers.
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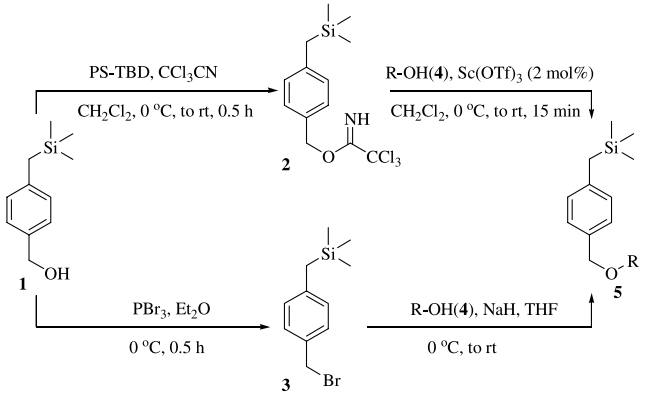
2. Results and discussion

Hence, the TIX group was easily introduced onto a hydroxyl moiety using a one-pot trichloroacetimidate protocol.[6] The known silyl alcohol **1**[7] was initially converted to its trichloroacetimidate derivative **2** using literature precedent in which Cl_3CCN, the alcohol **1**, and DBU were combined.

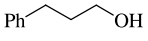
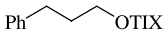
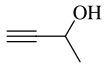
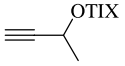
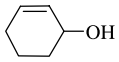
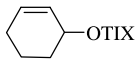
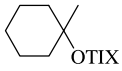
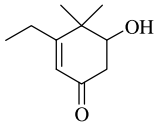
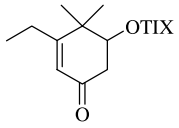
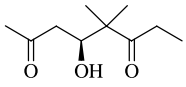
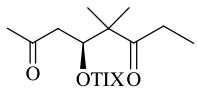
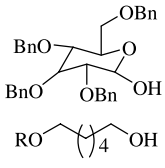
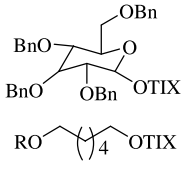


Scheme 1.

The imidate **2**, thus formed, would then be purified by chromatography or distillation. However, in our hands, this imidate was insufficiently stable to silica gel chromatography, so we opted to proceed without further purification. Thus **1**, after reaction with DBU, was treated with the alcohol followed by a slight excess (with respect to DBU) of *p*-toluenesulfonic acid (*p*TSA) or its pyridinium salt (PPTS). The yields in these cases were moderate to good, but unreacted alcohols (**1** and ROH) were present, undoubtedly due to the presence of traces of water or other contaminants associated with the combining of reaction steps.

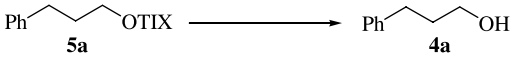
To forestall lengthy low-yielding purifications of imidate **2**, we took advantage of solid-supported chemistries now readily available. Thus, reaction of **1** with a commercially available polymer-supported base related to DBU, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), in the presence of Cl_3CCN in dichloromethane at 0 °C followed by a simple filtration furnished essentially pure imidate **2**. For catalysis of the ensuing ether formation with ROH **4**, because no DBU was present to contend with, harsh, hygroscopic sulfonic acids could be eliminated and a catalytic amount of

Table 1. TIX protection of alcohols[a]

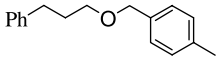
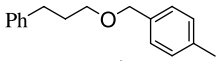
Entry	Alcohol		Product		Isolated yield (%)
1		**4a**		**5a**	81, 80[b]
2		**4b**		**5b**	82
3		**4c**		**5c**	88
4		**4d**		**5d**	76, 78[b]
5		**4e**		**5e**	91
6		**4f**		**5f**	79
7		**4g**		**5g**	80
8		**4h**		**5h**	92
9	R = Bn	**4i**	R = Bn	**5i**	82
10	*p*-xylyl	**4j**	*p*-xylyl	**5j**	91
11	PMB	**4k**	PMB	**5k**	78
12	SEM	**4l**	SEM	**5l**	80
13	Ac	**4m**	Ac	**5m**	82
14	Bz	**4n**	Bz	**5n**	95
15	TBDMS	**4o**	TBDMS	**5o**	85, 87[b]
16	TBDPS	**4p**	TBDPS	**5p**	80
17	MEM	**4q**	MEM	**5q**	80

[a] Conditions: imidate **2**, $Sc(OTf)_3$ (2 mol%), CH_2Cl_2, 0 °C to rt, 15 min.
[b] Yields under basic conditions: bromide **3**, NaH, THF, rt, 2–5 h.

Table 2. Removal of TIX group under various conditions



5a **4a**

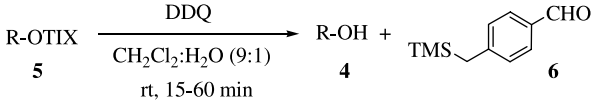
Entry	Reagent	Solvent/temp (°C)	Time (h)	Product	Isolated yield (%)
1	TFA (20 equiv)	CH_2Cl_2/0	0.25	**4a**	52
2	*n*-BU_4NF	THF/rt	0.5	 **4a′**	94
3	CsF	DMF/90[a]	2.5	 **4a′**	88
4	HF-pyridine	THF/rt	4	No reaction	—
5	$BF_3 \cdot Et_2O$	CH_2Cl_2/rt	2	No reaction	—
6	$ZnCl_2$	CH_2Cl_2/rt	2	No reaction	—
7	$MgBr_2$–Et_2O, Me_2S	CH_2Cl_2/rt	3	No reaction	—
8	CAN	THF–H_2O (9:1)/rt	0.5	**4a**	62
9	DDQ	CH_2Cl_2–H_2O (9:1)/rt	0.25	**4a**	91

[a] No reaction at rt.

a mild Lewis acid such as scandium triflate could be usefully employed instead to furnish the protected compound **5** in good to excellent yields. Since acid sensitive groups are unstable under the above reaction conditions for the protection of alcohols, we have also prepared the bromide **3** and used it to protect the hydroxyl group as the TIX ether **5** under basic conditions using NaH (Scheme 1).

To check for generality and functional group compatibility, the protection reaction was performed on a variety of alcohols, for example, 1, 2, 3°, benzylic, allylic and anomeric, bearing functionalities such as a β-keto group, an enone, olefin, acetylenic unit, or a variety of other protecting groups. To examine the issue of the chemoselectivity of these protection conditions, 1,6-hexanediol was differentially protected on one side with TBDMS, TBDPS, SEM, benzyl, PMB, ester, etc., while the remaining hydroxyl group was subjected to the protection protocol.

Table 3. Removal of TIX group using DDQ[a]



Entry	TIX ether	Alcohol	Isolated yield (%)
1	**5a**	**4a**	91
2	**5b**	**4b**	82
3	**5c**	**4c**	74
4	**5d**	**4d**	84
5	**5e**	**4e**	71
6	**5f**	**4f**	81
7	**5g**	**4g**	83
8	**5h**	**4h**	87
9	**5i**	**4i**	92
10	**5j**	**4j**	93
11	**5l**	**4l**	90
12	**5m**	**4m**	89
13	**5n**	**4n**	92
14	**5o**	**4o**	93
15	**5p**	**4p**	91
16	**5q**	**4q**	88

[a] Aldehyde **6** could be isolated in each case.

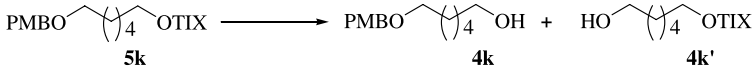
The TIX group was installed without generally affecting the other protecting groups (Table 1).

After developing the new protecting group, its removal was investigated. Accordingly, 3-phenyl-1-propanol TIX ether **5a** was initially treated with TFA leading to the formation of the deprotected alcohol **4a** in low yields. Furthermore, removal of contaminants was found to be quite difficult. Among the by-products were high-R_f aromatic compounds that presumably resulted from facile polymerization of *p*-quinone dimethide (*p*-xylylene).[8] We also used certain fluoride reagents, Lewis acids and oxidizing agents, the results of which are summarized in Table 2. Among these, DDQ provided a mild and chemoselective oxidative cleavage of the TIX moiety in the presence of other functionalities and protecting groups. Entry 7 demonstrates that the deprotection of **5g** occurred with the retention of stereochemistry to produce the **4g** in 83% yield. This deprotection method resulted in high yields, adding an advantage to the use of this protecting group compared to its removal under acidic conditions (Table 3).

Since the cleavage of the TIX group is similar to the PMB group, we were interested in studying the stability of the TIX ether over the PMB ether (Table 4). We subjected **5k** to typical PMB ether deprotection conditions and observed that in most cases the TIX group was stable. Using $ZrCl_4$ in CH_3CN, the PMB group could be selectively removed in the presence of TIX in 95% yield. Furthermore, the TIX group in PMBO–$(CH_2)_6$–OTIX **5k** could be selectively cleaved with DDQ at −10 °C leaving the PMB in place, giving PMB–$(CH_2)_6$–OH **4k** in 74% yield. The TIX group is stable under commonly used basic conditions such as LDA and *n*-BuLi (Tables 2 and 4). As expected, cleavage of both PMB and TIX occurs under catalytic hydrogenation conditions.

Mechanistically, cleavage of the TIX group by DDQ is likely to be similar to that of the PMB group; for, in all the cases, we could isolate *p*-trimethylsilylmethyl benzaldehyde **6** as a by-product. As shown in Scheme 2, the silyl group enhances the rate of benzyl ether cleavage relative to a

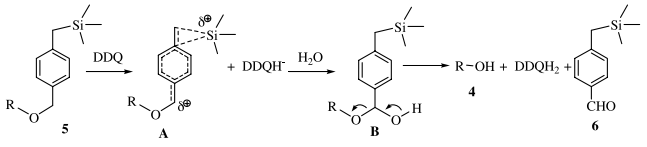
Table 4. Stability of the TIX ether over the PMB ether



Entry	Reagent	Solvent/temp (°C)	Time (h)	Product	Isolated yield (%)
1	5% TFA[4a]	CH_2Cl_2/0	0.5	**4k′**	80[a]
2	$LiBF_4$ (10 mol%)	CH_3CN/reflux	2	**4k′**	90
3	$ZrCl_4$ (20 mol%)[4b]	CH_3CN/rt	0.75	**4k′**	94
4	$CeCl_3\cdot 7H_2O$, NaI[4c]	CH_3CN/reflux	15	**4k′**	76[a]
5	AcOH[4d]	—/90	0.5	**4k′**	78
6	LDA	THF/−30 to rt	5	No reaction	—
7	BuLi	THF/0 to rt	6	No reaction	—
8	DDQ	CH_2Cl_2–H_2O (9:1)/−10	0.25	**4k**	74
9	H_2–Pd/C	EtOH/rt	2	HO 4 OH	48

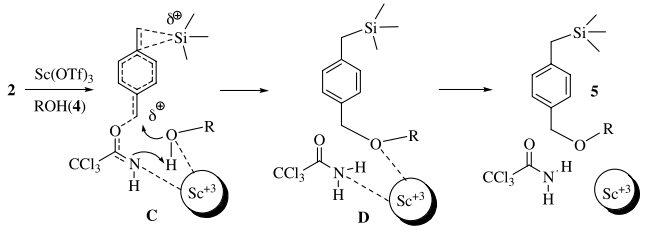
[a] 5–10% of **4k** also observed.

non-silylated version (i.e., the *p*-xylyl benzyl ether **5j** or simple benzyl ether **5i**, Table 1) by stabilization of **A** and/or by the transition state leading to **A**. The resultant intermediate **A** is then captured by water to furnish a hemiacetal **B** that undergoes reversal to aldehyde **6** and the desired deprotected alcohol **4**. The exact mechanism by which DDQ accepts the benzylic proton of **5**, leading to **A** is a matter of debate.[9]



Scheme 2.

To further assess the role of the silyl group in both protection and deprotection steps, we prepared a few representative *p*-methylbenzyl (xylyl) ethers. Surprisingly, while *p*-methylbenzyl alcohol readily underwent imidate formation, it was reluctant to undergo acid-catalyzed ether formation with comparable, or even marginally similar, efficacy compared to the TIX group. This fact implied that the protection step was promoted by the presence of the 1,6-silyl group and presumably by a mechanism reminiscent of the deprotection step outlined in Scheme 2. Thus, the fact that *p*-methylbenzyl ethers would not form in acceptable yields or at acceptable rates with either 0.02 or even 0.10 mol equiv of scandium triflate, while imidate **2** reacted rapidly and cleanly with 0.02 mol equiv (entry 10, Table 1), strongly implicated a silyl-assisted transition state for the protection step (Scheme 3).



Scheme 3.

Furthermore, DDQ was quite selective for the rapid removal of the TIX group in the presence of a *p*-methylbenzyl group as had been the case for the benzyl ether (entries 8–10 in Table 3).

3. Conclusion

We expect that the TIX group will prove to be a new 'PMB-like' versatile protecting group for hydroxyl functions in natural product synthesis and carbohydrate chemistry. It can be introduced under both acidic and basic reaction conditions and removed with DDQ, even in the presence of other commonly used protecting groups. The stability of the TIX group towards acidic as well as basic conditions is an added advantage.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere, unless otherwise stated. Thin layer chromatography (TLC) was performed on precoated silica gel G and GP Uniplates. The plates were visualized with a 254-nm UV light, iodine chamber, or charring with acid. Flash chromatography was carried out on silica gel 60 (particle size 32–63 μm, pore size 60 Å). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 100 MHz, respectively. The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane, and *J*-values are in Hz. IR spectra were recorded on FT-IR spectrometer on a germanium crystal plate as neat solids or liquids. The high-resolution mass spectra (HRMS) were recorded on a Waters/Micromass Q-TOF Micro mass spectrometer with ESI lock spray source. Dry dichloromethane was prepared by distilling it over calcium hydride. Commercially available polystyrene-bound 1,5,7-triazabicyclo[4.4.0]dec-5-ene (PS-TBD), trichloroacetonitrile and scandium (III) triflate were used directly without further purification. The trimethylsilyl alcohol **1** was prepared in two steps starting from the commercially available 4-bromobenzyl bromide using the literature procedure.[7]

4.2. General procedure for the TIX protection of the alcohols

PS-TBD (250 mg/mmol of **1**) was suspended in dry dichloromethane (5 mL/mmol of **1**) under argon at 0 °C, to which silyl alcohol **1** (1 mol equiv) was added. After stirring for 5 min at 0 °C, trichloroacetonitrile (1 mol equiv) was added. The reaction mixture was brought to room temperature and stirred for 15 min. The organic solution was separated from the polymer beads, and the clear dichloromethane solution of **2** was then cooled to 0 °C. One molar equivalent of a representative alcohol **4** was added followed by scandium triflate (0.02 mol equiv). The reaction mixture was stirred at room temperature for 15 min and diluted with dichloromethane (15 mL/mmol). The organic layer was washed with water and brine, dried (anhydrous Na_2SO_4), and concentrated. Simple purification was accomplished by flash column chromatography over silica gel using EtOAc/hexanes, providing the TIX ethers **5** in good yields (Table 1).

4.2.1. 4-[(Trimethylsilyl)methyl]benzyl 2,2,2-trichloroethanimidoate (2). Colorless oil which upon standing at room temperature to give colorless crystals, mp 32–35 °C; ^{1}H NMR ($CDCl_3$): δ 8.41 (bs, 1H), 7.32 (d, 2H, J=7.9 Hz), 7.05 (d, 2H, J=7.9 Hz), 5.32 (s, 2H), 2.13 (s, 2H), 0.04 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 162.7, 140.9, 130.9, 129.2, 128.1 (2C), 127.9 (2C), 71.0, 27.0, −1.9 (3C); IR (neat): 645, 841, 1074, 1294, 1662, 2953 cm^{-1}.

4.2.2. Trimethyl{4-[(3-phenylpropoxy)methyl]benzyl}silane (5a). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.32–7.21 (m, 7H), 7.01 (d, J=7.6 Hz, 2H), 4.47 (s, 2H), 3.51 (t, J=6 Hz, 11.6 Hz, 2H), 2.74 (t, J=7.6, 15.2 Hz, 2H), 2.10 (s, 2H), 1.98–1.94 (m, 2H), 0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 142.3, 140.1, 134.2, 128.7 (2C), 128.5 (2C), 128.3 (2C), 128.1 (2C), 126.0, 73.2, 69.6, 32.7, 31.6, 27.0, −1.66 (3C); IR (neat): 851, 1099, 1246, 2921, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{20}H_{28}OSi$, 335.1801 $(M+Na)^+$, found 335.1803.

4.2.3. Trimethyl{4-[(1-phenylethoxy)methyl]benzyl}silane (5b). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.38 (d, 2H), 7.30–7.23 (m, 3H), 7.16 (d, 2H, J=7.6 Hz), 6.97 (d, 2H, J=7.6 Hz), 4.51 (m, 1H), 4.40 (d, 1H, J=11.4 Hz), 4.25 (d, 1H, J=11.6 Hz), 2.07 (s, 2H), 1.48 (d, 3H, J=6.4 Hz), −0.006 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 144.0, 139.8, 133.9, 128.8 (2C), 128.1 (2C); 127.9 (2C); 127.5, 126.5 (2C), 77.2, 70.5, 26.9, 24.4, −1.8 (3C); IR (neat): 760, 845, 1107, 1246, 1511, 2889 cm^{-1}.

4.2.4. Trimethyl(4-{[(1-methylprop-2-yn-1-yl)oxy]methyl}benzyl)silane (5c). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.24 (d, 2H, J=7.6 Hz), 7.01 (d, 2H, J=7.6 Hz), 4.76 (d, 1H, J=11.2 Hz), 4.47 (d, 1H, J=11.2 Hz), 4.25–4.22 (m, 1H), 2.48 (s, 1H), 2.10 (s, 2H), 1.93 (d, 3H, J=6.8 Hz), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.1, 133.0, 128.1 (2C), 127.9 (2C), 83.7, 73.0, 70.4, 63.9, 26.7, 22.0, −2.0 (3C); IR (neat): 850, 1103, 1250, 1516, 2962, 3294 cm^{-1}; HRMS (ESI): calcd for $C_{15}H_{22}OSi$, 269.1333 $(M+Na)^+$, found 269.1344.

4.2.5. {4-[(Cyclohex-2-en-1-yloxy)methyl]benzyl}(trimethyl)silane (5d). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.19 (d, J=7.6 Hz, 2H), 6.95 (d, J=8 Hz, 2H), 5.86–5.78 (m, 2H), 4.51 (dd, J=11.6 Hz, 2H), 3.94 (bs, 1H), 2.05 (s, 2H), 1.96–1.72 (m, 6H), 0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.6, 131.3 (2C), 128.2 (2C), 128 (2C), 72.3, 70.3, 28.6, 27.0, 25.5, 19.5, −1.7 (3C); IR (neat): 845, 1076, 1246, 1504, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{26}OSi$, 297.1645 $(M+Na)^+$, found 297.1647.

4.2.6. Trimethyl(4-{[(1-methylcyclohexyl)oxy]methyl}benzyl)silane (5e). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.20 (d, J=7.6 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 4.35 (s, 2H), 2.05 (s, 2H), 1.83–1.78 (m, 2H), 1.68–1.62 (m, 2H), 1.46–1.25 (m, 6H), 1.22 (s, 3H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.4, 135.6, 128.2 (2C), 127.5 (2C), 74.0, 62.9, 36.8 (2C), 26.9, 26.0, 25.1, 22.5 (2C), −1.7 (3C); IR (neat): 847, 1068, 1123, 1245, 2856, 2921 cm^{-1}; HRMS (ESI): calcd for $C_{18}H_{30}OSi$, 313.1964 $(M+Na)^+$, found 313.1959.

4.2.7. 3-Ethyl-4,4-dimethyl-5-({4-[(trimethylsilyl)methyl]benzyl}oxy)cyclohex-2-en-1-one (5f). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.15 (d, J=8 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 5.83 (s, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.36 (d, J=11.2 Hz, 1H), 3.54 (dd, J=4, 8 Hz, 1H), 2.73 (dd, J=4, 16 Hz, 1H), 2.57 (dd, J=8.8, 16.8 Hz, 1H), 2.26 (distorted doublet J=6.8 Hz, 2H), 2.06 (s, 2H), 1.16 (d, J=4.8 Hz, 6H), 1.08 (t, J=7.2, 14.4 Hz, 3H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 197.9, 172.8, 140.3, 133.7, 128.2 (2C), 128.1 (2C), 123.7, 81.3, 71.6, 39.1, 29.9, 27.0, 25.0, 24.6, 21.5, 11.8, −1.70 (3C); IR (neat): 850, 1075, 1245, 1664, 2921, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{32}O_2Si$, 345.2250 $(M+H)^+$, found 345.2241.

4.2.8. (−)-4*S*-5,5-Dimethyl-4-({4-[(trimethylsilyl)methyl]benzyl}oxy)octane-2,6-dione (5g). Colorless oil; $[\alpha]_D^{25}$ = −38.76 (c=0.56, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 7.08 (d, J=8 Hz, 2H), 6.93 (d, J=8 Hz, 2H), 4.42 (dd, J=11.2, 29.6 Hz, 2H), 4.25 (dd, J=3.2, 7.2 Hz, 1H), 2.62 (dd, J=7.6, 17.2 Hz, 1H), 2.54–2.46 (m, 3H), 2.14 (s, 3H), 2.04 (s, 2H), 1.15 (s, 3H), 1.10 (s, 3H), 0.98 (t, J=6.8, 14, 7.2 Hz, 3H), −0.03 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 215.6, 207.5, 140.1, 134.1, 128.1 (2C), 127.8 (2C), 79.7, 73.8, 52.2, 45.9, 31.9, 27.0, 23.9, 21.2, 21.1, 8.07, −1.7 (3C); IR (neat): 847, 1075, 1245, 1705, 2951 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{34}O_3Si$, 385.2175 $(M+Na)^+$, found 385.2180.

4.2.9. 4-[(Trimethylsilyl)methyl]benzyl 2,3,4,6-tetra-*O*-benzylhexopyranoside (5h). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.31–7.19 (m, 20H), 7.14 (d, J=7.6 Hz, 2H), 6.98 (d, J=7.6 Hz, 2H), 5.03–4.81 (m, 4H), 4.73–4.46 (m, 6H), 4.05 (t, J=9.2, 18.4 Hz, 1H), 3.83–3.56 (m, 6H), 2.1 (s, 2H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.4, 139.0, 138.4, 138.3, 138.1, 132.6, 128.8 (2C), 128.5 (8C), 128.1 (4C), 128.05 (4C), 128.0 (4C), 127.8, 127.7, 95.3, 82.3, 79.9, 77.8, 75.8, 75.1, 73.5, 72.8, 70.4, 69.2, 68.5, 26.9, −1.7 (3C); IR (neat): 702, 845, 1078, 1245, 1458, 2892 cm^{-1}; HRMS (ESI): calcd for $C_{45}H_{52}O_6Si$, 739.3431 $(M+Na)^+$, found 739.3394.

4.2.10. [4-({[6-(Benzyloxy)hexyl]oxy}methyl)benzyl](trimethyl)silane (5i). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.36–7.25 (m, 5H), 7.20 (d, J=8 Hz, 2H), 6.98 (d, J=8 Hz, 2H), 4.52 (s, 2H), 4.45 (s, 2H), 3.50–3.45 (m, 4H), 2.08 (s, 2H),

1.66–1.62 (m, 4H), 1.42–1.39 (m, 4H), −0.05 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 138.9, 134.8, 128.6 (2C), 128.3, 128.2, 128.0 (2C), 127.9 (2C), 127.7, 73.1 (2C), 70.6, 70.5, 30.0 (2C), 27.0, 26.3 (2C), −1.7 (3C); IR (neat): 847, 1099, 1242, 2853, 2931 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{36}O_2Si$, 407.2382 $(M+Na)^+$, found 407.2371.

4.2.11. Trimethyl{4-[({6-[(4-methylbenzyl)oxy]hexyl}-oxy)methyl]benzyl}silane (5j). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.23 (d, 2H, J=7.6 Hz), 7.18 (d, 2H, J=7.6 Hz), 7.15 (d, 2H, J=7.6 Hz), 6.97 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 4.44 (s, 2H), 3.45 (dd, 4H, J=6.4 Hz), 2.34 (s, 3H), 2.07 (s, 2H), 1.60 (m, 4H), 1.38 (m, 4H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.8, 137.1, 135.7, 134.1, 129.0 (2C), 128.0 (2C), 127.8 (2C), 127.8 (2C), 72.9, 72.8, 70.3, 70.2, 29.7, 27.1, 26.8, 26.1 (2C), 21.2, −1.8 (3C); IR (neat): 694, 857, 1098, 1245, 1507, 2949 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}O_2Si$, 437.2278 $(M+K)^+$, found 437.2263.

4.2.12. {4-[({6-[(4-Methoxybenzyl)oxy]hexyl}oxy)-methyl]benzyl}(trimethyl)silane (5k). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.29 (d, 2H, J=8.4 Hz), 7.21 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 6.90 (d, 2H, J=8.4 Hz), 4.46 (s, 4H), 3.83 (s, 3H), 3.46 (dd, 4H, J=6.4, 13.2 Hz), 2.09 (s, 2H), 1.68–1.60 (m, 4H), 1.42–135 (m, 4H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 159.1, 139.8, 134.0, 130.8, 129.2 (2C), 127.9 (2C), 127.7 (2C), 113.7 (2C), 72.8, 72.5, 70.3, 70.1, 55.3, 29.7 (2C), 26.8, 26.1 (2C), −1.9 (3C); IR (neat): 845, 1099, 1246, 1511, 2856, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{25}H_{38}O_3Si$, 437.2488 $(M+Na)^+$, found 437.2470.

4.2.13. 2,2-Dimethyl-15-{4-[(trimethylsilyl)methyl]-phenyl}-5,7,14-trioxa-2-silapentadecane (5l). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, J=7.6 Hz, 2H), 6.95 (d, J=7.6 Hz, 2H), 4.65 (s, 2H), 4.42 (s, 2H), 3.60 (t, J=8.4, 16.8 Hz, 2H), 3.52 (t, J=6.8, 13.2 Hz, 2H), 3.45 (t, J=6.8, 13.2 Hz, 2H), 2.06 (s, 2H), 1.61–1.56 (m, 4H), 1.38–1.25 (m, 4H), 0.93 (t, J=8.4, 16.8 Hz, 2H), 0.01 (s, 9H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.2, 128.2 (2C), 128.0 (2C), 95.0, 73.1, 70.5, 68.0, 65.1, 29.9 (2C), 27.0, 26.3, 26.2, 18.3, −1.2 (3C), −1.7 (3C); IR (neat): 854, 1061, 1106, 12.52, 2863, 2945 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{44}O_3Si_2$, 447.2727 $(M+Na)^+$, found 447.2726.

4.2.14. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexyl acetate (5m). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.20 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 4.07 (t, 2H, J=6.4 Hz), 3.48 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 2.06 (s, 3H), 1.70–1.62 (m, 4H), 1.46–1.36 (m, 4H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 171.2, 139.8, 134.0, 128.0 (2C), 127.7 (2C); 72.9, 70.1, 64.5, 29.6, 28.6, 26.8, 25.9, 25.8, 21.0, −1.9 (3C); IR (neat): 854, 1103, 1246, 1740, 2860, 2950 cm^{-1}; HRMS (ESI): calcd for $C_{19}H_{32}O_3Si$, 359.2018 $(M+Na)^+$, found 359.2027.

4.2.15. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexyl benzoate (5n). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 8.07 (d, 2H, J=7.2 Hz), 7.58 (t, 1H, J=7.6 Hz), 7.46 (t, 2H, J=7.2 Hz), 7.20 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=7.6 Hz), 4.47 (s, 2H), 4.34 (t, 2H, J=6.4 Hz), 3.50 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 1.83–1.76 (m, 2H), 1.70–1.62 (m, 2H), 1.54–1.42 (m, 4H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 166.7, 139.8, 134.0, 132.8, 130.5, 129.6 (2C), 128.5, 128.3, 128.0 (2C), 127.8 (2C), 72.9, 70.2, 65.0, 29.7, 28.7, 26.8, 26.0 (2C), −1.9 (3C); IR (neat): 711, 854, 1107, 1275, 1720, 2856, 2946 cm^{-1}; HRMS (ESI): calcd for $C_{24}H_{34}O_3Si$, 421.2175 $(M+Na)^+$, found 421.2184.

4.2.16. *tert*-Butyl(dimethyl){[6-({4-[(trimethylsilyl)-methyl]benzyl}oxy)hexyl]oxy}silane (5o). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 2H, J=7.6 Hz), 6.96 (d, 2H, J=7.6 Hz), 4.43 (s, 2H), 3.60 (t, 2H, J=6.4 Hz), 3.45 (t, 2H, J=6.4 Hz), 2.07 (s, 2H), 1.3–1.58 (m, 2H), 1.55–1.50 (m, 2H), 1.40–1.31 (m, 4H), 0.89 (s, 9H), 0.04 (s, 6H), −0.02 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 134.3, 128.2 (2C), 128.0 (2C), 73.1, 70.5, 63.4, 33.1, 30.0, 27.0, 26.2 (3C), 25.9, 25.8, 18.6, −1.7 (3C), −5.0 (2C); IR (neat): 776, 858, 1099, 1250, 2856, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{23}H_{44}O_2Si_2$, 447.2517 $(M+Na)^+$, found 447.2513.

4.2.17. *tert*-Butyl(diphenyl){[6-({4-[(trimethylsilyl)-methyl]benzyl}oxy)hexyl]oxy}silane (5p). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.70 (m, 4H), 7.41 (m, 6H), 7.21 (d, 2H, J=7.6 Hz), 6.99 (d, 2H, J=8.4 Hz), 4.46 (s, 2H), 3.68 (t, 2H, J=6.4 Hz), 3.47 (t, 2H, J=6.4 Hz), 2.09 (s, 2H), 1.67–1.57 (m, 4H), 1.44–1.30 (m, 4H), 1.07 (s, 9H), 0.01 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 140.0, 135.8 (4C), 134.5 (4C), 134.4 (2C), 129.8 (2C), 128.3 (2C), 128.0, 127.9 (2C), 73.2, 70.6, 64.2, 32.8, 30.1, 27.2 (3C), 27.1, 26.3, 26.0, 19.5. −1.6 (3C).; IR (neat): 702, 845, 1107, 1246, 1511, 2852, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{33}H_{48}O_2Si_2$, 571.2830 $(M+K)^+$, found 571.2850.

4.2.18. Trimethyl[4-(2,9,11,14-tetraoxapentadec-1-yl)-benzyl]silane (5q). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.17 (d, 2H, J=7.6 Hz), 6.96 (d, 2H, J=7.6 Hz), 4.70 (s, 2H), 4.42 (s, 2H), 3.68 (t, 2H, J=6.4 Hz), 3.56–3.51 (m, 4H), 3.45 (t, 2H, J=6.4 Hz), 2.06 (s, 2H), 1.61–1.57 (m, 4H), 1.41–1.34 (m, 4H), −0.02 (s, 9H). ^{13}C NMR ($CDCl_3$): δ 139.8, 134.0, 128.0 (2C), 127.7 (2C), 95.5, 72.9, 71.8, 70.3, 67.9, 66.7, 59.0, 29.7, 29.6, 26.8, 26.1, 26.0, −1.9 (3C); IR (neat): 853, 1045, 1106, 1249, 1511, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{21}H_{38}O_4Si$, 421.2176 $(M+K)^+$, found 421.2159.

4.3. General procedure for the deprotection of TIX ethers

The TIX ether (1 mol equiv) was taken in dichloromethane: water (9:1 or 5 mL/mmol). To this well stirred solution was added DDQ (1 mol equiv) at room temperature (generally 15–60 min). After completion of the reaction (as monitored by TLC for disappearance of starting material), the reaction mixture was filtered, and the filtrate was washed with dichloromethane (10 mL). The combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$, brine, dried (anhydrous Na_2SO_4), filtered and concentrated. Purification of the residue was readily achieved by flash column chromatography (silica gel 60, EtOAc/hexanes) affording the alcohols in excellent yields (Table 3).

4.3.1. 1-Methyl-4-[(3-phenylpropoxy)methyl]benzene (4a′). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.36–7.22 (m, 9H), 4.54 (s, 2H), 3.54 (t, 2H, J=6.4 Hz), 2.78 (t, 2H, J=

7.2 Hz); 2.42 (s, 3H); 2.03–1.96 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 142.1, 137.3, 135.6, 129.1 (2C), 128.6 (2C), 128.4 (2C), 127.9 (2C), 125.8, 72.9, 69.4, 32.5, 31.5, 21.3; IR (neat): 702, 845, 1107, 1246, 1511, 2852, 2933 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{20}O$, 279.4384 $(M+K)^+$, found 279.4388.

4.3.2. 6-[(4-Methylbenzyl)oxy]hexan-1-ol (4j). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.22 (d, 2H, J=7.6 Hz), 7.15 (d, 2H, J=7.6 Hz), 4.45 (s, 2H), 3.62 (t, 2H, J=6.4 Hz), 3.44 (t, 2H, J=6.4 Hz), 2.34 (s, 3H), 2.07 (s, 2H), 1.63–1.54 (m, 4H), 1.43–1.37 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 137.2, 135.4, 129.1 (2C), 127.8 (2C), 72.7, 70.2, 62.6, 32.6, 29.7, 26.0, 25.6, 21.2; IR (neat): 681, 804, 1074, 1262, 2945, 3374 cm^{-1}.

4.3.3. 6-({4-[(Trimethylsilyl)methyl]benzyl}oxy)hexan-1-ol (4k′). Colorless oil; ^{1}H NMR ($CDCl_3$): δ 7.19 (d, 2H, J=7.6 Hz), 6.98 (d, 2H, J=7.6 Hz), 4.46 (s, 2H), 3.65 (t, 2H, J=6.4 Hz), 3.48 (t, 2H, J=6.4 Hz), 2.08 (s, 2H), 1.63–1.58 (m, 4H), 1.46–1.37 (m, 4H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 139.8, 133.7, 127.9 (2C), 127.7 (2C), 72.8, 70.1, 62.6, 32.5, 29.5, 25.8, 25.5, 25.4, −2.0 (3C); IR (neat): 858, 1107, 1246, 1687, 2856, 2938, 3370 cm^{-1}; HRMS (ESI): calcd for $C_{17}H_{30}O_2Si$, 333.1652 $(M+K)^+$, found 333.1659.

4.3.4. 4a to 4e,[10] 4f and 4g,[11] 4h,[10] 4i,[12] 4k,[13] 4l,[14] 4m,[15] 4n,[16] 4o and 4p,[17] 4q[18] and 6.[19] ^{1}H NMR, IR and mass spectral data of these known compounds were identical with those of authentic samples.

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Epoxidation of α,β-unsaturated acids catalyzed by tungstate (VI) or molybdate (VI) in aqueous solvents: a specific direct oxygen transfer mechanism

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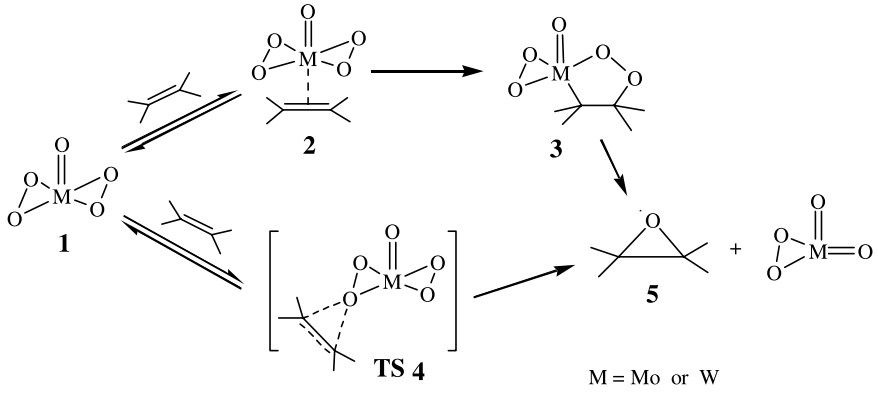
Abstract—The epoxidation mechanism of α,β-unsaturated acids catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents has been studied by means of kinetic experiments, MS, ^{31}P NMR and ^{13}C NMR. The results show Na_2WO_4 or Na_2MoO_4 and H_2O_2 can rapidly form the diperoxocomplex irreversibly in aqueous solvent. ^{31}P NMR and kinetics study reveal that –P═O in *cis*-1-propenylphosphonic acid (CPPA) can fast coordinate to the metal center (Mo or W) of the diperoxocomplex irreversibly to form a stable complex. The subsequent direct oxygen transfer from peroxo bond to double bond is a monomolecular process, thus the epoxidation is zero-order on CPPA. However, ^{13}C NMR shows the –C═O in α,β-unsaturated carboxylic acids cannot coordinate to metal center of the diperoxocomplex. Therefore, the oxygen transfer is a bimolecular process and the epoxidation is a first-order reaction on the acids. In the mechanism, the nucleophilic attack of double bond towards the peroxo bond is regarded as through a spiro-transition structure.

1. Introduction

On the mechanism of olefin epoxidation by using Mimoun type diperoxo complexes, such as $MoO(O_2)_2(OPR_3)$, R = NMe_2, two different descriptions have been suggested. One was suggested by Mimoun,[1,2] which follows a stepwise pathway (Scheme 1, top). The key steps are the coordination of double bond to the metal center and the subsequent cycloinsertion to yield a metalladioxolane. The other mechanism was suggested by Sharpless[3] in which the oxygen atom is directly transferred from metal peroxide to olefin through a transition state **TS4** (Scheme 1, below). Recently, important progress was made of the quantum chemical study on the epoxidation mechanism.[5] The calculations reveal that the epoxidation is a direct nucleophilic attack of olefin π-electrons toward σ^* orbital of the peroxo bond, thus strongly supporting the direct oxygen transfer mechanism suggested by Sharpless.

However, the results obtained from our study on epoxidation kinetics of *cis*-1-propenylphosphonic acid (CPPA) catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents



Scheme 1. The mechanisms of olefin epoxidation suggested by Mimoun and Sharpless.

Keywords: α,β-Unsaturated acid; *cis*-1-Propenylphosphonic acid; Epoxidation; Mechanism; Diperoxocomplex.
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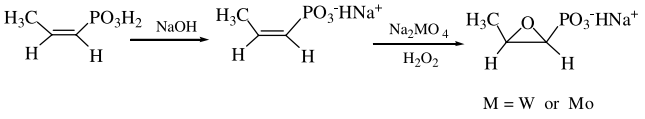
cannot be explained by either Mimoun' or Sharpless's mechanism. Moreover, the mechanism studies of olefin epoxidation were carried out in non-aqueous solvents before.[4] Therefore, the mechanism study on the epoxidation of α,β-unsaturated acids in aqueous solvents is an interesting subject.

2. Results and discussion

2.1. Epoxidation rate is zero-order on CPPA—an unusual result

The early kinetic study[6] on the epoxidation of α,β-unsaturated carboxylic acids such as maleic acid, citraconic acid, crotonic acid catalyzed by Na_2WO_4 or Na_2MoO_4 in H_2O showed that the epoxidation rate was zero-order on H_2O_2 and first-order on the acids and catalyst. As a general law, epoxidation rate is first-order on olefins either functional or nonfunctional, and no matter the epoxidation is carried out in H_2O or non-aqueous solvents. However, in our kinetic study on epoxidation of *cis*-1-propenylphosphonic acid (CPPA) catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents (Scheme 2), an unusual result was obtained. The rate of the epoxidation was zero-order on H_2O_2 and CPPA, and first-order only on the catalyst.[7] The result indicated that the reaction rate was independent on the concentrations of either H_2O_2 or CPPA and only dependent on the concentration of the catalyst. As far as we know, this is a unique example that epoxidation rate is zero-order on olefin.



Scheme 2. The epoxidation of CPPA catalyzed by Na_2WO_4 or Na_2MoO_4 in H_2O.

The aqueous solution of Na_2WO_4 or Na_2MoO_4 was alkaline (pH 7.5–8.0) and CPPA was a strong binary acid. The epoxidation of CPPA was carried out at pH 5.0–6.0. In this pH range, Na_2WO_4, Na_2MoO_4 and CPPA existed mainly in monoanion form ($HMoO_4^-$, HWO_4^-, $CH_3CH{=}CH\,PO_3^-H$) in H_2O and the epoxidation rate was the fastest.[7,8]

The kinetic study on CPPA was performed at the temperature range of 30–55 °C in pure water or ethanol–water (volume ratio 7:3) at a high concentration of hydrogen peroxide. The rate constants were shown in Table 1. The zero-order plots of epoxidation rate on CPPA were presented in Figures 1 and 2.

The zero-order on CPPA in aqueous solvents displays perfect linearity (Figs. 1 and 2). It indicated that rapid interaction of $CPPA^-$, H_2O_2 and HMO_4^- has formed irreversibly a stable intermediate. However, we need to have direct evidences to explain how they have linked up to each other and what species formed.

According to Sharpless' direct oxygen transfer mechanism, the epoxidation is a bimolecular process and thus the reaction should be first-order on CPPA. Although this mechanism has gained support of many experimental facts and been broadly accepted, it is unable to explain why the epoxidation is a zero-order reaction on CPPA. Therefore, for the epoxidation of CPPA, we need a specific mechanism to explain above kinetic facts.

Table 1. Zero-order rate constants on CPPA for the epoxidation catalyzed by Na_2WO_4 and Na_2MoO_4 in aqueous solvents at pH 5.5

Solvent	Temperature (°C)	$k\times10^4$ (mol L^{-1} min^{-1})	
		Na_2WO_4	Na_2MoO_4
H_2O	30	10.80±0.09	
	35	15.30±0.09	
	40	20.40±0.25	6.80±0.11
	50		17.00±0.21
	55		34.7±3.30
H_2O–C_2H_5OH	40	10.90±0.28	0.74±0.01
	50	20.10±0.52	2.33±0.05
	55	32.50±0.38	5.38±0.05

[CPPA]=0.17 mol L^{-1}, [Na_2WO_4]=7.77×10^{-4} mol L^{-1}, [Na_2MoO_4]=2.06×10^{-3} mol L^{-1}, [H_2O_2]=1.13 mol L^{-1}.

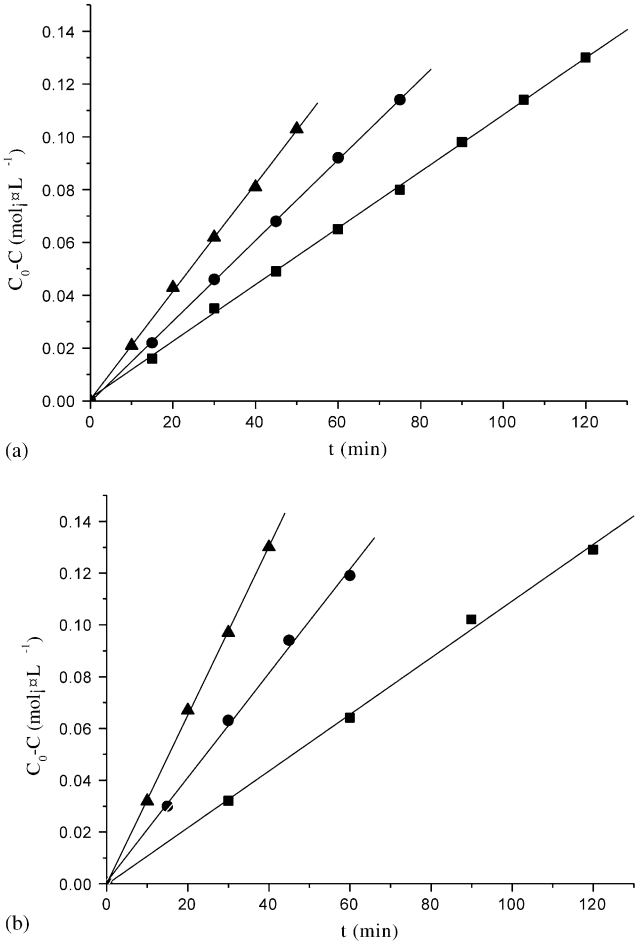


Figure 1. Zero-order plot on CPPA for the epoxidation catalyzed by Na_2WO_4 in different solvents and temperatures. (a) H_2O, (b) H_2O–C_2H_5OH (volume ratio 3:7). Molar concentration (mol L^{-1}): CPPA 0.174, hydrogen peroxide 1.13, Na_2WO_4 7.77×10^{-4}. Reaction temperature (±0.1 °C): (a) 30 °C (■), 35 °C (●), 40 °C (▲); (b) 40 °C (■), 50 °C (●), 55 °C (▲).

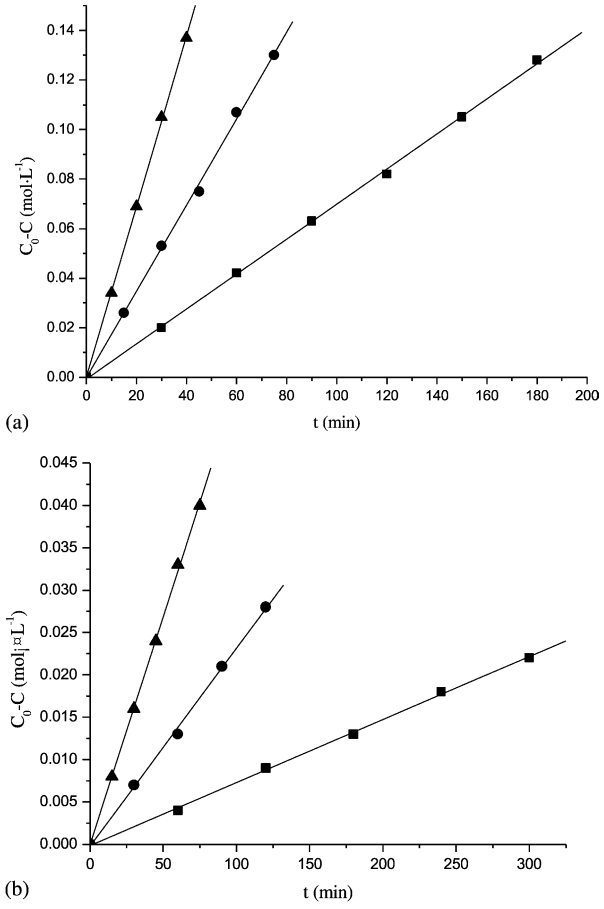


Figure 2. Zero-order plot on CPPA for the epoxidation catalyzed by Na_2MoO_4 in different solvents and temperatures. (a) H_2O, (b) H_2O–C_2H_5OH (volume ratio 3:7). Molar concentration (mol L^{-1}): CPPA 0.174, hydrogen peroxide 1.13, Na_2MoO_4 2.06×10^{-3}. Reaction temperature (±0.1 °C): (a) 40 °C (■), 50 °C (●), 55 °C (▲); (b) 40 °C (■), 50 °C (●), 55 °C (▲).

2.2. Coordination of $-PO_3^-H$, $-COO^-$ to metal center of diperoxocomplex

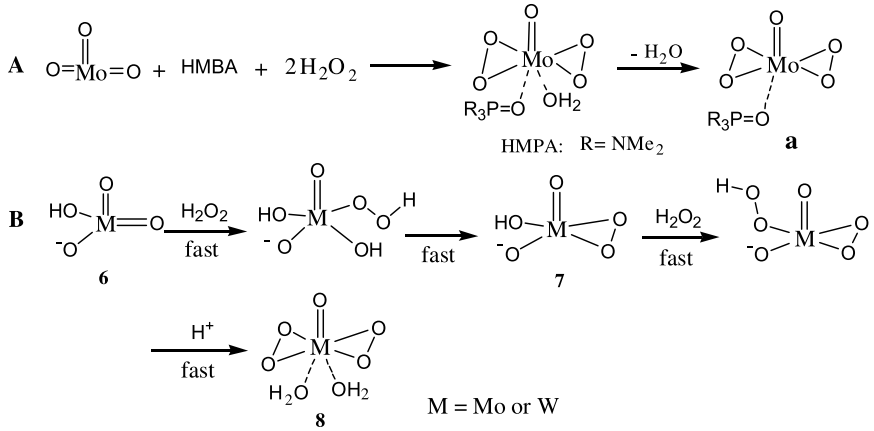
2.2.1. MS: Na_2WO_4 or Na_2MoO_4 can fast form irreversibly diperoxocomplexes with H_2O_2 in H_2O. Mimoun type diperoxocomplexes[9] were obtained from the reaction of molybdenum oxide MoO_3 and H_2O_2 in the presence of ligands such as HMPA. MoO_3 has three oxo oxygen atoms, among them two have been perhydrolyzed into the two metal-dioxygen ring to form a diperoxo-complex. Up to now, the remaining oxo oxygen has not been converted by H_2O_2 into a metal-dioxygen ring. In the diperoxocomplex there is one –P═O–Mo and one H_2O–Mo coordination. Mimoun found –P═O–Mo coordination was strong but H_2O–Mo was easily dehydrated to produce $MoO_5\cdot$HMPA (Scheme 3A, **a**), which is stable and highly soluble in organic solvents.

In our epoxidation system, Na_2WO_4 or Na_2MoO_4 mainly existed in monoanion form (HMO_4^-, M=Mo, W) at pH 5–6. HMO_4^- had only one oxo oxygen that can be perhydrolyzed into a metal-dioxygen ring. However, MS analysis indicated that HMO_4^- in H_2O was converted into a diperoxocomplex (Scheme 3, **8**) by H_2O_2. Figure 3(a) is the MS spectrum of one sample (Na_2MoO_4 +1 equiv HCl + 3 equiv H_2O_2 in H_2O, the concentration of Na_2MoO_4: $\sim10^{-4}$ mol/L). Mo has seven stable isotopes, their mass and abundance are 92 (15.8%), 94 (9.0%), 95 (15.7%), 96 (16.5%), 97 (9.5%), 98 (23.8%) and 100 (9.6%), respectively. In the MS spectrum, the peaks in mass range of 170–260 correspond to molecular ions, H^+ positive ion, sodium ion, or potassium ion of Mo diperoxocomplexes. The diperoxocomplexes have coordinated with 1–2 H_2O. They are

195—$MoO(O_2)_2$ (H_2O) (Mo=97)
209, 215, 217—$MoO(O_2)_2$ $(H_2O)_2$ H^+ (Mo=92, 98, 100)
195, 203—$MoO(O_2)_2Na^+$ (Mo=92, 100)
215, 237, 245, 251—$MoO(O_2)_2$ $(H_2O)_{0-2}$ K^+ (Mo=96, 100, 94, 96)

Figure 3(b) is the MS spectrum of (Na_2WO_4 +1 equiv HCl +3 equiv H_2O_2 in H_2O). The element W has four main stable isotopes, their mass and abundance are 182 (26.4%), 183 (14.4%), 184 (30.6%), 186 (28.4%), respectively. We found four peaks belonging to diperoxocomplexes and the peak of mass 307 is the strongest in the spectrum. They are,

301—$WO(O_2)_2$ $(H_2O)_2H^+$ (W=184)
307—$WO(O_2)_2$ $(H_2O)Na^+$ (W=186)
323—$WO(O_2)_2$ $(H_2O)_2Na^+$ (W=184)
325—$WO(O_2)_2$ $(H_2O)_2Na^+$ (W=186)



Scheme 3. A. Preparation of Mimoun-type diperoxocomplexes. B. $HMoO^-_4$ was fast perhydrolyzed by H_2O_2 into diperoxocomplex in H_2O.

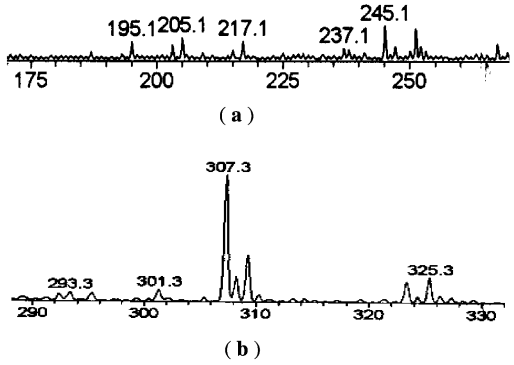
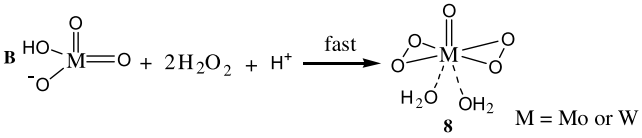


Figure 3. MS spectrum of (Na_2MO_4 +1 equiv HCl +3 equiv H_2O_2 in H_2O) M=Mo (a), W (b).

Among the above ion peaks, most ions have two H_2O as ligands, others have one or without H_2O. Obviously, two H_2O can coordinate to the metal center, but the coordination is weak and thus the coordinated H_2O easily break away or is replaced by other ligands. The detailed steps to produce the diperoxocomplexes are shown in Scheme 3B. The process is extremely fast and thus the lifetime of the intermediates is short. Therefore, for the process in Scheme 3B we have not considered the coordination of the intermediates with H_2O except **8**.

Deubel[5b] et al. have calculated Mo monoperoxo, diperoxo and triperoxo complexes by DFT at B3LYP level. The calculations indicate the formation of the diperoxo-complexes is particularly favored in the presence of OPH_3 and H_2O as ligands. In our above MS experiment, a very dilute solution of Na_2WO_4 or Na_2MoO_4 ($\sim 10^{-4}$ mol/L) was used that indicates even if H_2O exists as the sole ligand, Na_2WO_4 or Na_2MoO_4 is also particularly favorable to form diperoxocomplexes with H_2O_2. The kinetic experiments of epoxidation on α, β-unsaturated carboxylic acid or CPPA have proved the epoxidation rate is zero order on H_2O_2. The result shows Na_2WO_4 or Na_2MoO_4 easily form the diperoxocomplex with H_2O_2 and the process is rapid and irreversible (Scheme 3B). Therefore, the epoxidation of α, β-unsaturated acids in H_2O is also completed by the diperoxocomplexes of molybdate (VI) or tungstate (VI) as it did in non-aqueous solvents.

In the light of the above MS analysis, the given diperoxocomplex is a stable reactive intermediate. Though monoperoxocomplex (Scheme 3B, **7**) or cyclo-opening peroxocomplex may also appear, once formed, they would immediately transform into the diperoxocomplex. Therefore, the process can be shortened as follows:



2.2.2. –P=O in CPPA easily coordinate to metal center of diperoxocomplex. The organophosphorous compound R_3P=O (such as HMPA) was used for preparation of Mimoun-type diperoxocomplexes. This indicates –P=O moiety of the molecules has very strong coordination ability to the metal center.

On the basis of Mimoun's experiment and our MS results, two H_2O–M coordination bonds (M=Mo or W) in the diperoxocomplex (Scheme 3B, **8**) would form certainly and may expect a H_2O is easily replaced by a –P=O in CPPA. However, the epoxidation using equimolar portion of CPPA, Na_2WO_4 or Na_2MoO_4 and enough H_2O_2 in a relatively concentrated solution would be too fast to complete. Therefore, the use of ^{31}P NMR to directly monitor the coordination of –P=O in CPPA to the metal center of diperoxocomplex is not practical. Therefore, we have used CPPA's epoxide instead of CPPA. If the coordination of –P=O in the epoxide to metal center is proven, the coordination of –P=O in CPPA can also be confirmed. The ^{31}P NMR data of different systems are shown in Table 2, Figures 4 and 5. These results have confirmed the coordination of –P=O in CPPA's epoxide to the metal center of diperoxocomplex.

In preparations of the NMR samples, it requires to adjust pH with hydrochloric acid. It has to be handled very carefully because Na_2WO_4 or Na_2MoO_4 easily forms isopoly-acid or its salt under acidic condition. The isopoly-acid or its salt can complex with CPPA or its epoxide and thus result in some impurity peaks in ^{31}P NMR spectrum. However, after H_2O_2 was added into the sample, the impurity peaks usually disappeared.

For CPPA+Na_2MoO_4 or Na_2WO_4 system (Table 2, entries 2, 3), ^{31}P NMR chemical shifts approximately remain the same and the peak is still a singlet. This indicated –P=O of CPPA has not coordinated to the metal center of HMO_4^- (Scheme 4C). For epoxide+Na_2MoO_4 or Na_2WO_4 system (Table 2, entries 5, 8 and Figs. 4(a) and 5(d)), the similar

Table 2. ^{31}P NMR chemical shifts of different systems (pH 5.5–6.0)

No.	System	Mole ratio	CPPA/mol/L	δ (content)
1	CPPA		0.3	12.89
2	CPPA+Na_2MoO_4	1:1	0.3	12.30
3	CPPA+Na_2WO_4	1:1	0.3	12.35
4	Epoxide (monosodium salt)	1:1	0.3	12.94
5	Epoxide+Na_2MoO_4	1:1	0.3	11.99
6	Epoxide+Na_2MoO_4+H_2O_2	1:1:2	0.3	12.03, 14.61 (34.1%)
7	Epoxide+Na_2MoO_4+H_2O_2	1:1:2	0.6	11.39, 14.81 (47.1%)
8	Epoxide+Na_2WO_4	1:1	0.3	11.48
9	Epoxide+Na_2WO_4+H_2O_2	1:1:2	0.3	11.36, 13.68 (4.3%)
10	Epoxide+Na_2WO_4+H_2O_2	1:1:2	0.6	12.09, 13.79 (16.7%)

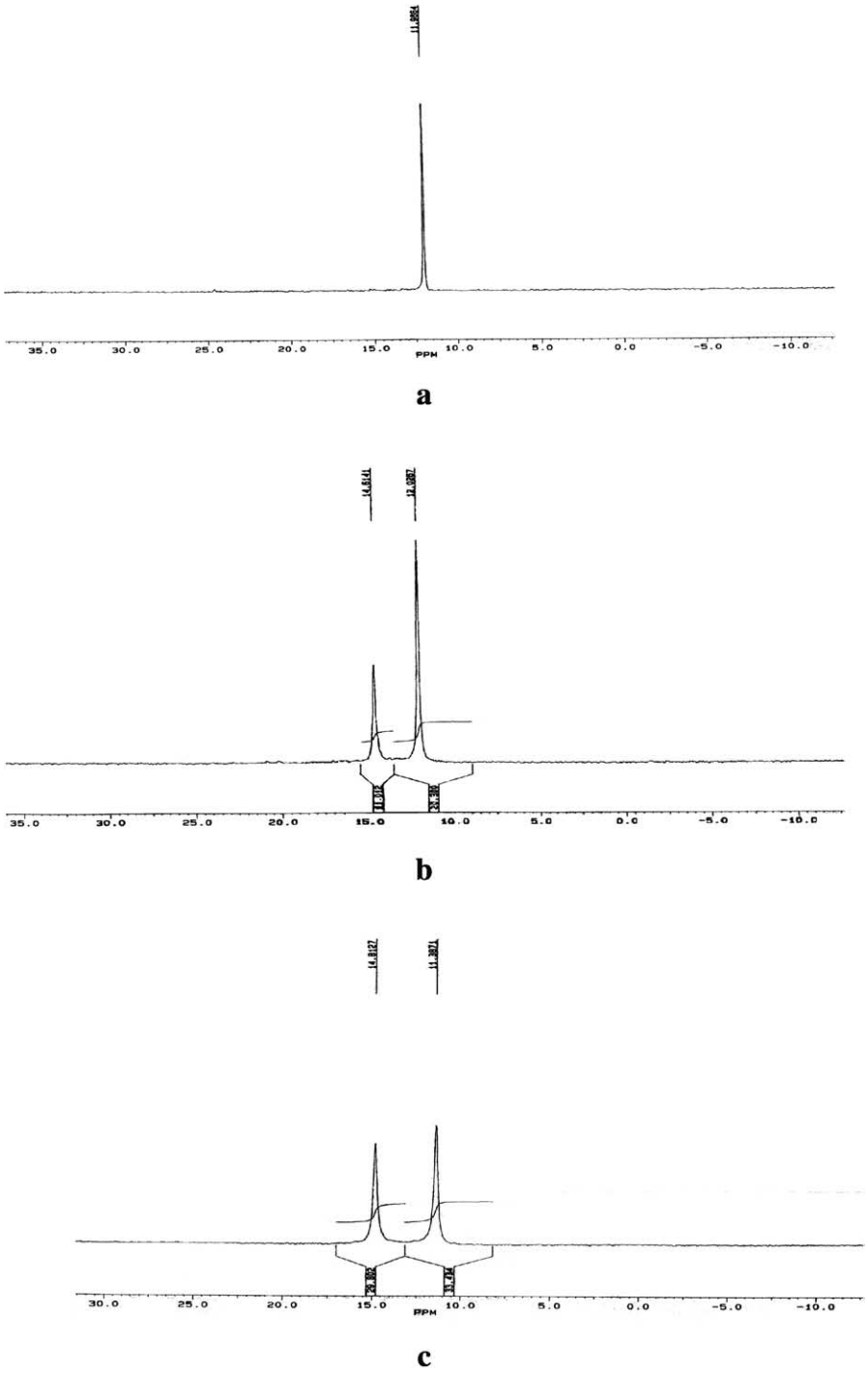


Figure 4. ^{31}P NMR of different system in H_2O (pH = 5.5–6.0). (a) Epoxide: 0.3 mol/L, Na_2MoO_4: 0.3 mol/L. (b) Epoxide: 0.3 mol/L, Na_2MoO_4: 0.3 mol/L, H_2O_2: 0.3 mol/L. (c) Epoxide: 0.6 mol/L, Na_2MoO_4: 0.6 mol/L, H_2O_2: 1.2 mol/L.

result was observed as using CPPA. Their chemical shifts are δ 11.99, 11.48 ppm, respectively. It indicated –P═O in CPPA's epoxide cannot coordinate to the metal-center of HMO_4^- either (Scheme 4D).

For epoxide:Na_2MO_4:H_2O_2 = 1:1:2 system (Table 2, entries 6, 9), a new ^{31}P NMR peak was observed. The chemical shifts are δ 14.61 and 13.68 ppm, for Mo (VI) and W (VI), respectively (Figs. 4(b) and 5(e)). The result showed –P═O had already coordinated to metal center of the diperoxo-complex. It is reasonable that the chemical shifts moved towards low field because partial electron on oxygen atom of –P═O has donated for the metal center of the diperoxocomplexes that induced a decrease of charge density on P atom. According to the peak integration, the δ 14.61 peak covers 34.1% and δ 13.68 peak covers 4.3%. Since HMO_4^- can fast combine with H_2O_2 to form diperoxocomplexes (Schemes 3 or 4, **8**), we deduce the –P═O in partial CPPA's epoxide has coordinated to the metal center of the diperoxocomplex, thus the ^{31}P NMR peak moved to lower field. However, the peak corresponding to the uncoordinated –P═O still exists and it has greater

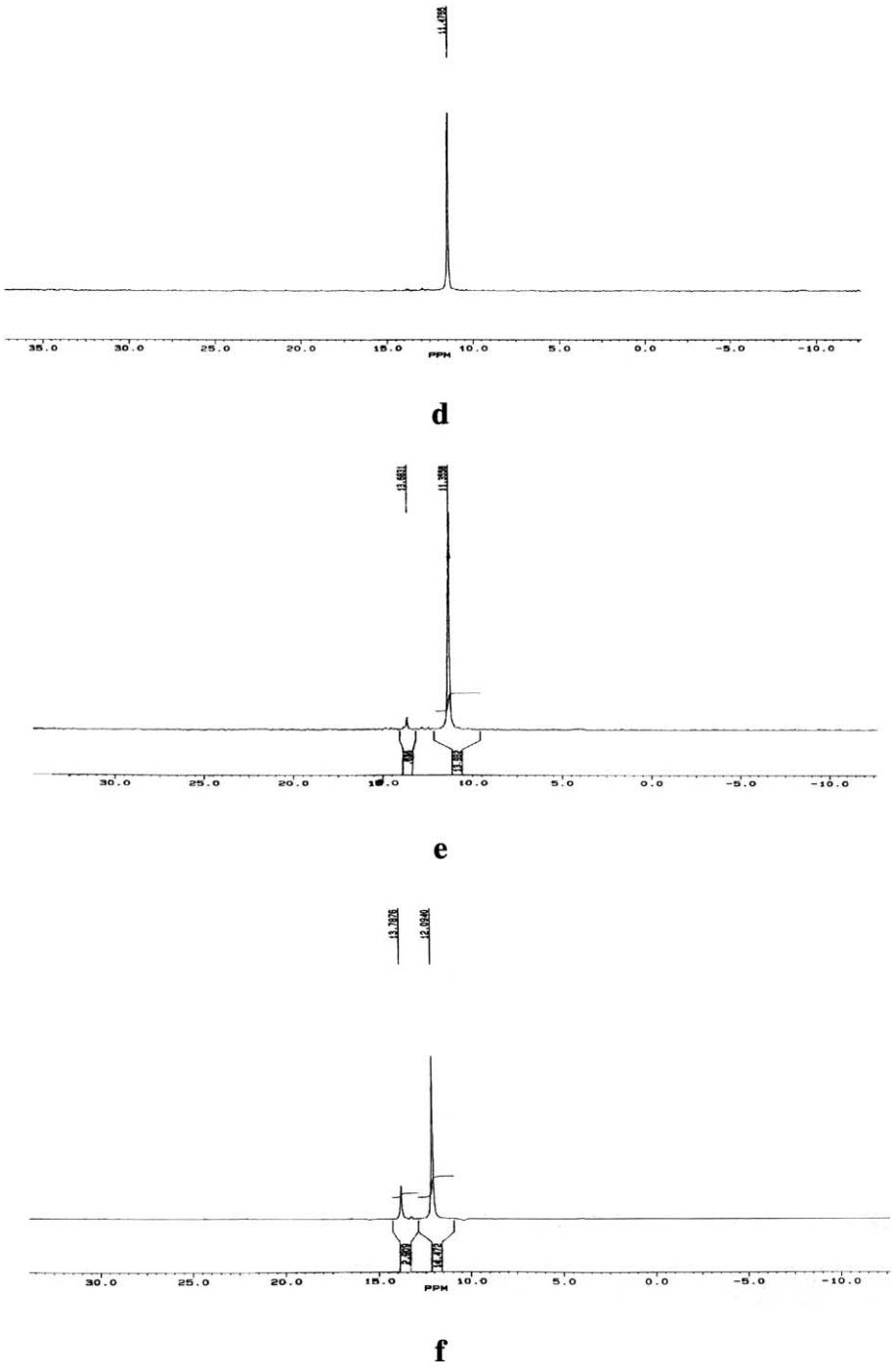
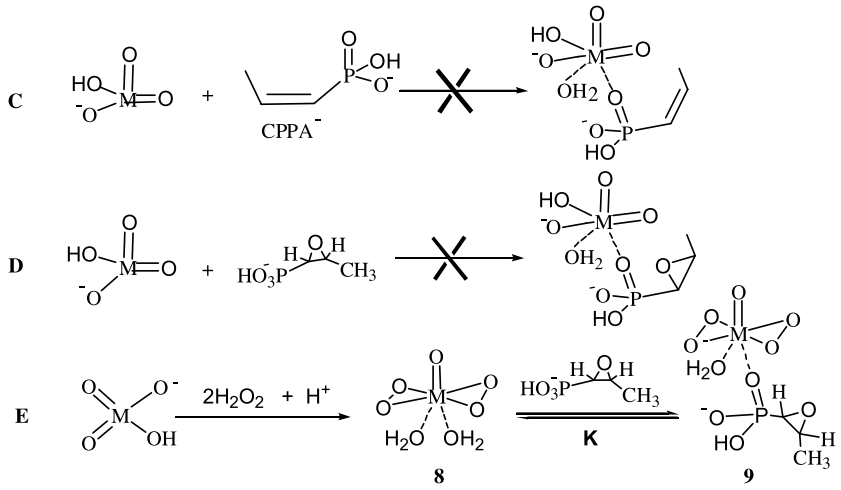


Figure 5. ^{31}P NMR of different system in H_2O (pH=5.5–6.0). (d) Epoxide: 0.3 mol/L, Na_2WO_4: 0.3 mol/L. (e) Epoxide: 0.3 mol/L, Na_2WO_4: 0.3 mol/L, H_2O_2: 0.3 mol/L. (f) Epoxide: 0.6 mol/L, Na_2WO_4: 0.6 mol/L, H_2O_2: 1.2 mol/L.

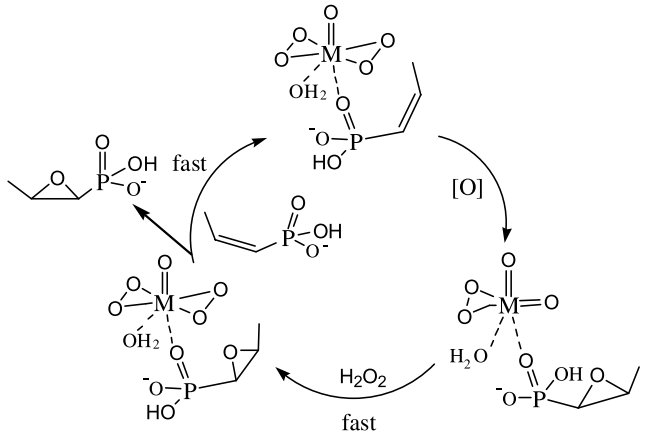
integration. This indicates the major part of CPPA's epoxide has not coordinated to the metal center of the diperoxo-complexes. It means the new complex (Scheme 4, **9**) is not stable, thus the coordination of –P═O in CPPA's epoxide with diperoxocomplex is an equilibrium (Scheme 4E, equilibrium constant K).

For Table 2, entries 7, 10, epoxide:Na_2MO_4:H_2O_2=1:1:2, which is a more concentrated system. The content of complex **9** has been remarkably increased, from 34.1 to 47.1% and 4.3 to 16.7%, for 6, 7 and 9, 10 (see Figs. 4(b,c) and 5(e,f)), respectively. It clearly shows that the higher the concentration is (equal to decreasing of solvent H_2O), the higher the content of coordination complex **9** is.

According to kinetic study of CPPA, the coordination of –P═O in CPPA to metal center is a rapid and irreversible process. This indicates the coordination ability of –P═O in CPPA is much stronger than that of –P═O in CPPA's epoxide. Therefore, once the epoxide has formed and the diperoxocomplex converted into a monoperoxocomplex, the monoperoxocomplex would rapidly combine with H_2O_2



Scheme 4. –P═O in CPPA's epoxide or CPPA can only coordinate to the metal center of the diperoxocomplex.



Scheme 5. The epoxidation of CPPA is easily completed. A reason is that the coordination ability of the epoxide to metal center of the diperoxocomplex is much weaker than that of CPPA.

to form a new diperoxocomplex, meanwhile the –P═O–M coordination of CPPA's epoxide would be replaced by that of CPPA. A new epoxidation process has begun (Scheme 5). The process indicates the epoxidation of CPPA is easily completed and the conclusion tallies with the experimental fact.

2.2.3. –C═O in $–COO^-$ cannot coordinate to metal center of diperoxocomplex. We already noticed the H_2O coordinated to metal center of the diperoxocomplex (Scheme 3B, **8**) is readily replaced by a –P═O in CPPA. Is it the same for the –C═O in α,β-unsaturated carboxylic acids? For crotonic acid, the ^{13}C NMR data of different systems shown in Table 3 and Figure 6. If any –C═O in crotonic acid has coordinated to the metal center, ^{13}C NMR chemical shifts of the carbon atom in $–COO^-$ would move considerably towards low field. In view of Table 3 and Figure 6, ^{13}C NMR chemical shifts of the carbon atom remain approximately the same and no new peak in low field was observed. It indicated the coordination ability of –C═O in α,β-unsaturated carboxylic acids is much weaker than H_2O and thus the –C═O cannot coordinate to the metal center of the diperoxocomplex. Therefore, the epoxidation of α,β-unsaturated carboxylic acids is completed by the diperoxocomplex with two H_2O ligands.

Our kinetic study on crotonic acid also shows epoxidation rate is first-order on the acid as in the reference.[6] When equimole of CPPA was added to the epoxidation system with CPPA:crotonic acid:H_2O_2 = 1:1:1, we found CPPA had been epoxidized entirely, while crotonic acid has not. It indicated that –P═O of CPPA readily coordinate to the metal center of diperoxocomplex irreversibly, but –C═O of crotonic acid did not have such ability to coordinate with the diperoxocomplex.

3. A specific direct oxygen transfer mechanism

In the light of above facts and discussion, the epoxidation mechanism of CPPA and α,β-unsaturated carboxylic acids is illustrated as follows (Scheme 6F and G).

(1) F is the mechanism on CPPA epoxidation. The characteristic of the mechanism is –P═O in CPPA can fast coordinate irreversibly to the metal center (Mo or W) of the diperoxocomplex and form a stable coordination complex (Scheme 6, **10**), which is the reactive intermediate to complete the epoxidation. Therefore, the epoxidation is a unimolecular process, and thus F is a specific direct oxygen transfer mechanism. G is the mechanism on epoxidation of

Table 3. ^{13}C NMR chemical shifts of the carboxylic group of crotonic acid (CTA) in different systems (pH ~ 6.0)

No.	System/D_2O	Mole ratio	CTA/mol/L	δ/ppm
A	CTA + NaOH	1:0.8	0.3	174.94
B	CTA + Na_2MoO_4	1:1	0.3	175.91
C	CTA + Na_2MoO_4 + H_2O_2	1:1:4	0.3	176.15
D	CTA + Na_2WO_4	1:1	0.3	176.11
E	CTA + Na_2WO_4 + H_2O_2	1:1:4	0.3	175.51

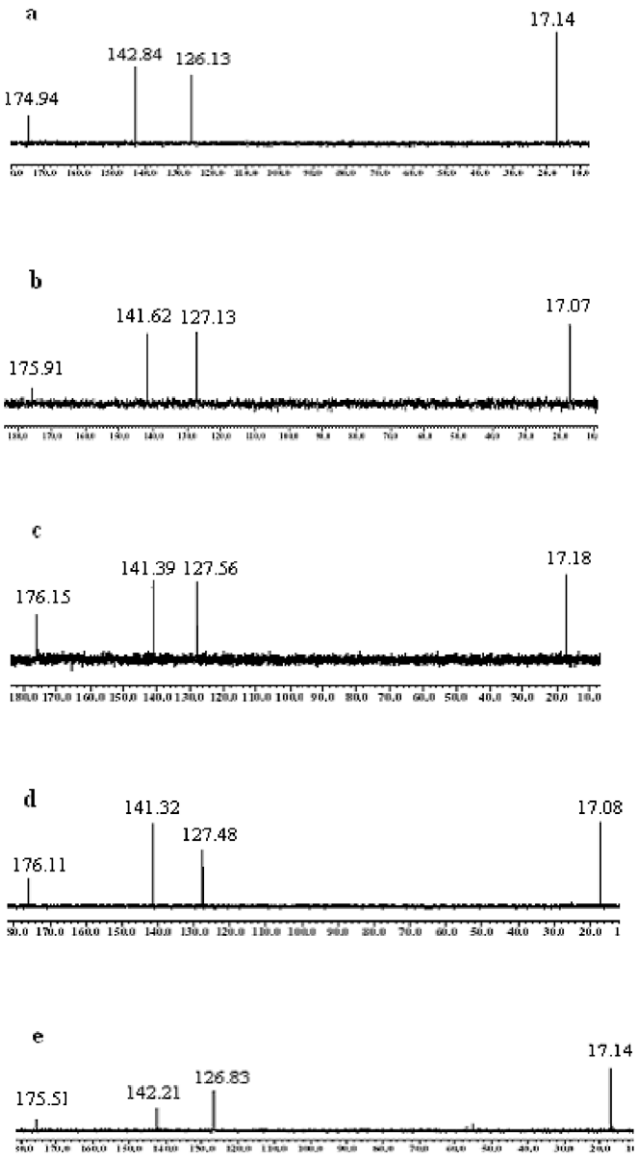


Figure 6. ^{13}C NMR of the different systems in H_2O (pH ~ 6.0) indicated –C═O in α,β-unsaturated carboxylic acids entirely cannot coordinate to metal center of diperoxocomplex. (a) Crotonic acid: 0.3 mol/L. (b) Crotonic acid: 0.3 mol/L, Na_2MoO_4: 0.3 mol/L. (c) Crotonic acid: 0.3 mol/L, Na_2MoO_4: 0.3 mol/L, H_2O_2: 1.2 mol/L. (d) Crotonic acid: 0.3 mol/L, Na_2WO_4: 0.3 mol/L. (e) Crotonic acid: 0.3 mol/L, Na_2WO_4: 0.3 mol/L, H_2O_2: 1.2 mol/L.

α,β-unsaturated carboxylic acids. Different from CPPA, –C═O in the acids cannot coordinate to the metal center of the diperoxocomplex, and thus the epoxidation is a direct oxygen transfer of the Sharpless pattern.

TS11, **TS12** is the transition structures in the direct oxygen transfer mechanisms. Take a note on structural characteristic of the transition states: the plane of the double bond and the peroxo bond are close to each other at approximately right angles and equal division of double bond. The orientation of double bond is favorable to the nucleophilic attack of its π-electron toward the σ^* orbital of the peroxo bond according to chemical bonding theory. The orientation in **TS11**, **TS12** is much like the spiro-transition state proposed by Murray[10] for dimethyldioxirane epoxidation.

(2) The epoxidation rate of CPPA is zero-order on CPPA and first-order on the catalyst from Scheme 6F.

$$\text{Epoxidation rate} = k_1\ [\mathbf{10}]$$
$$[\mathbf{10}] = [\mathbf{6}] = [\text{catalyst}]$$
$$\text{Epoxidation rate} = k_1\ [\text{catalyst}]$$

Most α,β-unsaturated acids are carboxylic acids (mono- or dicarboxylic acid). In the transition structure [**TS12**], –C═O of COO^- has not coordinated to metal center of diperoxocomplex. The epoxidation is a bimolecular process. Therefore, the epoxidation rate of α,β-unsaturated carboxylic acids is first-order on both the catalyst and the acids:

$$\text{Epoxidation rate} = k_2\ [\mathbf{8}]\ [\text{acid}]$$
$$[\mathbf{8}] = [\text{catalyst}]$$
$$\therefore \text{Epoxidation rate} = k_2\ [\text{acid}]\ [\text{catalyst}]$$

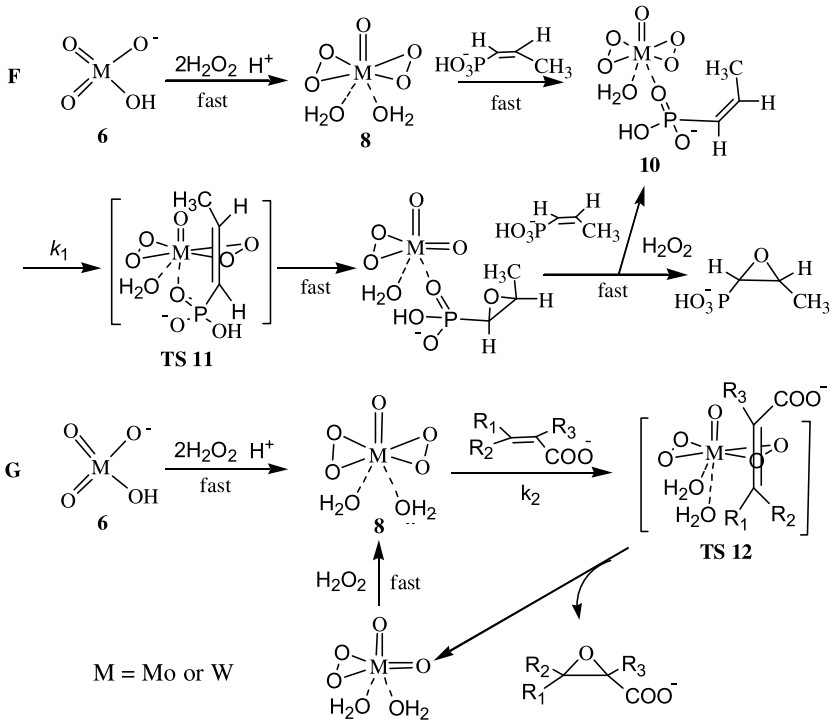
The kinetic studies[6] show the epoxidation rates of α,β-unsaturated carboxylic acids and CPPA are all zero-order on H_2O_2. Therefore, F and G in Scheme 6 both contain a rapid conversion of HMO_4^- (**6**) into the diperoxocomplex (**8**). This ensures the epoxidation rates are zero-order on H_2O_2.

(3) From Table 2, Figures 4 and 5, we found the content of the coordination complex (Scheme 4, **9**) obtained from Na_2MoO_4 is much more than that obtained from Na_2WO_4. That is 34.1, 47.1%, compared with 4.3, 16.7%. It implies that the coordination complex of Mo (VI) catalyst is more stable than that of W (VI) catalyst. However, according to a great number of experimental data,[6,7] the epoxidation rate evolved by Na_2MoO_4 as a catalyst is much slower than by Na_2WO_4 under the same reaction conditions. Our kinetic study on CPPA epoxidation in aqueous solvents shows that activation energy of CPPA epoxidation catalyzed by Na_2WO_4 was much lower than that catalyzed by Na_2MoO_4. These activation energies are obtained from Arrhenius plot of $\ln k$ vs. $1/T$ by using the data of rate constants from the kinetic studies and shown in Table 4. *Ea* was calculated by the equation as below:

$$b = -Ea/R$$

b represents the slope of the straight line in Arrhenius plot. The value of *R* is 8.314 J K^{-1} mol^{-1}.

We consider the phenomena should be attributed to the electron transfer of –P═O in CPPA to metal center of diperoxocomplex. The more the transfer amount is, the steadier the coordination complex (Scheme 6, **10**) is. In the two coordination complexes the amount of electron transfer of –P═O in CPPA into Mo (VI) is more than that into W (VI). $-PO_3^-H$ in CPPA is an electron-withdrawing group. The electron-withdrawing groups next to a double bond can reduce π-electron activity, which raise the activation barrier and slow down epoxidation rate. The electron transfer of –P═O toward metal center in coordination complex can further increase electron-withdrawing property of $-PO_3^-H$. The enhancement of electron-withdrawing property of $-PO_3^-H$ coordinated to Mo is greater than that to W. Therefore, the group coordinated to Mo (VI) would result in greater reduction on π-electron activity of the double bond than that coordinated to W (VI). This should be the main



Scheme 6. Mechanism on epoxidation of α,β-unsaturated acids catalyzed by tungstate (VI) or molybdate (VI) in aqueous solvents. Epoxidation mechanism (F) of CPPA is a specific direct oxygen transfer process. The mechanism (G) of α,β-unsaturated carboxylic acid is a direct oxygen transfer of Sharpless pattern.

Table 4. The activation energies of CPPA epoxidation catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents

Solvent	*Ea* (kJ mol^{-1})	
	Na_2WO_4	Na_2MoO_4
H_2O	43.48	89.71
H_2O–C_2H_5OH	59.11	104.67
H_2O–CH_3OH	65.43	105.92

[CPPA]=1.36 mol L^{-1}, [Na_2WO_4]=6.10×10^{-4} mol L^{-1}, [Na_2MoO_4]=1.62×10^{-3} mol L^{-1}, [H_2O_2]=8.65×10^{-2} mol L^{-1}, H_2O:C_2H_5OH=H_2O:CH_3OH=3:7 (volume ratio).

origin of the above kinetic phenomena in CPPA epoxidation.

The activation enthalpies and activation entropies of the reactions were also calculated, listed in Table 5. $\Delta H^{\neq}$ and $\Delta S^{\neq}$ were calculated using the following equations:

$$\Delta H^{\neq} = Ea - RT; \quad A = \frac{k_B T e}{h} \exp\left(\frac{\Delta S^{\neq}}{R}\right)$$

T represents absolute temperature, A represents pre-exponential factor, k_B is Boltzmann constant, and h is Planck constant. R value is 8.314 J K^{-1} mol^{-1}.

The $\Delta S^{\neq}$ values for the epoxidation of CPPA catalyzed by Na_2WO_4 were much more negative than the values for the epoxidation catalyzed by Na_2MoO_4 (Table 5). It is known that the negative value of $\Delta S^{\neq}$ indicated the structure of transition state was tighter than substrate molecules. It was obvious that the **TS11** in the epoxidation catalyzed by Na_2WO_4 was much tighter than that in the epoxidation catalyzed by Na_2MoO_4 and was tighter in pure water than that in ethanol–water. As above mentioned, the π-electron activity of double bond in the coordination complex of W (VI) as metal center is higher than that of Mo (VI). Therefore, the different tightness is due to the affinity of

Table 5. The activation enthalpies and the activation entropies of the epoxidation of CPPA catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents

Solvent	Temperature (°C)	$\Delta H^{\neq}$ (kJ mol^{-1})		$\Delta S^{\neq}$ (J mol^{-1} K^{-1})	
		Na_2WO_4	Na_2MoO_4	Na_2WO_4	Na_2MoO_4
H_2O	30	40.97	87.19	−194.30	−56.45
	35	40.92		−194.38	
	40	40.88	87.11	−194.55	−56.70
	50		87.02		−56.95
H_2O–C_2H_5OH	30	56.59		−157.47	
	40	56.51	102.07	−157.72	−27.85
	50	56.42	101.98	−157.97	−28.10
	55		101.94		−28.27
H_2O–CH_3OH	30	62.91	103.40	−137.43	−22.03
	40	62.83	103.32	−137.68	−22.28
	50	62.74	103.23	−137.935	−22.53

[CPPA]=1.36 mol L^{-1}, [Na_2WO_4]=6.10×10^{-4} mol L^{-1}, [Na_2MoO_4]=1.62×10^{-3} mol L^{-1}, [H_2O_2]=8.65×10^{-2} mol L^{-1}.

CPPA' double bond to the diperoxocomplex formed by Na_2WO_4 is much stronger than that by Na_2MoO_4. The tightness would be also reduced in ethanol–water system because ethanol has stronger affinity with moiety (CH_3-CH═CH–) of CPPA than water which weaken whole affinity between CPPA and the diperoxocomplex.

(4) Recent investigations[11] indicated that some complexes of Mo or W anions with phosphoric or phosphonic acids are very efficient catalysts for the epoxidation of alkenes, by far more efficient than the uncomplexed Mo or W anions. Having a large number of P–O–W or P–O–Mo bonds is an important structural feature of the complexes. Therefore, if the complexes were formed, ^{31}P chemical shifts must be changed greatly.[10a] However, our tracking of ^{31}P NMR spectra indicated that phosphonate ($-PO_3^-H$) of CPPA did not bond with tungstate or molybdate because no new ^{31}P peak appeared except ^{31}P peak of epoxide in the course of the epoxidation. Furthermore, the formation of P–O–W or P–O–Mo bonds needs to eliminate one molecule of H_2O; that is difficult for our epoxidation as it was carried out in H_2O. Therefore, in the light of our experimental results Na_2WO_4 or Na_2MoO_4 plays independently catalysis role in the epoxidation of CPPA in aqueous solvents.

4. Conclusion

The study explored the epoxidation mechanism of α,β-unsaturated acid catalyzed by Na_2WO_4 or Na_2MoO_4 in aqueous solvents.

(1) MS and kinetic study have proved Na_2WO_4 or Na_2MoO_4 and H_2O_2 in H_2O can rapidly form the diperoxocomplex irreversibly. Therefore, the epoxidation of α,β-unsaturated acids in H_2O were completed by the diperoxocomplexes of Mo (VI) or W (VI) as did in non-aqueous solvents.
(2) –P═O of CPPA can rapidly and irreversibly coordinate to metal center (Mo or W) of the diperoxocomplex to form a stable complex. Therefore, the epoxidation rate is zero-order on CPPA. However, α,β-unsaturated carboxylic acids are unable to form the coordination complex and thus their rate is first-order on the acids. The epoxidation rates of α,β-unsaturated acids always are zero-order on H_2O_2 and first-order on catalyst.
(3) The mechanism is able to explain the kinetic facts of the epoxidations and is consistent with the direct oxygen transfer mechanism suggested by Sharpless.

5. Experiment

Unless otherwise specified, all reagents were purchased from commercial suppliers and used without purification. The temperature was controlled by thermostat with variation of ±0.1 °C. ^{31}P, ^{13}C NMR spectra were recorded on Bruker AC 300 MHz or Bruker AC 200 MHz or JOEL JNM–ECA 600 MHz spectrometer in D_2O or H_2O with TMS or H_3PO_4 as the internal reference. The MS spectrograms were recorded on Bruker ESQUIRE-LC ion trap spectrometer.

5.1. Kinetics on CPPA

CPPA (0.50 g, 4.1 mmol) was dissolved in H_2O (15 mL) at room temperature. NaOH (0.16 g, 4.1 mmol) was added to neutralize the solution to pH 5.5 followed by addition of sodium tungstate (5 mg, 0.015 mmol, dissolved in 1 mL H_2O) or sodium molybdate (10 mg, 0.041 mmol, dissolved in 1 mL H_2O). The reaction flask loaded with the mixture was then fitted with a thermostat. After stirring for half an hour, the mixture was kept at a certain temperature. Hydrogen peroxide (2.5 mL, 30% aqueous solution, 22 mmol) was then added to the solution. The reactions were carried out at several invariable temperatures during which aliquots were taken out at intervals for the iodometric titration analysis to determine the concentration of hydrogen peroxide.

5.2. Kinetics on crotonic acid

Crotonic acid (0.50 g, 5.8 mmol) was dissolved in H_2O (20 mL) at room temperature. NaOH (0.12 g, 3.0 mmol) was added to neutralize the solution to pH 5.5 followed by addition of sodium tungstate (50 mg, 0.15 mmol). The reaction flask loaded with the mixture was then fitted with a thermostat. After stirring for half an hour, the mixture was kept at 60 °C. Hydrogen peroxide (3.0 mL, 30% aqueous solution, 26 mmol) was added to the solution. The reactions were carried out at 60 °C during which aliquots were taken out at intervals for the iodometric titration analysis to determine the concentration of hydrogen peroxide.

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Ionic liquids as a convenient recyclable medium for the generation of transient carbonyl ylides: syntheses of oxa and dioxa-bridged polycyclic systems

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Abstract—The tandem cyclization-cycloaddition reactions of α-diazo ketones in the presence of rhodium(II) acetate, rhodium(II) octanoate or copper(II) acetyl acetonate as catalyst were performed in different imidazole based ionic liquids as solvent. A successful generation of the transient five- or six-membered-ring carbonyl ylides, followed by the 1,3-dipolar cycloaddition with olefin or carbonyl functional groups in ionic liquid is described to furnish the oxa and dioxa-bridged polycyclic systems with high stereoselectivity. Significant advantages of this process are the recovery of rhodium catalyst, the re-use of ionic liquid, replacement of hazardous organic solvents and the resulting high stereoselectivity.

1. Introduction

α-Diazo ketones are important intermediates as they undergo very useful tandem cyclization-cycloaddition transformations in a highly productive manner. They continue to be a subject of considerable interest and intensive investigation in synthetic organic chemistry.[1] Intramolecular carbenoid–carbonyl group cyclization has been recognized as one of the most effective methods for generating carbonyl ylides; subsequent 1,3-dipolar cycloadditions with π-bonds to construct hetero/carbocyclic ring systems are well documented.[2] Based on this diazo carbonyl chemistry, the synthesis of many bioactive natural products such as brevicomin,[3] illudins,[4] phorbol ester derivatives,[5] zaragozic acid A[6] and various alkaloids[7] have been ingeniously approached using an olefin or a carbonyl group as a dipolarophile. As a result, there has been growing interest in the use of rhodium(II)-generated carbonyl ylides as 1,3-dipoles for the construction of many important natural/unnatural derivatives.

Many of the organic solvents particularly chlorinated hydrocarbons and benzene possess volatile, hazardous and carcinogenic properties. Consequently, methods that successfully minimize their use are the focus of much attention. In this aspect, a recent development is the use of ionic liquids as a novel green solvent media for various organic and biochemical transformations.[8] Ionic liquids, particularly those based on 1,3-dialkylimidazolium cations, have been shown to be good 'solvents' for a wide range of inorganic and organic reactions.[9] This is mainly due to their non-volatile nature, insolubility in common organic solvents and ability to dissolve catalysts. Although many types of reactions have been investigated in ionic liquids, examples of tandem reactions are absent from the literature. Furthermore, there has been no example demonstrated on the use of ionic liquids for the possible generation of the transient carbonyl ylide intermediates. As a part of our ongoing research program[10] to study the reactivity profile of carbonyl ylides, we wish to report the use of ionic liquids in the tandem cyclization-cycloaddition process using rhodium and copper metal complexes as catalyst.

2. Results and discussion

To demonstrate this process, we have synthesized a series of acyclic α-diazo ketones **1**, **4**, tetralone derived diazo ketone **3**, α-diazo ketones tethered on a cyclopropane **5** or cycloalkanone **2**, **6** ring systems (Fig. 1), which will, in principle, generate five- or six-membered-ring carbonyl ylide intermediates. Initially, we planned to study generation of the transient six-membered-ring carbonyl ylides and the reaction with olefin dipolarophiles in the ionic liquid (IL) medium. Among various imidazole derivatives

Keywords: Carbonyl ylides; Diazo ketones; 1,3-Dipolar cycloadditions; Ionic liquid; Rhodium(II) acetate dimer.
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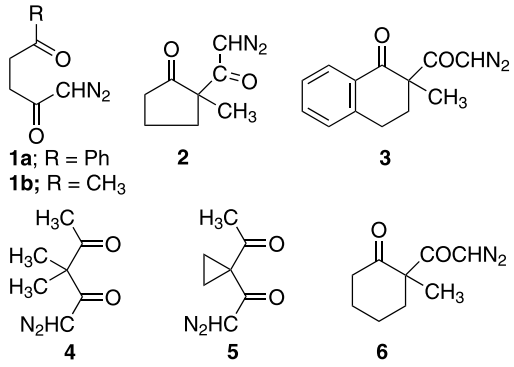
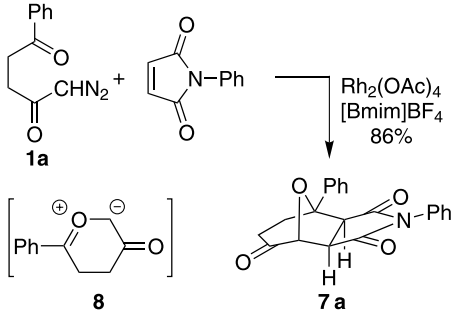


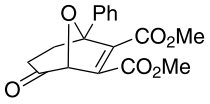
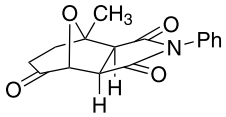
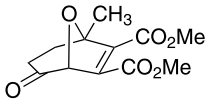
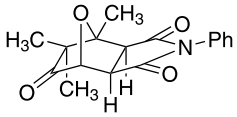
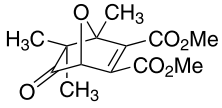
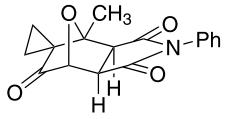
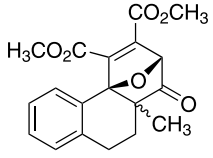
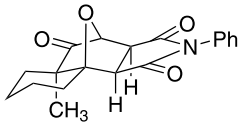
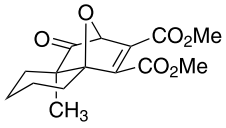
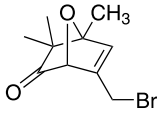
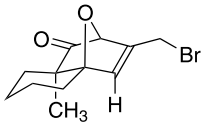
Figure 1. Synthesized α-diazo ketones.

reported as ionic liquids, we have chosen 1-*n*-butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), 1-*n*-butyl-3-butylimidazolium tetrafluoroborate ([bbim]BF_4), 1-*n*-methyl-3-methylimidazolium tetrafluoroborate ([mmim]BF_4) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6), as solvents for our present study. Initially, the reaction of α-diazo ketone **1a** and *N*-phenylmaleimide (NPM) in [bmim]BF_4 ionic liquid solution was carried out at room temperature in the presence of rhodium(II) acetate catalyst under an argon atmosphere. The reaction was stirred at room temperature for 2 h and, after washing with 50% ethyl acetate/hexane solution, furnished the crude reaction mixture, which was purified by passing through silica gel column chromatography to afford the oxa-bridged compound **7a** in 86% yield with complete diastereoselectivity (Scheme 1). Alternatively, the crude reaction mixture can also be passed through by silica column chromatography without extraction procedure to obtain the same yield. The presence of a singlet resonance at δ 4.75 in the ^{1}H NMR spectrum for the bridgehead proton implies *exo*-addition. The structure of the product **7a** confirms the successful generation of the transient six-membered-ring carbonyl ylide dipole **8** followed by the 1,3-dipolar cycloaddition with NPM in the polar ionic liquid medium. Interested by the above tandem cyclization-cycloaddition reaction in ionic liquid, we generalized this reaction. This tandem process of α-diazo ketone was repeated in the presence of dimethyl acetylenedicarboxylate (DMAD) as a dipolarophile instead of NPM to furnish the respective oxa-bridged compound (entry **b**, Table 1) in 95% yield. Similar reactions were performed with α-diazo ketone **1b** in the presence of dipolarophiles (NPM or DMAD) to furnish the corresponding oxa-bridged seven-membered-ring compounds (entries **c**, **d**, Table 1) in high yields.



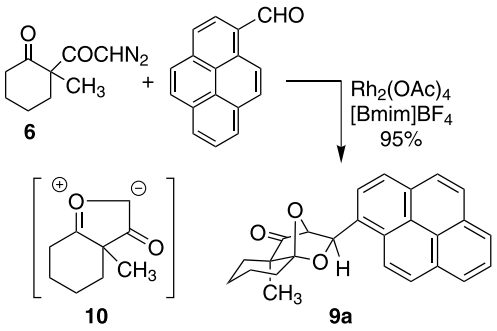
Scheme 1. Rhodium(II)-catalyzed tandem reaction of α-diazo ketone and NPM in [bmim]BF_4 ionic liquid.

Table 1. Synthesis of oxa-bridged compounds using ionic liquid

Entry	α-Diazo ketone	Oxa-bridged cycloadducts	Yield (%)[a] IL(DCM)
b	**1a**[b]		95 (93)[3]
c	**1b**[c]		90 (87)[3]
d	**1b**[b]		84 (88)[3]
e	**4**[c]		87 (81)
f	**4**[b]		92 (85)
g	**5**[c]		95 (93)[11]
h	**3**[b,d]		88 (85)
i	**6**[c]		91 (88)[10c]
j	**6**[b]		87 (76)[10c]
k	**4**[e]		72 (66)
l	**6**[e]		68 (65)[10c]

[a] Yields are unoptimized and refer to isolated pure compounds.
[b] Reaction with DMAD.
[c] Reaction with NPM.
[d] Inseparable mixture of diastereomers in the ratio of 1:3.
[e] Reaction with propargyl bromide.

Next, we elaborated our work to demonstrate the generation of the transient five-membered-ring carbonyl ylides in ionic liquid medium. To this end, we have utilized the appropriate α-diazo ketones **3**–**6** to perform the rhodium(II)-catalyzed reactions as described above. The [bmim]BF_4 ionic liquid



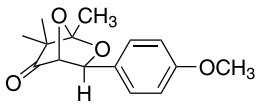
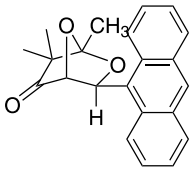
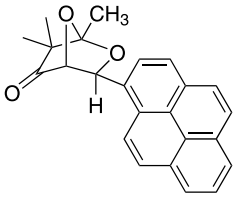
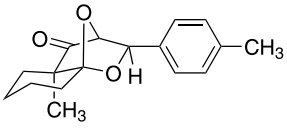
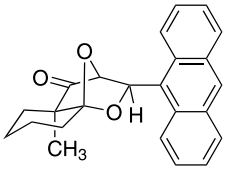
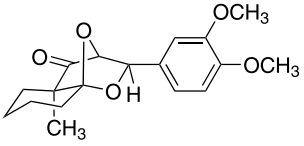
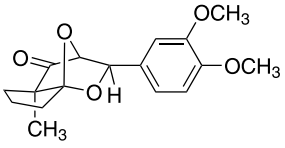
Scheme 2. Rhodium(II)-catalyzed tandem reaction of α-diazo ketone and an aldehyde in [bmim]BF_4 ionic liquid.

mediated reactions in the presence of NPM, DMAD or propargyl bromide were also afforded the oxa-bridged six-membered-ring systems (entries **e**–**l**, Table 1). All the reactions were performed at room temperature to obtain the products in high yield. Notably, these reactions provided high diasteroselectivity with NPM (entries **a**, **c**, **e**, **g**, **i**) and high regioselectivity with propargyl bromide (entries **k**, **l**). The presence of a singlet for the bridgehead proton in the ^{1}H NMR spectra confirms the regioselective addition of propargyl bromide with α-diazo ketones.

To develop this process further, we considered to carry out the tandem cyclization-cycloaddition reactions of α-diazo ketones in the presence of carbonyl group as a hetero-dipolarophile. To this end, we have performed the rhodium(II)-catalyzed reactions of α-diazo ketones with various aromatic aldehydes in ionic liquids. For example, the rhodium(II) acetate catalyzed reaction of diazo ketone **6** and pyrene-1-carboxaldehyde in [bmim]BF_4 ionic liquid at room temperature for an hour afforded the dioxa-bridged compound **9a** in 95% yield with high regio- and *exo*-selectivity (Scheme 2). The *exo*-selectivity in **9a** was confirmed based on a characteristic singlet resonance around δ 4.5 for the bridgehead proton in the ^{1}H NMR spectrum. The product **9a** confirms the successful generation of fused five-membered-ring carbonyl ylide **10** in the ionic liquid medium. We have further generalized the above reaction by synthesizing several dioxa-bridged compounds (**9b**–**h**) in high yield using [bmim]BF_4 ionic liquid (Table 2). Generally, the above ionic liquid reactions led to improvement in the yields of the products (compared with dry dichloromethane [DCM] as solvent, Tables 1 and 2) without lowering the selectivity. Further, the crude ^{1}H NMR spectrum of the above reactions indicated the formation of a single isomer. In all the above reactions, 1 mol% of rhodium(II) acetate catalyst was used, which is completely soluble in [bmim]BF_4 ionic liquid. The polar nature of the ionic liquids helps to stabilize the 1,3-dipole generated from α-diazo ketone and subsequent addition of the dipolarophile led to the improvement in the yield of the product.

To generalize the metal-catalyzed carbonyl ylide generation from diazo carbonyl compounds in ionic liquid, a representative reaction of diazo compound **4** with *p*-methoxybenzaldehyde was carried out in other ionic liquids and the results are depicted in Table 3. The ionic liquids having BF_4-counter anion in the presence of Rh(II)-catalysts afforded the product in high yield. But, we have found

Table 2. Synthesis of dioxa-bridged compounds using ionic liquid

Entry	α-Diazo ketone	Dioxa-bridged cycloadducts	Yield (%)[a] IL (DCM)
b	**4**[b]		84 (79)
c	**4**[c]		91 (85)
d	**4**[d]		97 (89)
e	**6**[e]		85 (79)[10a]
f	**6**[c]		86 (84)
g	**6**[f]		89 (81)
h	**2**[f]		85 (80)

[a] Yields are unoptimized and refer to isolated pure compounds.
[b] Reaction with *p*-methoxybenzaldehyde.
[c] Reaction with 9-anthraldehyde.
[d] Reaction with pyrene-1-carboxaldehyde.
[e] Reaction with *p*-tolualdehyde.
[f] Reaction with 3,4-dimethoxybenzaldehyde.

that the carbonyl ylide generation in [bmim]PF_6 gave poor yield. There are no considerable differences in reaction rates and yields by changing the substitution on the imidazole ring. The efficiency of the ionic liquid was strongly influenced by the nature of the anion. These results indicate that anions play an important role in this reaction. The reaction furnished the product in very good yield in the presence of rhodium(II) catalysts rather than copper(II)-catalyst.

Finally, we were interested to study the recovery and recycling of the expensive rhodium catalyst, which is extensively used in diazo carbonyl chemistry.

Table 3. Reactions with different ionic liquids and catalysts

Ionic liquids	Catalysts	Reaction conditions	Yield (%)[a]
[bmim]BF_4	Rhodium(II) acetate	1 h, rt	84
[bmim]BF_4	Rhodium(II) octanoate	1 h, rt	86
[bmim]BF_4	Copper(II) acetylacetonate	5 h, 80 °C	66
[bbim]BF_4	Rhodium(II) octanoate	2 h, rt	85
[bbim]BF_4	Rhodium(II) acetate	2 h, rt	82
[bbim]BF_4	Copper(II) acetylacetonate	5 h, 80 °C	62
[bmim]PF_6	Rhodium(II) acetate	2 h, rt	55
[bmim]PF_6	Copper(II) acetylacetonate	5 h, 80 °C	35
[mmim]BF_4	Rhodium(II) acetate	1 h, rt	88
[mmim]BF_4	Rhodium(II) octanoate	1 h, rt	90

[a] Yields are unoptimized and refer to isolated pure compound **9b**.

Representatively, the reaction of α-diazo ketone **4** and *p*-methoxybenzaldehyde was performed (entry **b**, Table 2) in [bmim]BF_4 ionic liquid. The reaction mixture was extracted with ethyl acetate/hexane solution to provide the product **9b** leaving a pale-yellowish ionic liquid, which was dried under reduced pressure. The above reaction was repeated in the recovered ionic liquid and $Rh_2(OAc)_4$ catalyst by adding the required starting materials to provide the corresponding dioxa-bridged product **9b** with the same yield. Notably, this process was repeated five times and the successive reuse of the recovered ionic liquid and catalyst in the above reaction furnished the product with a yield as high as that of the first cycle (Table 4). The insolubility of ionic liquid in common organic solvents and the very good solubility of rhodium(II) acetate catalyst in ionic liquid help to productively recycle the catalyst. In our process, the catalyst $Rh_2(OAc)_4$ could be immobilized in [bmim]BF_4 at the end of this cyclization-cycloaddition reaction.

Table 4. Studies on the reuse of $Rh_2(OAc)_4$ and [bmim]BF_4

Cycles time	Yield of **9b** (%)[a]	Ionic liquid recovered (%)
1	84	99
2	88	98
3	85	99
4	86	98
5	85	98

[a] Yields are unoptimized and refer to isolated pure compound **9b**.

3. Conclusion

In conclusion, we have demonstrated for the first time that the tandem cyclization-1,3-dipolar cycloaddition reaction of α-diazo ketones induced by rhodium(II) acetate catalyst in [bmim]BF_4 ionic liquid as a solvent at room temperature. This process was also studied in other ionic liquids with different rhodium and copper catalysts. In view of 'green chemistry', the solvent [bmim]BF_4 and the expensive catalyst $Rh_2(OAc)_4$ can be recovered conveniently and reused efficiently. Further, this process involving the generation of the transient five- as well as six-membered-ring cyclic carbonyl ylide 1,3-dipoles in industrially and environmentally benign polar ionic liquid medium furnished the stereoselective products with improvement in the yield. Significantly with all the advantages mentioned above, this process bearing the characteristic of atom economy and many bonds formation in a single synthetic step provides the novel alternative method to synthesize oxa and dioxa-bridged polycyclic systems.

4. Experimental

4.1. General

Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Bruker DPX 200 at 200 MHz using $CDCl_3$, Acetone-d_6 and DMF-d_7 in ppm (δ) related to tetramethylsilane ($\delta = 0.00$) as an internal standard and are reported as follows; chemical shift (ppm), multiplicity (s = singlet, t = triplet, quat = quartet, m = multiplet), coupling constant (Hz) and integration. Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded at 50.3 MHz in $CDCl_3$. Chemical shifts are reported in delta (δ) units, parts per million (ppm) relative to the centre of the triplet at 77.7 ppm for $CDCl_3$. Carbon types were determined from ^{13}C NMR and DEPT experiments. IR spectra were recorded on a Perkin–Elmer Spectrum GX FT-IR spectrophotometer using KBr pellets or CH_2Cl_2. Mass analyses were performed on Jeol DX-303 (with an ionizing voltage of 70 eV), Jeol M Station 700 (FD^+ method in absolute dichloromethane) mass spectrometers and reported as *m*/*z* (relative intensity). Elemental analyses were performed on a Perkin Elmer Model 2400 analyzer. Melting points were determined on a capillary melting point apparatus and are uncorrected. Thin layer chromatography was performed on silica plates and components were visualized by observation under iodine or sulfuric acid charring. 1-*n*-Butyl-3-methylimidazolium tetrafluoroborate ([bmim]BF_4), 1-*n*-butyl-3-butylimidazolium tetrafluoroborate ([bbim]BF_4), 1-*n*-methyl-3-methylimidazolium tetrafluoroborate ([mmim]BF_4) and 1-*n*-butyl-3-methylimidazolium hexafluorophosphate ([bmim]PF_6) are prepared as described in the literature,[12] purified and well-dried for 30 h under reduced pressure at 100 °C and stored under an argon atmosphere. Rhodium(II) acetate dimer, rhodium(II) octanoate dimer and copper(II) acetyl acetonate were purchased from Aldrich.

4.2. General experimental procedure for the synthesis of compounds 7 and 9

Method A for rhodium catalyzed reactions. A mixture of α-diazo ketone (1.0 mmol) and the appropriate olefin or carbonyl compound (1.1 mmol) was taken in a well-dried ionic liquid (3.0 mL) under an argon atmosphere. The reaction mixture was stirred at room temperature for 5 min duration to obtain a clear oily solution. To this ionic liquid solution, 1 mol% of rhodium(II) acetate dimer catalyst was added and stirred at room temperature for an appropriate time. The reaction was followed by ^{1}H NMR. After

completion of the reaction, the crude reaction mixture was washed with 50% ethyl acetate in hexane (5×10 mL) till the absence of any organic compound in the solvent layer. The combined extracts were concentrated in vacuo and the resulting residue subjected on a 100–200 mesh silica gel column chromatography to afford the appropriate oxa or dioxa-bridged compound. Alternatively, the crude reaction mixture was directly loaded into a short silica gel column (50:50 EtOAc–hexane) to afford the appropriate product.

Method B for copper catalyzed reactions. The procedure was followed as in method A and the reaction mixture was heated to 80 °C. The heating was continued till the absence of starting diazo ketone and purified as described above.

4.3. Typical procedure for recycling the ionic liquid and catalyst

Representatively, a mixture of α-diazo ketone **4** (0.15 g, 1.1 mmol) and *p*-methoxybenzaldehyde (0.17 g, 1.2 mmol) was taken in a well-dried [bmim]BF_4 (3 mL) liquid and stirred for 5 min. To the above reaction mixture, 1 mol% of rhodium(II) acetate dimer catalyst was added and stirred at room temperature for 1 h. After completion of reaction, the crude reaction mixture was washed with 50% ethyl acetate in hexane (5×10 mL) till the absence of any organic compound in the solvent layer to provide a pale-yellowish ionic liquid. The evaporation of combined organic solvent and column purification afforded the product **9b** (0.21 g, 84%). The recovered ionic liquid and rhodium(II) acetate catalyst was well-dried by heating to 100 °C under reduced pressure for 7 h to afford 99% yield. The same reaction was repeated with an additional amount of starting materials [α-diazo ketone **4** (0.15 g, 1.1 mmol), *p*-methoxybenzaldehyde (0.17 g, 1.2 mmol)] to furnish the product **9b** in 88% yield. We repeated this cycle up to five times and the results are delineated in Table 4.

4.4. Characterization data of new compounds

4.4.1. 1,4-Diphenyl-11-oxa-4-azatricyclo[5.3.1.$0^{2,6}$]undecane-3,5,8-trione (7a). A mixture of *N*-phenylmaleimide (0.19 g, 1.1 mmol), α-diazo ketone **1a** (0.20 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (40:60 EtOAc–hexane) to afford product **7a** (0.292 g, 86%) as a colourless solid; mp 218–220 °C (dec) (chloroform/hexane); R_f 0.35 (40:60 EtOAc–hexane). IR (KBr) ν 3063, 2978, 1736, 1711, 1496, 1383, 1185, 1055, 1031, 745, 697 cm^{-1}. ^1H NMR (200 MHz, Acetone-d_6) δ 7.59–7.51 (m, 2H, Arom-*H*), 7.42–7.30 (m, 6H, Arom-*H*), 7.10–7.06 (m, 2H, Arom-*H*), 4.75 (s, 1H, OC*H*), 4.11 (d, 1H, J=7.5 Hz), 4.03 (d, 1H, J=7.5 Hz), 3.11–2.92 (m, 2H), 2.71–2.56 (m, 1H), 2.39–2.23 (m, 1H). ^{13}C NMR (50.3 MHz, DMF-d_7) δ 203.0 (*C*=O), 174.9 (N*C*=O), 173.2 (N*C*=O), 139.1 (quat-*C*), 132.0 (quat-*C*), 128.4 (=*C*H), 128.0 (=*C*H), 127.5 (=*C*H), 127.3 (=*C*H), 126.2 (=*C*H), 124.7 (=*C*H), 86.4 (quat-*C*), 83.4 (O*C*H), 52.0 (*C*H), 50.7 (*C*H), 37.0 (CH_2), 32.0 (CH_2). MS (EI) *m*/*z* (%) 347 (M^+, 54), 242 (11), 173 (46), 158 (17), 144 (35), 128 (11), 115 (26), 105 (100), 91 (13), 77 (28). Anal. Calcd for $C_{21}H_{17}NO_4$: C, 72.61; H, 4.93; N, 4.03. Found: C, 72.50; H, 4.88; N, 3.98%.

4.4.2. 1,9,9-Trimethyl-4-phenyl-10-oxa-4-azatricyclo-[5.2.1.$0^{2,6}$]decane-3,5,8-trione (7e). A mixture of *N*-phenylmaleimide (0.19 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (20:80 EtOAc–hexane) to afford product **7e** (0.252 g, 87%) as a colourless solid; mp 185–187 °C (chloroform/hexane); R_f 0.55 (20:80 EtOAc–hexane). IR (KBr) ν 2971, 1763, 1714, 1386, 1283, 1197 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.52–7.40 (m, 3H, Arom-*H*), 7.28–7.24 (m, 2H, Arom-*H*), 4.82 (s, 1H, OC*H*), 3.32 (d, 1H, J=7.0 Hz), 3.22 (d, 1H, J=7.0 Hz), 1.58 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.09 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 214.1 (*C*=O), 175.1 (N*C*=O), 174.6 (N*C*=O), 132.3 (quat-*C*), 129.9 (=*C*H), 128.6 (=*C*H), 127.0 (=*C*H), 92.0 (quat-*C*), 82.6 (O*C*H), 51.3 (quat-*C*), 48.2 (*C*H), 47.6 (*C*H), 21.1 (CH_3), 19.7 (CH_3), 13.9 (CH_3). MS (EI) *m*/*z* (%) 299 (M^+, 100), 257 (27), 201 (14), 174 (22), 138 (17), 126 (61), 109 (82), 95 (21), 82 (30), 77 (21). Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.36; H, 5.81; N, 4.58%.

4.4.3. 1,6,6-Trimethyl-5-oxo-7-oxabicyclo[2.2.1]hept-2-ene-2,3-dicarboxylic acid dimethyl ester (7f). A mixture of dimethyl acetylenedicarboxylate (0.15 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (10:90 EtOAc–hexane) to afford product **7f** (0.24 g, 92%) as a colourless oil, R_f 0.53 (20:80 EtOAc–hexane). IR (neat) ν 2981, 2957, 1766, 1728, 1642, 1438, 1391, 1321, 1269, 1046, 738 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 4.92 (s, 1H, OC*H*), 3.86 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 1.85 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.12 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 210.8 (*C*=O), 164.2 (*C*=O), 161.8 (*C*=O), 153.1 (quat-*C*), 138.7 (quat-*C*), 94.9 (quat-*C*), 83.8 (O*C*H), 53.2 (OCH_3), 43.8 (quat-*C*), 22.8 (CH_3), 21.4 (CH_3), 13.9 (CH_3). MS (EI) *m*/*z* (%) 268 (M^+, 3), 199 (4), 167 (17), 70 (100), 42 (19). Anal. Calcd for $C_{13}H_{16}O_6$: C, 58.20; H, 6.01. Found: C, 58.03; H, 5.92%.

4.4.4. 6-Bromomethyl-3,3,4-trimethyl-7-oxabicyclo-[2.2.1]hept-5-en-2-one (7k). A mixture of propargyl bromide (0.13 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (10:90 EtOAc–hexane) to afford product **7k** (0.172 g, 72%) as a colourless liquid, R_f 0.62 (20:80 EtOAc–hexane). IR (neat) ν 2972, 2935, 1754, 1466, 1386, 1310, 1212, 1126, 1011, 857 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 6.39 (s, 1H, =C*H*), 4.61 (s, 1H, OC*H*), 4.11 (s, 2H, CH_2), 1.51 (s, 3H, CH_3), 1.13 (s, 3H, CH_3), 0.99 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, CDCl3) δ 213.4 (*C*=O), 142.4 (=*C*H), 141.8 (quat-*C*), 91.9 (quat-*C*), 85.0 (O*C*H), 44.1 (quat-*C*), 25.2 (CH_2), 24.2 (CH_3), 21.1 (CH_3), 14.7 (CH_3). MS (EI) *m*/*z* (%) 246 (M^++1, 0.5), 244

(M^+-1, 0.5), 218 (2), 216 (2), 203 (4), 201 (4), 176 (10), 174 (10), 137 (10), 95 (100), 70 (86), 41 (42). Anal. Calcd for $C_{10}H_{13}BrO_2$: C, 49.00; H, 5.35. Found: C, 49.19; H, 5.26%.

4.4.5. 6-Methyl-9-pyren-1-yl-10,11-dioxatricyclo-[6.2.1.0^{1,6}]undecan-7-one (9a). A mixture of pyrene-1-carboxaldehyde (0.25 g, 1.1 mmol), α-diazo ketone **6** (0.18 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (10:90 EtOAc–hexane) to afford product **9a** (0.36 g, 95%) as a white solid; mp 212–214 °C (chloroform/hexane); R_f 0.72 (20:80 EtOAc–hexane). IR (KBr) ν 2932, 2863, 1759, 1461, 1372, 1272, 1224, 1187, 1098, 1035, 985, 846 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.18–7.99 (m, 9H, Arom-*H*), 5.88 (s, 1H, OC*H*), 4.70 (s, 1H, OC*H*), 2.41–1.56 (m, 8H, CH_2), 1.35 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 214.2 (*C*=O), 132.0 (quat-*C*), 131.8 (quat-*C*), 131.2 (quat-*C*), 129.1 (=*C*H), 128.2 (=*C*H), 127.4 (quat-*C*), 126.7 (=*C*H), 126.3 (=*C*H), 126.1 (=*C*H), 125.4 (=*C*H), 124.7 (=*C*H), 121.9 (=*C*H), 114.4 (quat-*C*), 86.8 (O*C*H), 75.5 (O*C*H), 53.0 (quat-*C*), 31.6 (*C*H_2), 27.5 (*C*H_2), 23.9 (*C*H_2), 20.9 (*C*H_2), 16.5 (*C*H_3). MS (FD$^+$) *m*/*z* 382 (M^+). Anal. Calcd for $C_{26}H_{22}O_3$: C, 81.65; H, 5.80. Found: C, 81.51; H, 5.89%.

4.4.6. 3-(4-Methoxyphenyl)-1,6,6-trimethyl-2,7-dioxabicyclo[2.2.1]heptan-5-one (9b). A mixture of *p*-methoxybenzaldehyde (0.14 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (15:85 EtOAc–hexane) to afford product **9b** (0.22 g, 84%) as a white solid; mp 75–77 °C (chloroform/hexane); R_f 0.45 (25:75 EtOAc–hexane). IR (KBr) ν 2998, 2979, 1767, 1751, 1611, 1514, 1392, 1297, 1256, 1030, 975 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.28 (d, 2H, Arom-*H*, J=8.0 Hz), 6.88 (d, 2H, Arom-*H*, J=8.0 Hz), 4.75 (s, 1H, OC*H*), 4.42 (s, 1H, OC*H*), 3.79 (s, 3H, OCH_3), 1.70 (s, 3H, CH_3), 1.16 (s, 3H, CH_3), 1.11 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 214.2 (*C*=O), 160.3 (quat-*C*), 131.7 (quat-*C*), 128.2 (=*C*H), 114.7 (quat-*C*), 114.5 (=*C*H), 86.6 (O*C*H), 77.6 (O*C*H), 55.8 (O*C*H_3), 53.0 (quat-*C*), 21.2 (*C*H_3), 19.5 (*C*H_3), 15.2 (*C*H_3). MS (EI) *m*/*z* (%) 262 (M^+, 10), 150 (41), 137 (54), 121 (19), 97 (100), 77 (10), 69 (22), 41 (29). Anal. Calcd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.41; H, 6.86%.

4.4.7. 3-Anthracen-9-yl-1,6,6-trimethyl-2,7-dioxabicyclo[2.2.1]heptan-5-one (9c). A mixture of 9-anthraldehyde (0.22 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (10:90 EtOAc–hexane) to afford product **9c** (0.29 g, 91%) as a pale yellow viscous oil, R_f 0.72 (20:80 EtOAc–hexane). IR (neat) ν 3053, 2976, 2938, 1766, 1466, 1446, 1396, 1266, 1135, 1105, 1001, 888 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.56 (d, 2H, Arom-*H*), 8.17 (s, 1H, Arom-*H*), 7.78 (d, 2H, Arom-*H*), 7.42–7.30 (m, 4H, Arom-*H*), 6.09 (s, 1H, OC*H*), 4.69 (s, 1H, OC*H*), 1.82 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.09 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 213.4 (*C*=O), 131.9 (quat-*C*), 130.0 (quat-*C*), 129.8 (=*C*H), 129.5 (=*C*H), 127.7 (quat-*C*), 126.5 (=*C*H), 125.2 (=*C*H), 124.7 (=*C*H), 115.8 (quat-*C*), 87.1 (O*C*H), 77.8 (O*C*H), 52.8 (quat-*C*), 21.1 (*C*H_3), 20.0 (*C*H_3), 15.0 (*C*H_3). MS (EI) *m*/*z* (%) 332 (M^+, 27), 219 (25), 207 (54), 178 (14), 97 (100), 84 (20), 69 (23), 41 (35). Anal. Calcd for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.31; H, 6.14%.

4.4.8. 1,6,6-Trimethyl-3-pyren-1-yl-2,7-dioxabicyclo-[2.2.1]heptan-5-one (9d). A mixture of pyrene-1-carboxaldehyde (0.25 g, 1.1 mmol), α-diazo ketone **4** (0.15 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (10:90 EtOAc–hexane) to afford product **9d** (0.34 g, 97%) as a pale yellow solid; mp 190–192 °C (EtOAc/hexane); R_f 0.70 (20:80 EtOAc–hexane). IR (KBr) ν 3034, 2973, 2944, 1759, 1470, 1397, 1270, 1134, 1101, 995, 849 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.14–7.95 (m, 9H, Arom-*H*), 5.81 (s, 1H, OC*H*), 4.64 (s, 1H, OC*H*), 1.84 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 214.6 (*C*=O), 131.9 (quat-*C*), 131.7 (quat-*C*), 131.1 (quat-*C*), 129.0 (=*CH*), 128.1 (=*C*H), 127.3 (quat-*C*), 126.6 (=*C*H), 126.2 (=*C*H), 126.0 (=*C*H), 125.3 (=*C*H), 124.6 (=*C*H), 121.8 (=*C*H), 115.4 (quat-*C*), 86.4 (O*C*H), 75.6 (O*C*H), 53.6 (quat-*C*), 21.3 (*C*H_3), 19.7 (*C*H_3), 15.5 (*C*H_3). MS (EI) *m*/*z* (%) 356 (M^+, 65), 270 (8), 244 (21), 231 (100), 215 (29), 201 (18), 126 (8), 97 (92), 69 (18). Anal. Calcd for $C_{24}H_{20}O_3$: C, 80.88; H, 5.66. Found: C, 80.67; H, 5.72%.

4.4.9. 9-Anthracen-9-yl-6-methyl-10,11-dioxatricyclo-[6.2.1.0^{1,6}]undecan-7-one (9f). A mixture of 9-anthraldehyde (0.22 g, 1.1 mmol), α-diazo ketone **6** (0.18 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (20:80 EtOAc–hexane) to afford product **9f** (0.31 g, 86%) as a pale yellow viscous oil, R_f 0.45 (20:80 EtOAc–hexane). IR (neat) ν 3055, 2943, 2867, 1765, 1450, 1377, 1267, 1039, 983, 737 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.61 (d, 2H, Arom-*H*, J=8.8 Hz), 8.31 (s, 1H, Arom-*H*), 7.90 (d, 2H, Arom-*H*, J=8.1 Hz), 7.51–7.35 (m, 4H, Arom-*H*), 6.17 (s, 1H, OC*H*), 4.76 (s, 1H, OC*H*), 2.60–1.57 (m, 8H, CH_2), 1.32 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 213.2 (*C*=O), 132.0 (quat-*C*), 130.1 (quat-*C*), 129.8 (=CH), 129.6 (=*C*H), 127.8 (quat-*C*), 126.7 (=*C*H), 125.3 (=*C*H), 124.8 (=*C*H), 114.9 (quat-*C*), 87.6 (O*C*H), 77.9 (O*C*H), 52.1 (quat-*C*), 31.5 (*C*H_2), 27.2 (*C*H_2), 23.8 (*C*H_2), 20.6 (*C*H_2), 16.8 (*C*H_3). MS (FD$^+$) *m*/*z* 358 (M^+). Anal. Calcd for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.55; H, 6.06%.

4.4.10. 9-(3,4-Dimethoxyphenyl)-6-methyl-10,11-dioxatricyclo[6.2.1.0^{1,6}]undecan-7-one (9g). A mixture of 3,4-dimethoxybenzaldehyde (0.18 g, 1.1 mmol), α-diazo ketone **6** (0.18 g, 1.0 mmol) and 1 mol% of rhodium(II) acetate dimer (4.3 mg) in 1-*n*-butyl-3-methylimidazolium tetrafluoroborate (3.0 mL) was allowed to react according to method A followed by chromatographic purification (20:80

EtOAc–hexane) to afford product **9g** (0.284 g, 89%) as a white solid; mp 112–114 °C (chloroform/hexane); R_f 0.51 (20:80 EtOAc–hexane). IR (KBr) ν 2937, 2853, 1767, 1518, 1464, 1327, 1255, 1241, 1135, 1032, 1005 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 6.91–6.81 (m, 3H, Arom-*H*), 4.76 (s, 1H, OC*H*), 4.49 (s, 1H, OC*H*), 3.89 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 2.24–1.45 (m, 8H, CH_2), 1.20 (s, 3H, CH_3). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 213.7 (*C*=O), 149.6 (quat-*C*), 132.0 (quat-*C*), 119.3 (=*C*H), 113.5 (quat-*C*), 111.6 (=*C*H), 110.0 (=*C*H), 96.3 (quat-*C*), 86.8 (O*C*H), 77.5 (O*C*H), 56.4 (OCH_3), 56.3 (OCH_3), 52.4 (quat-*C*), 31.4 (CH_2), 27.3 (CH_2), 23.6 (CH_2), 20.6 (CH_2), 16.2 (CH_3). MS (FD^+) *m*/*z* 318 (M^+). Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 67.72; H, 6.89%.

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Comparative study of azobenzene and stilbene bridged crown ether *p-tert*-butylcalix[4]arene

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Abstract—Photo-switchable calixarenes consisting of a stilbene or azobenzene bridge, spanning the narrow rim as a switching unit, were synthesized through reductive coupling of *o*-, *m*- and *p*-bis-benzaldehyde and bis-nitrobenzene-substituted calix[4]arenes. Both *cis*- and *trans*-stilbenes were produced from the reductive coupling of the *o*- and *m*-bis-benzaldehyde with the *cis* isomer being predominant for both regioisomers, whilst the coupling of *p*-bis-benzaldehyde gave only *cis* product. On the other hand, the only isolable product obtained from the reductive coupling of bis-*o*- and bis-*m*-nitrobenzene was the corresponding *trans*-azobenzene and the coupling product from bis-*p*-nitrobenzene was not stable. Each of the synthesized compounds showed a photostationary state in their *cis–trans* isomerization. The complexation of alkali metal ions was observed for only the *o*-azobenzene derivative suggesting that the lone pair of N-atom in the azo bridge participates in this process.

1. Introduction

On a cell membrane, there are plenty of specific receptors that control the diffusion of molecules or ions in and out of the cell; these include the potassium channel,[1] maltoporin[2] and sucroporin,[3] which control the diffusion of potassium ion, maltose and sucrose respectively. To specifically complex each particular molecule or ion, the shape and size of the receptor must exclusively fit with the preferred guest. An extraordinary natural molecule that is always chosen as an example of a receptor because of its extremely high binding specificity, is valinomycin, which can specifically complex potassium ions.[4,5] This cyclic molecule is composed of numerous oxygen donor atoms forming a nice pocket that fits perfectly around a potassium ion guest.

Aspiring to mimic or at least understand such natural processes, chemists have tried to design and synthesize novel molecules having particularly desired functions. The crown ether family is an appealing class of structures, which has been developed to mimic valinomycin by entrapment of a desired cation using the electron-rich pocket of donor atoms.[6] Since their discovery crown ether based ion receptors have been exploited extensively. Synthetic cation channels containing crown ether rings, called hydraphiles, have been reported recently.[7] These hydraphile channels can kill *Escherichia coli* bacteria effectively via incorporation into the surface membrane, thus disturbing sodium ion transport rate across the bacteria cell membrane.

Beside the donor atoms themselves, the pre-organized structure of the binding pocket is also a vital factor of binding properties. Calix[4]arene has become one of the most interesting platforms on which to construct a selective receptor molecule because of its four pre-organized conformations; cone, partial-cone, 1,2 alternating-cone and 1,3 alternating-cone.[8] The very first application of this well-ordered molecule as a cation receptor was calix[4]-arene crown ether, which can be used to trap a cesium ion as a result of its optimal fit.[9] Many receptors developed nowadays are calixarene-based but there is a crucial drawback of such a perfect fit host-guest pairs. The stronger the binding, the more difficult it becomes to regenerate the receptor after use. A proper attachment of a molecular switching unit to the receptor molecule should overcome this problem. There are many switching systems available, but among them, the photo-switching mode is one of the

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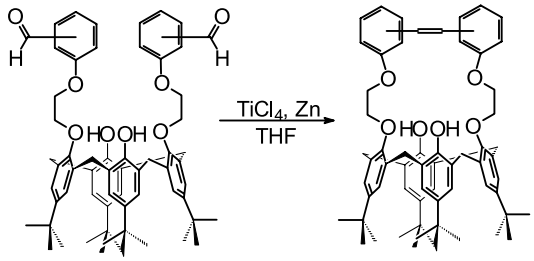
most easy-to-operate systems.[10] Azobenzene and stilbene are widely used because of their facile *cis–trans* photoisomerization.[11] Additionally, another appealing advantage potentially gained from switchable receptors is that amphiphilic-binding may be achieved.[12,13] During isomerization the binding cavity is altered and the binding property is then switched. This may be from binding to unbinding or from binding of one ion to another as a result of the change in the size and shape of the binding pocket before and after isomerization.

We report herein the synthesis of two series of photoswitchable calix[4]arene derivatives. One series incorporates a stilbene and the other an azobenzene switching unit as a bridge across the narrow rim of the calixarene platform. Photoisomerization and complexation properties of the synthesized compounds are also compared.

2. Results and discussion

2.1. Synthesis

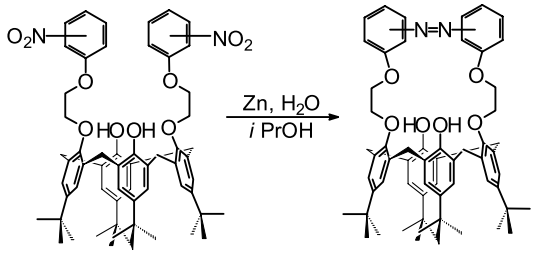
Three positional isomers, *o*-, *m*- and *p*-stilbene crown ether *p-tert*-butylcalix[4]arenes (1) were synthesized from the corresponding bis-benzaldehydes by the McMurry coupling (Scheme 1).[14,15] The bis-benzaldehydes were prepared from the corresponding (2-bromoethoxy)benzaldehydes by nucleophilic substitution of *p-tert*-butylcalix[4]arene with the corresponding (2-bromoethoxy)benzaldehyde.



1

Scheme 1. Synthesis of stilbene crown ether calixarenes.

Analogously, all of the isomers of the azobenzene crown ether calixarenes (2) were synthesized by reductive coupling of the corresponding bis-nitrobenzenes (Scheme 2), these latter having been prepared by nucleophilic substitution of the corresponding (2-bromoethoxy)-nitrobenzene analogues.[12]



2

Scheme 2. Synthesis of azobenzene crown ether calixarenes.

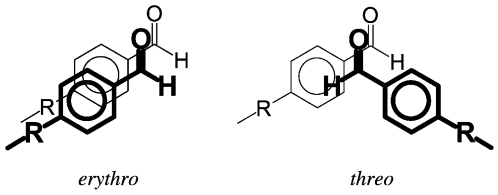
The *m*-stilbene derivatives were prepared under modified McMurry conditions to give both *cis*- and *trans*-stilbenes in 28% total yield (Table 1). This reaction also gave 20% of the corresponding pinacol byproduct. The coupling reaction of the *o*- and *p*-bisbenzaldehydes gave higher yields of the stilbenes *o*-**1** and *p*-**1** (67 and 51% respectively) without any observable pinacol product. Both *cis*- and *trans*-stilbenes were obtained from the coupling reactions involving the *o*- and *m*-bis-benzaldehydes but that for the *p*-isomer gave only *cis*-stilbene. It is important to note here that McMurry coupling proceeded successfully despite the presence of phenolic O H groups in the starting materials.

Table 1. Products from the synthesis of stilbene and azobenzene crown ether calixarenes

Products	% Yield	
	cis	*trans*
o-**1**	57	10
m-**1**	20	8
p-**1**	51	0
o-**2**	0	8
m-**2**	0	59[a]
p-**2**	0	0

[a] via high-pressure method.

The predominant preference for formation of *cis* over *trans* products in the McMurry coupling suggests that the preorganized structure of the starting bis-benzaldehyde *p-tert*-butylcalix[4]arene may play an important role in controlling the geometry of the products. The short ethylene glycol linkages attached to the small and rigid lower rim of the *p-tert*-butylcalix[4]arene are unlikely to allow formation of the *threo* orientation of the two benzaldehyde moieties (Fig. 1) resulting in no evidence for formation of the *trans*-product.



erythro *threo*

Figure 1. The proposed orientations, *erythro* and *threo*, of the two benzaldehyde groups that would lead to the formation of *cis* and *trans* products.

In the synthesis of the *o*-azobenzene crown ether calixarene at ambient pressure, only *trans* isomer was isolated in 8% yield. The *cis* isomer could not be obtained in a pure form because of its rapid thermal isomerization. In the case of the *m*-isomer a higher yield of the azobenzene product was observed compared to that obtained for the *o*-isomer because the high-pressure method was used (Table 1). The *p*-isomer however seemed to be unstable as the color of the solution at the end of the reaction changed rapidly from bright orange to dark brown upon exposure to air and moisture and none of the desired product could be isolated.

2.2. Characterization of products

Since all of the *cis*- and *trans*-stilbene derivatives possess a C_2 symmetry axis, the coupling between two vinylic protons

in ^{1}H NMR, which would normally be used for distinguishing between *cis* and *trans* isomers, does not exist. The assignment of *cis* and *trans* geometries was thus initially based on the chemical shift of vinylic protons and the UV–Vis absorption spectra using the parent *cis* and *trans* unsubstituted stilbenes as references. According to the chemical shifts observed for unsubstituted stilbenes, the *cis* geometry was assigned to the isomer possessing the vinylic protons with lower chemical shift values (Table 2). This assignment is consistent with the data from UV–Vis spectra that showed shorter λ_{max} and lower extinction coefficients for all *cis* isomers.

Table 2. ^{1}H NMR (in $CDCl_3$) and electronic absorption (in CH_2Cl_2) data of the synthesized stilbene-calix derivatives in comparison with stilbene

Compound	δ for vinylic proton (ppm)	λ_{max} (nm)	ε (cm^{-1} M^{-1})
cis-o-**1**	7.25	292	19,321
trans-o-**1**	7.74	291	30,106
		333	28,492
cis-m-**1**	6.71	286	20,955
		291	27,488
trans-m-**1**	7.24	308	24,866
		320	24,629
cis-p-**1**	6.68	283	16,632
cis-stilbene	6.57	223	20,600
		276	10,900
trans-stilbene	7.15	227	21,000
		294	33,200
		307	32,100

The structural assignments were confirmed by X-ray crystallography. The proposed *cis-o*-**1** was successfully isolated as a single crystal (Fig. 2). The X-ray data was in agreement with the proposed structure.

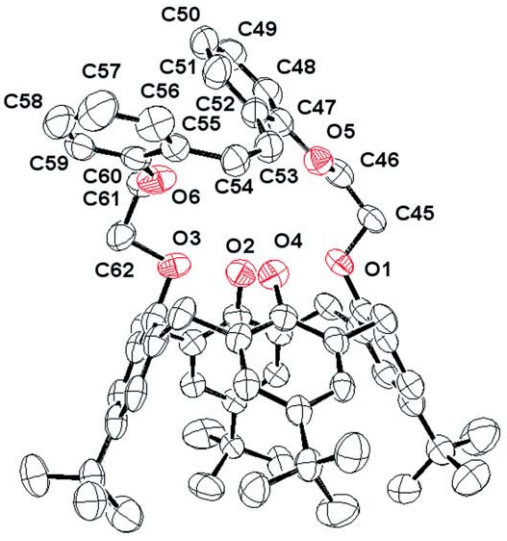


Figure 2. X-ray crystallographic structure of *cis-o*-**1**.

In the synthesis of azobenzene derivatives, only one product was isolated for each regioisomer, *o*-**2** and *m*-**2**. Since only one stereoisomer of each azobenzene derivative is available and, in the absence of protons on the nitrogen atoms providing an NMR probe, the assignment of *cis* and *trans* geometry was only possible through X-ray crystallography. Fortunately, both azobenzene derivatives (*o*-**2** and *m*-**2**) could be obtained as single crystals suitable for X-ray crystallography. The solid-state structures of these azobenzene derivatives revealed that both compounds were the *trans* isomers (Fig. 3).

2.3. Isomerization study

Whilst none of the stilbene crown ether *p-tert*-butylcalix[4]-arenes reported here isomerized in ambient light, they readily did so under UV irradiation (medium pressure mercury lamp). The *cis* and *trans* isomer-percentages for each derivative at the photostationary state were determined by ^{1}H NMR spectroscopy using the ratios of the peak areas of the best resolved resonances corresponding to each geometric isomer (Fig. 4).

The resonances of the corresponding protons in the *cis* and *trans* forms of each regioisomer (aromatic protons *ortho* to vinylic carbon for *o*-**1**, *t*-butyl protons for *m*-**1**, ethylene glycolic protons for *p*-**1**, methylene bridge protons in *o*-**2** and ethylene glycolic protons for *m*-**2**) were selected for the ratio calculation. The photo-stationary states were observed for all isomers and the percentages of *cis* and *trans* isomers were obtained from the ^{1}H NMR data (Table 3).

For stilbene derivatives, the same photostationary state was reached, no matter which geometrically pure isomer, *cis* or *trans*, was used as the starting material. However, in the case of the azobenzene analogues, the irradiation was performed on the only available, *trans* isomer.

Unlike the stilbene derivatives, the azobenzene calixarenes isomerized even in the absence of light because of the usual thermal isomerization of the diazo (N=N) unit.[16] While the photoisomerization of both stilbenes and azobenzenes under a medium pressure Hg lamp took minutes, the thermal isomerization of the azobenzenes was much slower, taking over a week to reach the equilibrium. Both thermal and photochemical isomerizations of the azobenzene derivatives produced the same final *cis*:*trans* product ratios implying that, under our experimental conditions, the product ratio from the photoizomerization directly correlates with the relative thermal stability of each isomer.

2.4. Complexation study

Picrate salt extraction was chosen for the complexation study. The complexation can be observed by several techniques: color change, ^{1}H NMR, and UV–Visible spectroscopy. To our surprise, (^{1}H NMR) complexation studies using each of the compounds synthesized revealed that only *o*-**2** showed any evidence for complexation with sodium and potassium picrate (Fig. 5).

The complexation results suggested that the lone pair electrons on nitrogen of the diazo group participated in the binding with the metal ions. Thus, only *o*-**2**, which possesses at least one nitrogen lone pair of electrons pointing into the crown ether biding cavity, can form a host-guest complex. It is also interesting to point out here that the complexation of *o*-**2** with Na^+ and K^+ ion shifted the thermal equilibrium between the *cis* and *trans* isomers in opposite directions.

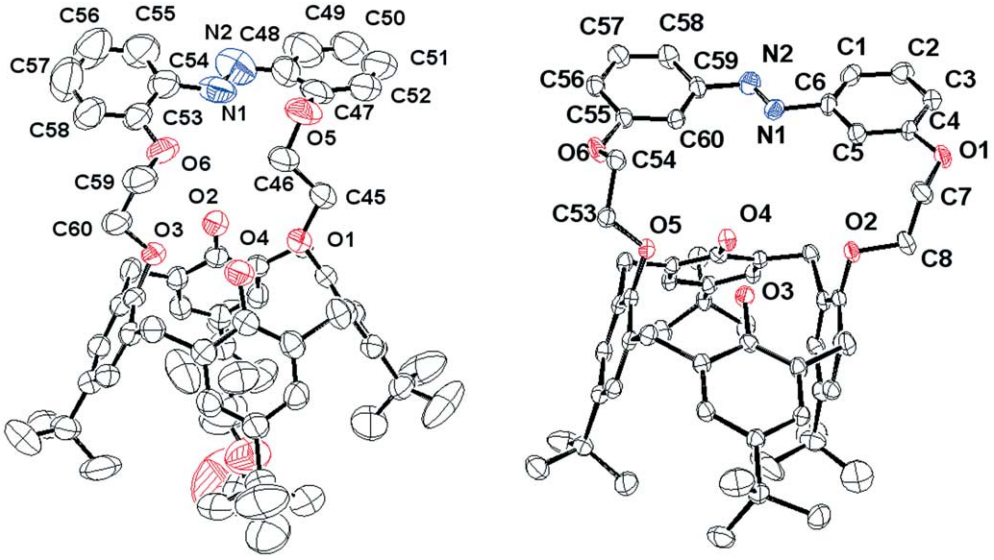


Figure 3. X-ray crystallographic structure of *trans-o*-**2**·$CH_3CO_2CH_2CH_3$ and *trans-m*-**2**.

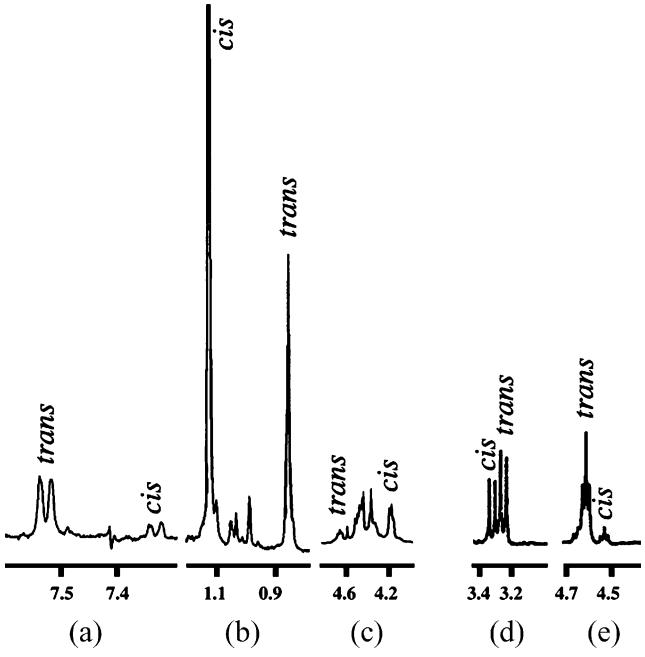


Figure 4. ^{1}H NMR signals used for calculation of *cis*/*trans* ratio at the photostationary state: (a) aromatic protons *ortho* to vinylic carbon in *o*-**1**; (b) *t*-butyl protons in *m*-**1**; (c) ethylene glycolic protons in *p*-**1**; (d) methylene bridge protons in *o*-**2**; and (e) ethylene glycolic protons in *m*-**2**.

Table 3. The percentages of *cis* and *trans* isomers at the photostationary states

Compound	% Isomer at photostationary state	
	cis	*trans*
o-**1**	15	85
m-**1**	70	30
p-**1**	75	25
o-**2**	36	64
m-**2**	13	87

The complexation with K^+ resulted in the equilibrium shift toward the *trans* isomer (compare Fig. 5c with b) while the complexation with Na^+ moved the equilibrium toward the *cis* isomer (compare Fig. 5d with b).

Unfortunately, we have not been able to crystallize the *o*-**2** metal complex as a single crystal to confirm our hypothesis about the participation of the nitrogen lone pair in the complexation. However, we have studied the complexation of the model compounds, calixarene derivatives **3** and **4** with sodium and potassium picrates. When solid sodium (or potassium) picrate was added to the colorless solution of **4** in CH_2Cl_2, the solution turned yellow and the UV–Visible spectrum showed a strong absorption band of the picrate ion

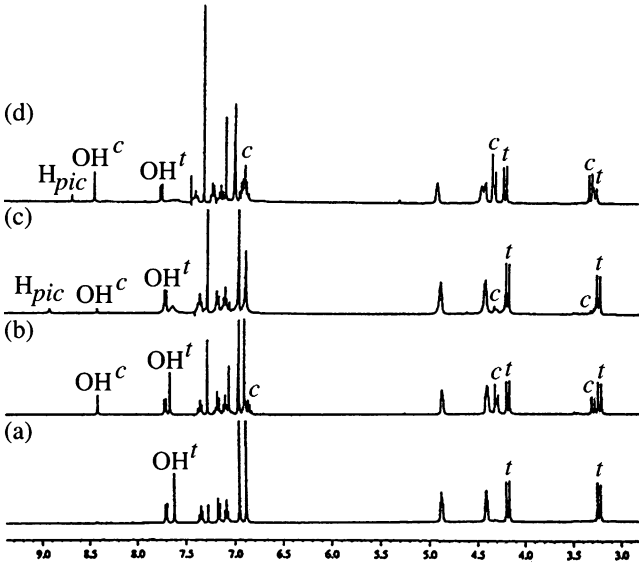


Figure 5. ^{1}H NMR spectra of: (a) *trans-o*-**2**; (b) *cis*- and *trans-o*-**2** at the photostationary state; (c) *o*-**2** with potassium picrate; and (d) *o*-**2** with sodium picrate. (*pic*=picrate, *c*=*cis*, *t*=*trans*).

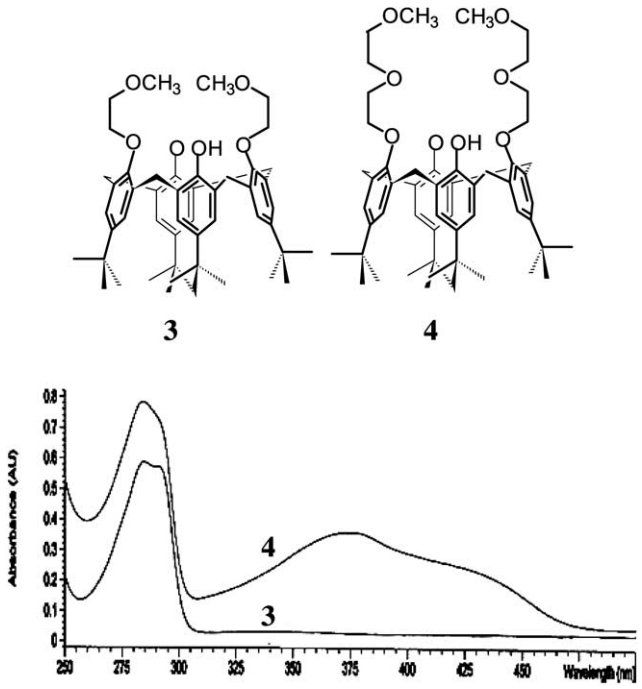


Figure 6. UV–Vis spectra of **3** and **4** in CH_2Cl_2 in the presence of sodium picrate salt added as a solid.

around 375 nm (Fig. 6), although there were minimal changes in the ^{1}H NMR spectrum upon complex formation. The mixture of **3** and sodium (or potassium) picrate in CH_2Cl_2, on the other hand, showed no absorption band corresponding with picrate anion. These results indicated that while compound **4** which contains eight oxygen donor atoms complexed with sodium and potassium ions, compound **3** which contains only six oxygen donor atoms complexed with neither ions. The results thus support our hypothesis that the presence of six ethereal oxygen donor atoms in this calixarene-based system is not sufficient for the binding of alkali metal cations.

3. Conclusion

We have successfully synthesized and fully characterized two series of photoswitchable calix[4]arenes incorporating different regioisomers of stilbene and azobenzene bridges. The *cis–trans* isomerization study indicates that the stilbene derivatives are isomerized only under UV irradiation while the azobenzene derivatives undergo either thermally or photochemically induced isomerization. Only the *o*-azobenzene derivative shows complexation with sodium and potassium ions presumably as a result of the participation of the nitrogen atom of the diazo group in coordination with these ions. The results represent a rare example of the coordination of the nonpolar diazo nitrogen to an alkali-metal cation. This complexation also induces a thermal equilibrium shift between *cis* and *trans* isomers of the azobenzenes. The present findings will lead to the design and synthesis of new, more effective, photoswitchable ionophores for sodium and potassium ions.

4. Experimental

4.1. Data for compounds

4.1.1. Synthesis of bis-benzaldehyde. In a 1 L, two-necked, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser, *p-tert*-butyl-calix[4]arene (7.8 mmol, 5.00 g) and K_2CO_3 (57.9 mmol, 8.00 g) were dissolved in CH_3CN (300 mL). The mixture was stirred for 30 min at room temperature and (2-bromoethoxy)-benzaldehyde (17.5 mmol, 4.00 g) was then added dropwise. The mixture was refluxed for 60 h and then allowed to cool to room temperature. The mixture was filtered and washed with acetone and CH_2Cl_2. The filtrate was combined and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (150 mL) and then extracted with aqueous HCl (2 M, 4×25 mL). The organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure. The product was further purified by crystallization in CH_2Cl_2/CH_3OH yielding a white solid as the product.

o-isomer (5.5 mmol, 5.16 g, 70%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.24 (s, 18H), 3.29 (d, 4H, J= 13.0 Hz), 4.29 (d, 4H, J=13.0 Hz), 4.38–4.40 (m, 8H), 6.85 (s, 4H), 7.00 (s, 4H) 6.94–7.04 (m, 4H), 7.50 (s, 4H), 7.45–7.55 (m, 2H), 7.82 (dd, 2H, J=7.5, 2.0 Hz), 10.48 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.7, 31.8, 33.8, 34.0, 67.5, 73.6, 112.4, 121.0, 125.2, 125.2, 125.8, 127.7, 128.2, 132.6, 135.8, 141.7, 147.3, 149.8, 150.3, 160.8, 190.2.

m-isomer (4.7 mmol, 4.42 g, 60%). Mp (decompose)= 184.8–185.3 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 18H), 1.27 (s, 18H), 3.32 (d, 4H, J=13.0 Hz), 4.30–4.40 (m, 12H), 6.85 (s, 4H), 7.04 (s, 4H) 7.20–7.45 (m, 8H), 9.93 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.7, 31.7, 33.8, 34.0, 66.9, 73.7, 113.4, 122.4, 123.6, 125.2, 125.7, 127.8, 130.2, 132.8, 137.8, 141.5, 147.1, 149.7, 150.5, 159.2, 192.1; IR (neat) ν_{max} 3336 (phenolic O–H stretching), 3050, 2958, 2869 (aldehydic C–H stretching), 2731 (aldehydic C–H stretching), 1697 (aldehydic C=O stretching), 1597, 1485, 1450, 1265 cm^{-1}; Anal. Calcd for $C_{62}H_{72}O_8$: C, 78.78; H, 7.68; Found: C, 76.80; H, 7.95.

p-isomer (4.3 mmol, 4.05 g, 55%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.18 (s, 18H), 1.50 (s, 18H), 3.49 (d, 4H, J= 13.0 Hz), 4.80–4.52 (m, 8H), 4.54 (d, 4H, J=13.0 Hz), 7.02 (s, 4H), 7.19 (d, 4H, J=8.5 Hz), 7.24 (s, 4H), 7.42 (s, 2H), 10.06 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.0, 31.5, 31.7, 33.8, 34.0, 66.9, 73.5, 115.1, 125.2, 125.7, 127.8, 130.2, 131.9, 132.6, 141.6, 147.2, 149.6, 150.4, 163.5, 190.8.

4.1.2. Synthesis of bis-nitrobenzene. In a 500 mL, round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser, a mixture of potassium carbonate (0.43 mmol, 6.0 g), (2-bromoethoxy)nitrobenzene (40.64 mmol, 10.0 g)and *p-tert*-butyl calyx[4]arene (18.85 mmol, 8.0 g) were stirred in CH_3CN (200 mL). The mixture was kept stirring at reflux temperature overnight. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2

(150 mL) and then extracted with water for several times. The combined organic phase was separated and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum. The product was further purified crystallisation using CH_2Cl_2/MeOH solvent system. The purified product was obtained as a yellow crystal.

o-isomer (12.44 mmol, 12.2 g, 66%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 18H), 1.26 (s, 18H), 3.31 (d, 4H, J=13.0 Hz), 4.33 (s, 8H), 4.35 (d, 4H, J=13.0 Hz), 6.85 (s, 4H), 7.03 (s, 4H), 7.24 (ddd, 2H, J=8.0, 2.0, 1.0 Hz), 7.35 (s, 2H), 7.40 (t, 2H, J=8.0 Hz), 7.74 (t, 2H, J=2.0 Hz), 7.81 (ddd, 2H, 8.0, 2.0, J=1.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.7, 31.7, 33.9, 34.0, 67.4, 73.4, 109.1, 116.2, 122.2, 125.2, 125.8, 127.8, 130.0, 132.8, 141.8, 147.5, 149.1, 149.5, 150.3, 159.1; Anal. Calcd for $C_{60}H_{70}N_2O_{10}$: C, 73.60; H, 7.21; N, 2.386; Found: C, 73.62; H, 7.27; N, 2.73: mp=205–207 °C.

m-isomer (13.28 mmol, 13.0 g, 70%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 18H), 1.26 (s, 18H), 3.31 (d, 4H, J=13.0 Hz), 4.33 (s, 8H), 4.35 (d, 4H, J=13.0 Hz), 6.85 (s, 4H), 7.03 (s, 4H), 7.24 (ddd, 2H, J=8.0, 2.0, 1.0 Hz), 7.35 (s, 2H), 7.40 (t, 2H, J=8.0 Hz), 7.74 (t, 2H, J=2.0 Hz), 7.81 (ddd, 2H, 8.0, 2.0, J=1.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.1, 31.7, 31.7, 33.9, 34.0, 67.4, 73.4, 109.1, 116.2, 122.2, 125.2, 125.8, 127.8, 130.0, 132.8, 141.8, 147.5, 149.1, 149.5, 150.3, 159.1.

p-isomer (15.1 mmol, 14.8 g, 80%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.96 (s, 18H), 1.27 (s, 18H), 3.30 (d, 4H, J=13.0 Hz), 4.31 (s, 8H), 4.35 (d, 4H, J=13.0 Hz), 6.80 (s, 4H), 6.98 (d, 4H, J=9.0 Hz), 7.05 (s, 4H), 7.07 (s, 2H), 8.18 (d, 4H, J=9.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 31.0, 31.5, 31.7, 33.9, 34.0, 67.4, 73.5, 114.8, 125.2, 125.7, 125.9, 127.7, 132.5, 141.8, 141.8, 147.3, 149.4, 150.4, 163.5.

4.1.3. Synthesis of 1. Typically, $TiCl_4$ (3.17 mmol, 0.60 g) was charged into a two-necked, round-bottomed flask under a N_2 atmosphere. Anhydrous THF (30 mL) was added dropwise and activated Zn powder (6.35 mmol, 0.41 g) was added cautiously. After 1 h reflux, the bisbenzaldehyde (1.06 mmol, 1.00 g) in THF (10 mL) was added dropwise. The mixture was refluxed for additional 15 h and it was allowed to cool to room temperature. A solution of K_2CO_3 (15% w/v) was added to quench the excess $TiCl_4$. The precipitate was filtered over celite and washed with acetone and CH_2Cl_2. The filtrate was evaporated to give the residue which was dissolved in CH_2Cl_2 (20 mL) and then extracted with water (3×25 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed to give the crude product. The *cis* and *trans* isomers was separated by column chromatography using 5% ethyl acetate in hexane as eluent (*cis* isomers have a higher R_f value).

cis-o-**1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.03 (s, 18 C(CH_3)$_3$), 1.22 (s, 18 C(CH_3)$_3$), 3.25 (d, 4 Ar$_2$CH_2, J=13.0 Hz), 4.16 (broad, 4 OCH_2), 4.26 (broad, 4 OCH_2), 4.35 (d, 4 Ar$_2$CH_2, J=13.0 Hz), 6.83 (t, 2 stilbene-ArH, J=7.5 Hz), 6.88 (d, 2 stilbene-ArH, J=7.5 Hz), 6.90 (s, 4 calix-ArH), 6.97 (s, 4 calix-ArH), 7.17 (t, 2 stilbene-ArH, J=7.5 Hz), 7.25 (s, 2 CH=CH), 7.29 (d, 2 stilbene-ArH, J=7.5 Hz), 7.70 (s, 2 OH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.1 (6 C(*C*H$_3$)$_3$), 31.7 (6 C(*C*H$_3$)$_3$), 31.9 (4 Ar$_2$*C*H$_2$), 33.8 (2 *C*(CH$_3$)$_3$), 34.0 (2 *C*(CH3)3), 67.8 (2 O*C*H$_2$), 74.1 (2 O*C*H$_2$), 113.4 (2 stilbene-Ar*C*), 120.8 (2 stilbene-Ar*C*), 125.1 (4 calix-Ar*C*), 125.4 (2 *C*H=*C*H), 125.7 (4 calix-Ar*C*), 127.7 (4 calix-Ar*C*), 127.9 (2 stilbene-Ar*C*), 129.0 (2 stilbene-Ar*C*), 129.5 (2 stilbene-Ar*C*), 133.3 (4 stilbene-Ar*C*), 141.0 (2 calix-Ar*C*), 147.0 (2 calix-Ar*C*), 149.6 (2 calix-Ar*C*), 150.8 (2 calix-Ar*C*), 155.7 (2 stilbene-Ar*C*); Anal. Calcd for $C_{62}H_{72}O_6\cdot CH_2Cl_2$: C, 75.88; H, 7.38; Found: C, 76.12; H, 7.25: mp=292–294 °C (decomposed).

trans-o-**1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (s, 18 C(CH_3)$_3$), 1.18 (s, 18 C(CH_3)$_3$), 3.21 (d, 4 Ar$_2$CH_2, J=12.5 Hz), 4.23 (d, 4 Ar$_2$CH_2, J=12.5 Hz), 4.51 (broad, 4 OCH_2), 4.68 (broad, 4 OCH_2), 6.82 (d, 2 stilbene-ArH, J=8.0 Hz), 6.93 (m, 4 calix-ArH and 2 stilbene-ArH), 6.97 (s, 4 calix-ArH), 7.15 (t, 2 stilbene-ArH, J=8.0 Hz), 7.50 (d, 2 stilbene-ArH, J=8.0 Hz), 7.74 (s, 2 CH=CH), 8.43 (s, 2 OH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.2 (6 C(*C*H$_3$)$_3$), 31.6 (6 C(*C*H$_3$)$_3$), 32.1 (4 Ar$_2$*C*H$_2$), 33.8 (2 *C*(CH$_3$)$_3$), 34.1 (2 *C*(CH3)3), 66.6 (2 O*C*H$_2$), 73.6 (2 O*C*H$_2$), 111.1 (2 stilbene-Ar*C*), 120.8 (2 stilbene-Ar*C*), 125.0 (4 calix-Ar*C*), 125.9 (4 calix-Ar*C*), 127.5 (4 calix-Ar*C*), 127.5 (2 *C*H=*C*H), 127.7 (2 stilbene-Ar*C*), 128.0 (2 stilbene-Ar*C*), 129.6 (2 stilbene-Ar*C*), 133.7 (4 calix-Ar*C*), 141.2 (2 calix-Ar*C*), 147.4 (2 calix-Ar*C*), 149.3 (2 calix-Ar*C*), 150.7 (2 calix-Ar*C*), 155.9 (2 stilbene-Ar*C*); Anal. Calcd for $C_{62}H_{72}O_6$: C, 81.54; H, 7.95; Found: C, 81.41; H, 7.94: mp=278–280 °C (decomposed).

cis-m-**1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 18 C(CH_3)$_3$), 1.25 (s, 18 C(CH_3)$_3$), 3.32 (d, 4 Ar$_2$CH_2, J=12.5 Hz), 3.94 (broad, 4 OCH_2), 4.12 (broad, 4 OCH_2), 4.38 (d, 4 Ar$_2$CH_2, J=12.5 Hz), 6.69 (broad, 2 stilbene-ArH), 6.71 (s, 2 CH=CH), 6.89 (m, 4 stilbene-ArH), 6.97 (s, 4 calix-ArH), 7.02 (s, 4 calix-ArH), 7.24 (t, 2 stilbene-ArH, J=8.5 Hz), 8.08 (s, 2 OH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.2 (6 C(*C*H$_3$)$_3$), 31.7 (6 C(*C*H$_3$)$_3$), 31.7 (4 Ar$_2$*C*H$_2$), 33.8 (2 *C*(CH$_3$)$_3$), 34.1 (2 *C*(CH$_3$)$_3$), 66.2 (2 O*C*H$_2$), 73.7 (2 O*C*H$_2$), 111.8 (2 stilbene-Ar*C*), 117.0 (2 stilbene-Ar*C*), 121.5 (2 stilbene-Ar*C*), 125.0 (4 calix-Ar*C*), 125.7 (4 calix-Ar*C*), 127.3 (4 calix-Ar*C*), 129.6 (2 *C*H=*C*H), 130.9 (2 stilbene-Ar*C*), 133.5 (4 calix-Ar*C*), 138.3 (2 stilbene-Ar*C*), 140.9 (2 calix-Ar*C*), 147.2 (2 calix-Ar*C*), 149.2 (2 calix-Ar*C*), 151.1 (2 calix-Ar*C*), 158.2 (2 stilbene-Ar*C*); Anal. Calcd for $C_{62}H_{72}O_6$: C, 81.54; H, 7.95; Found: C, 81.48; H, 7.92: mp=264–265 °C.

trans-m-**1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 18 C(CH_3)$_3$), 1.31 (s, 18 C(CH_3)$_3$), 3.29 (d, 4 Ar$_2$CH_2, J=13.5 Hz), 4.25 (t, 4 OCH_2, J=5.0 Hz), 4.41 (d, 4 Ar$_2$CH_2, J=13.5 Hz), 4.57 (t, 4 OCH_2, J=5.0 Hz), 5.84 (s, 2 OH), 6.60 (s, 4 calix-ArH), 6.87 (t, 2 stilbene-ArH, J=8.5 Hz), 7.06 (s, 4 calix-ArH), 7.14 (d, 2 stilbene-ArH, J=7.5 Hz), 7.24 (s, 2 CH=CH), 7.25 (t, 2 stilbene-ArH, J=7.5 Hz), 7.74 (s, 2 stilbene-ArH); ^{13}C NMR (200 MHz, $CDCl_3$) δ 30.8 (6 C(*C*H$_3$)$_3$), 31.2 (4 Ar$_2$*C*H$_2$), 31.7 (6 C(*C*H$_3$)$_3$), 33.8 (2 *C*(CH$_3$)$_3$), 33.9 (2 *C*(CH3)3), 69.3 (2 O*C*H$_2$), 75.0 (2 O*C*H$_2$), 114.3 (2 stilbene-Ar*C*), 118.0 (2 stilbene-Ar*C*), 119.9 (2 stilbene-Ar*C*), 125.3 (4 calix-Ar*C*), 125.4 (4 calix-Ar*C*), 128.5 (4 calix-Ar*C*), 128.9 (2 *C*H=*C*H), 129.8 (2 stilbene-Ar*C*), 131.6 (4 calix-Ar*C*), 139.1 (2 stilbene-Ar*C*), 141.8 (2 calix-Ar*C*), 146.7 (2 calix-Ar*C*), 150.3 (2 calix-Ar*C*), 150.8 (2 calix-Ar*C*), 158.8 (2 stilbene-Ar*C*);

Anal. Calcd for $C_{62}H_{72}O_6$: C, 81.54; H, 7.95; Found: C, 81.59; H, 8.00: mp=281–283 °C (decomposed).

cis-p-**1**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 18 C(CH_3)$_3$), 1.31 (s, 18 C(CH_3)$_3$), 3.28 (d, 4 Ar_2CH_2, J=13.5 Hz), 4.17 (t, 4 OCH_2, J=4.0 Hz), 4.38 (d, 4 Ar_2CH_2, J=13.5 Hz), 4.45 (t, 4 OCH_2, J=4.0 Hz), 6.29 (s, 2 O*H*), 6.66 (s, 4 calix-Ar*H*), 6.68 (s, 2 C*H*=C*H*), 6.85 (d, 4 stilbene-Ar*H*, J=9.0 Hz), 6.93 (d, 4 stilbene-Ar*H*, J=9.0 Hz), 7.06 (s, 4 calix-Ar*H*); ^{13}C NMR (200 MHz, $CDCl_3$) δ 31.0 (6 C(*C*H$_3$)$_3$), 31.1 (4 Ar_2CH_2), 31.8 (6 C(*C*H$_3$)$_3$), 33.8 (2 *C*(CH$_3$)$_3$), 33.8 (2 *C*(CH3)3), 68.4 (2 O*C*H$_2$), 74.8 (2 O*C*H$_2$), 115.8 (4 stilbene-Ar*C*), 125.2 (4 calix-Ar*C*), 125.4 (4 calix-Ar*C*), 128.1 (4 calix-Ar*C*), 130.4 (4 stilbene-Ar*C*), 130.8 (2 *C*H=*C*H), 131.3 (2 stilbene-Ar*C*), 132.0 (4 calix-Ar*C*), 141.4 (2 calix-Ar*C*), 146.8 (2 calix-Ar*C*), 149.9 (2 calix-Ar*C*), 150.5 (2 calix-Ar*C*), 157.7 (2 stilbene-Ar*C*); Anal. Calcd for $C_{62}H_{72}O_6$: C, 81.54; H, 7.95; Found: C, 81.57; H, 8.14: mp=290–291 °C (decomposed).

4.1.4. Synthesis of 2. *Ambient pressure method*. In a 50 mL round-bottomed flask equipped with a magnetic bar and a reflux condenser, a mixture of 25,27-bis-2-(2-nitrophenol)-ethoxy-*p*-*tert*-butylcalix[4]arene, (0.71 mmol, 0.70 g) in isopropanol (8 mL), sodium hydroxide (7.0 mmol, 0.28 g) in water (4 mL) and zinc (3.06 mmol, 0.20 g) was stirred. The mixture was refluxed under nitrogen atmosphere for 48 h and it was then allowed to cool to room temperature. The mixture was filtered off and washed with CH_2Cl_2. The filtrate was evaporated and the residue was dissolved in CH_2Cl_2 and then extracted with 2 M HCl (2×20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed to give the crude product, which was purified by column chromatography using 15% ethyl acetate in hexane as eluent. The *trans* isomers was collected and crystallized in CH_2Cl_2/CH_3OH mixture to give orange crystals.

High pressure method. In a 100 mL high-pressure glass tube equipped with pressure gauge and a magnetic bar, a mixture of 25,27-bis-2-(2-nitrophenol)ethoxy-*p*-*tert*-butylcalix[4]-arene, (0.71 mmol, 0.70 g) in isopropanol (8 mL), sodium hydroxide (7.0 mmol, 0.28 g) in water (4 mL) and zinc (3.06 mmol, 0.20 g) was added and stirred. The reaction was operated under 3 atm nitrogen atmosphere for overnight at 130 °C and it was then allowed to cool to room temperature. The mixture was filtered off and washed with CH_2Cl_2. The filtrate was evaporated to give the residue which was dissolved in CH_2Cl_2 and then extracted with 2 M HCl (2× 20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent was removed to give the crude product, which was purified by column chromatography using 5% ethyl acetate in hexane as eluent. The *trans* isomers was separated and crystallized in CH_2Cl_2/CH_3OH mixture to give orange crystals.

trans-o-**2**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.03 (s, 18 C(CH_3)$_3$), 1.20 (s, 18 C(CH_3)$_3$), 3.20 (d, 4 Ar_2CH_2, J=13.0 Hz), 4.15 (d, 4Ar_2CH_2, J=13.0 Hz), 4.38 (br t, 4 OCH_2), 4.84 (br t, 4 OCH_2), 6.86 (s, 4 calix-Ar*H*), 6.92 (s, 4 calix-Ar*H*), 7.08 (d, 2 azobenzene-Ar*H*, J=6.0 Hz), 7.16 (d, 2 azobenzene-Ar*H*, J=8.0 Hz), 7.34 (t, 2 azobenzene-Ar*H*, J=6.0 Hz), 7.61 (s, 2 O*H*), 7.70 (d, 2 azobenzene-Ar*H*, J=8.0 Hz); Anal. Calcd for $C_{60}H_{70}N_2O_6$: C, 78.74; H, 7.71; N, 3.06; Found: C, 77.21; H, 7.51, N 2.72 mp: 195–197 °C (decomposed).

trans-m-**2**. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (s, 18 C(CH_3)$_3$), 1.28 (s, 18 C(CH_3)$_3$), 3.26 (d, 4 Ar_2CH_2, J=13.0 Hz), 4.38 (t, 4 OCH_2, J=5.0 Hz), 4.34 (d, 4 Ar_2CH_2, J=13.0 Hz), 4.66 (t, 4 OCH_2, J=5.0 Hz), 6.07 (s, 2 O*H*), 6.61 (s, 4 calix-Ar*H*), 7.03 (s, 4 calix-Ar*H*), 7.08 (d, 2 azobenzene-Ar*H*, J=8.0 Hz), 7.39 (t, 2 azobenzene-Ar*H*, J=8.0 Hz), 7.60 (d, 2 azobenzene-Ar*H*, J=8.0 Hz), 8.19 (s, 2 azobenzene-Ar*H*); ^{13}C NMR (200 MHz, $CDCl_3$) δ 30.9 (6 C(*C*H$_3$)$_3$), 31.2 (4 Ar_2CH_2), 31.7 (6 C(*C*H$_3$)$_3$), 33.8 (2 *C*(CH$_3$)$_3$), 33.8 (2 *C*(CH3)3), 69.1 (2 O*C*H$_2$), 74.4 (2 O*C*H$_2$), 110.9 (2 azobnzene-Ar*C*), 116.2 (2 azobnzene-Ar*C*), 121.4 (2 azobnzene-Ar*C*), 125.2 (4 calix-Ar*C*), 125.5 (4 calix-Ar*C*), 128.2 (4 calix-Ar*C*), 129.8 (2 azobnzene-Ar*C*), 131.7 (4 calix-Ar*C*), 141.6 (2 calix-Ar*C*), 146.7 (2 calix-Ar*C*), 150.4 (2 calix-Ar*C*), 150.7 (2 calix-Ar*C*), 153.7 (2 azobnzene-Ar*C*), 159.4 (2 stilbene-Ar*C*); Anal. Calcd for $C_{60}H_{70}N_2O_6$: C, 78.74; H, 7.71; N, 3.06; Found: C, 78.41; H, 7.78, N 3.01 mp: 351–352 °C.

4.2. Complexation study

For the ^{1}H NMR study, the studied calixarene derivative (10 mg) was dissolved in $CDCl_3$ (0.7 mL) in an NMR tube and the ^{1}H NMR spectrum was collected. Sodium or potassium picrate (20 mg) was added as a solid into the solution. The mixture was sonicated for 1 h before the spectrum was collected again. The color would turn to deep yellow and a singlet signal of the aromatic picrate proton could be observed around 9.0 ppm if complexation had taken place. If the signal was not observed by ^{1}H NMR, the results was confirmed by UV–Vis which was the cases for compounds **4** that the complexation was clearly observed in UV–Vis spectra but barely seen from the ^{1}H NMR spectra.

4.3. Isomerization study

The studied compound was dissolved in $CDCl_3$ at 0.0060 mol and into an NMR tube. Using a Hanovia 450 W medium pressure murcury lamp equipped with a cooling Jacket, the sample was irradiated at 30 cm away from the lamp for a specific period of time. The ^{1}H NMR was checked. Once the NMR spectra were unchanged, the *cis*:*trans* ratio of that specific analogue was determined by NMR integration of a selected signal.

4.4. Crystallographic data

4.4.1. *cis-o*-1. $C_{63}H_{74}Cl_2O_6$, monoclinic, space group $P2_1/c$, a=20.7486(5) Å, b=12.3713(4) Å, c=22.6335(5) Å, β=109.373(2)°, U=5480.8(3) Å^3, D_c=1.210 Mg m^{-3}, Z=4, T=120(2) K, colourless block, 0.24×0.18×0.12 mm^3. Data collection was carried out using a Bruker–Nonius KappaCCD area detector and SHELXS-97 and SHELXL-97 programs were used for structure solution and refinement. 32,983 reflections collected, 12,074 independent [R(int)=0.0700], giving R_1=0.0931 for observed unique reflections [$F^2>2\sigma(F^2)$] and wR_2=0.3186 for all data. The max. and min. residual electron densities on the final difference Fourier map were 0.975 and −0.588e Å^{-3}, respectively. The asymmetric unit contains a disordered molecule of

dichloromethane and exhibits conformational disorder in one of the lower rim cage arms and rotational disorder in one of the tertiary butyl groups. Supplementary data have been deposited with the CCDC in CIF format with the deposition number CCDC249144.

4.4.2. *trans-o*-2. $C_{64}H_{78}N_2O_8$, Monoclinic, space group *Cc*, $a=15.1260(3)$ Å, $b=31.1347(3)$ Å, $c=12.6692(3)$ Å, $\beta=98.4970(10)°$, $U=5900.99(19)$ Å^3, $D_c=1.129$ Mg m^{-3}, $Z=4$, $T=293(2)$ K, dark-orange block, $0.60\times0.30\times0.30$ mm^3. Data collection was carried out using a Bruker SmartCCD detector and SHELXS-97 and SHELXL-97 programs were used for structure solution and refinement. 21,046 reflections collected, 14,604 independent [R(int)=0.0190], giving $R_1=0.0731$ for observed unique reflections [$F^2>2\sigma(F^2)$] and $wR_2=0.1982$ for all data. The max. and min. residual electron densities on the final difference Fourier map were 0.225 and -0.211e Å^{-3}, respectively. Supplementary data have been deposited with the CCDC in CIF format with the deposition number CCDC137509.

4.4.3. *trans-m*-2. $C_{60}H_{70}N_2O_6$, Triclinic, space group *P*-1, $a=11.8283(3)$ Å, $b=12.7292(4)$ Å, $c=19.5738(8)$ Å, $\alpha=82.2330(10)°$, $\beta=74.9430(10)°$, $\gamma=66.7110(10)°$, $U=2612.32(15)$ Å^3, $D_c=1.163$ Mg m^{-3}, $Z=2$, $T=120(2)$ K, dark-orange block, $0.40\times0.20\times0.15$ mm^3. Data collection was carried out using a Bruker–Nonius KappaCCD area detector and SHELXS-97 and SHELXL-97 programs were used for structure solution and refinement. 39,735 reflections collected, 11,605 independent [R(int)=0.1407], giving $R_1=0.0777$ for observed unique reflections [$F^2>2\sigma(F^2)$] and $wR_2=0.2157$ for all data. The max. and min. residual electron densities on the final difference Fourier map were 0.801 and -0.556e Å^{-3}, respectively. Supplementary data have been deposited with the CCDC in CIF format with the deposition number CCDC249145.

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Photochemically catalyzed Diels–Alder reaction of arylimines with *N*-vinylpyrrolidinone and *N*-vinylcarbazole by 2,4,6-triphenylpyrylium salt: synthesis of 4-heterocycle-substituted tetrahydroquinoline derivatives

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Abstract—Photochemically promoted Diels–Alder reactions of *N*-arylimines with *N*-vinylpyrrolidinone and *N*-vinylcarbazole were achieved by using 2,4,6-triphenylpyrylium tetrafluoroborate as a catalyst to produce corresponding 2-oxopyrrolidin-1-yl and carbazol-9-yltetrahydroquinolines in high yields.

1. Introduction

The chemistry of tetrahydroquinoline derivatives has long been an area of intense interest for organic chemists due to the presence of these scaffolds within the framework of numerous biologically active natural products and pharmaceutical agents. Many new methods for the synthesis of tetrahydroquinoline derivatives have been developed.[1,2] Among them, the imino Diels–Alder reaction between *N*-arylimines and electron-rich alkenes that has been a topic of continuing interest for 40 years.[3,4] This imino Diels–Alder reaction has been reported to be catalyzed by $BF_3 \cdot Et_2O$ and other Lewis acids,[3a–d] Lanthanide triflate,[3e–f] triphenyl phosphonium perchlorate,[3g] 2,3-dichloro-5,6-dicyano-*p*-benzoquinone,[3h] and protic acids.[3i–j] As a part of our ongoing research program on synthetic potential of radical and radical cation mediated reaction,[4] we recently found a facile synthesis of quinoline derivatives[4a] by photochemically promoted imino Diels–Alder reaction catalyzed by 2,4,6-triphenylpyrylium tetrafluoroborate (**TPT**) which has been widely used as a photosensitizer to induce Diels–Alder reactions.[5] Since tetrahydroquinolines with *N*-heterocycle moiety exhibit interesting properties[6,7] that make them attractive for synthetic and pharmacological use, while the synthesis of 4-*N*-heterocycle-substituted 1,2,3,4-tetrahydroquinolines has been scarcely explored.[7] We were interested in extending this photochemical approach to the synthesis of 4-*N*-heterocycle-substituted 1,2,3,4-tetrahydroquinolines. We report herein a facile synthesis of 4-(2-oxopyrrolidin-1-yl) and 4-(carbazol-9-yl)tetrahydroquinolines by photochemically promoted imino Diels–Alder reaction of arylimines and *N*-vinyl-2-pyrrolidinone (**2a**) or *N*-vinylcarbazole (**2b**). It is well known that **2b** and **2a** are easily oxidized to the corresponding cation radicals by metallic salts,[8] aminium salts[9] and photoinduced electron transfer[8,10] leading to cyclodimerization, cycloaddition and polymerization.

2. Results and discussion

Irradiation at $\lambda \geq 345$ nm of a deaerated anhydrous CH_2Cl_2 solution of the *N*-arylimine (**1**) with *N*-vinyl-2-pyrrolidinone (**2a**) and a catalytic amount of 2,4,6-triphenylpyrylium tetrafluoroborate (**TPT**) at ambient temperature afforded corresponding 4-(2-oxopyrrolidin-1-yl)tetrahydroquinolines (**3**) in high yields (Table 1). The reaction was completely regioselective giving only the isomers depicted in Scheme 1. Several arylimines with different substituents were examined and the results are listed in Table 1. In all cases investigated, the products obtained were exclusively *cis* stereoisomers which were easily separated by column, chromatography. The structure of compounds **3a–h** were characterized by ^1H, ^{13}C and 2D NMR spectroscopy, MS and elemental analysis. The *cis* configuration of the C-2 and C-4 substituents in **3a** was assigned by the large vicinal

Keywords: *N*-Vinylpyrrolidinone; *N*-vinylcarbazole; Arylimines; Photocycloaddition; 4-(2-Oxopyrrolidin-1-yl)tetrahydroquinolines; 4-(Carbazol-9-yl)tetrahydroquinolines; 2,4,6-Triphenylpyrylium tetrafluoroborate.
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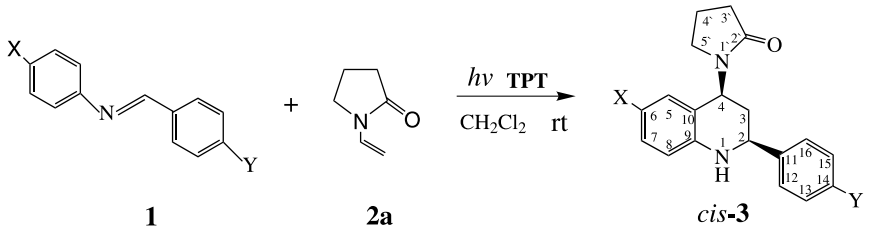
Table 1. Preparation of 4-(2-oxopyrrolidin-yl)tetrahydroquinolines (**3**)

Entry	Arylimine			*t* (h)	Conv.[a] (%)	Yield *cis*-**3** (%)[b]
		X	Y			
1	**1a**	H	H	12	95	84
2	**1b**	Cl	H	12	90	85
3	**1c**	CH_3O	H	12	85	75
4	**1d**	CH_3	Cl	12	98	91
5	**1e**	CH_3	CH_3O	12	90	85
6	**1f**	H	NO_2	12	97	90
7	**1g**	CH_3	NO_2	8	98	88
8	**1h**	CH_3O	NO_2	16	78	76

[a] Conversion based on **1**.
[b] Isolated yield based on **1**.



Scheme 1.

coupling constants $J_{2-3}=10.5$ Hz and $J_{4-3}=11.4$ Hz, both were indicative for the *anti* axial–axial orientation of one proton in C-3 position with H-2 and H-4, which could be deduced that the orientation of H-2 and H-4 was parallel. The *cis* configuration was also supported by NOESY as depicted in Figure 1. All reciprocal interactions were observed among H-4, H-3a and H-2 in accord with the *cis* configuration.

Furthermore, we examined the photoreactivity of arylimine **1** with *N*-vinylcarbazole (**2b**) catalyzed by **TPT**. According to our method, the deaerated anhydrous CH_2Cl_2 solution of arylimine (**1**) and *N*-vinylcarbazole (**2b**) as well as a catalytic amount of **TPT** was irradiated at ambient temperature to afford corresponding 4-(carbazol-9-yl)-2-aryltetrahydroquinolines as a mixture of *cis* and *trans* stereoisomers as depicted in Scheme 2. Similar results were obtained with all the arylimines. Therefore, *N*-vinylcarbazole exhibited a different behavior from that of *N*-vinyl-2-pyrrolidinone. We found, unfortunately, it was difficult to separate the *cis* and *trans* isomers completely by column chromatography in most cases. The further separation was

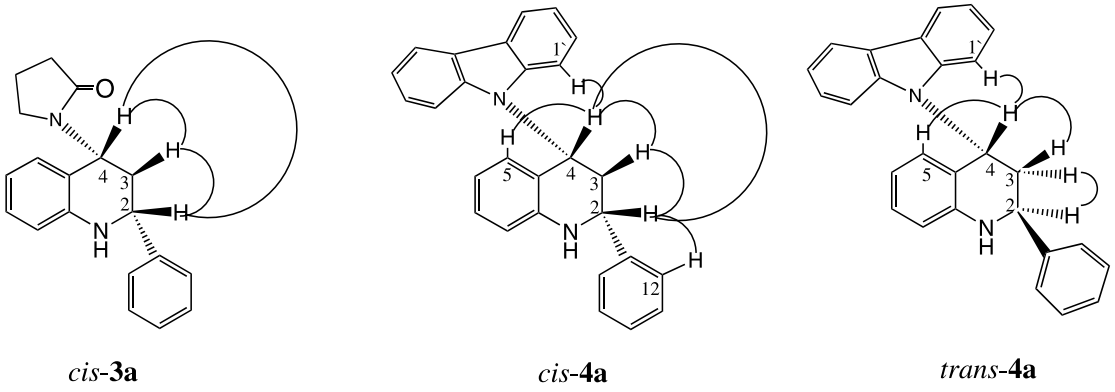
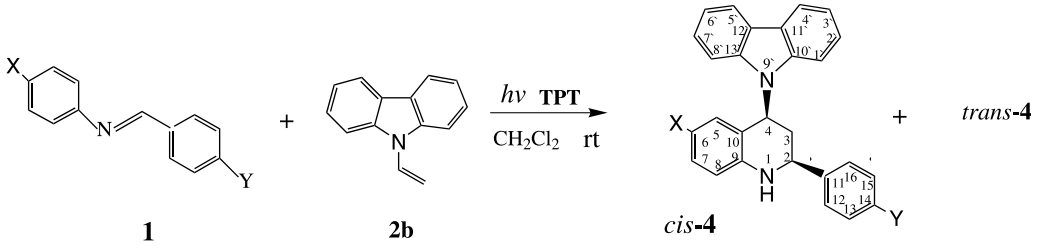


Figure 1. NOESY correlations of the *cis*-**3a**, the *cis*-**4a** and *trans*-**4a**.



Scheme 2.

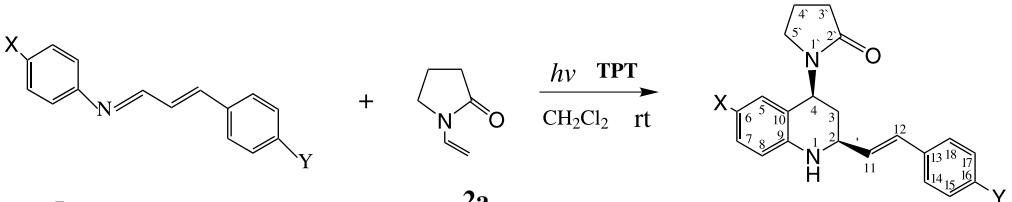
Table 2. Preparation of 4-(carbazol-9-yl)-tetrahydroquinolines (**4**)

Entry	Arylimine			*t* (h)	Conv.[a] (%)	Yield (%)[b] **4** (*cis*/*trans*)[c]
		X	Y			
1	**1a**	H	H	8	95	78 (58:42)
2	**1i**	H	CH_3O	8	90	85 (54:46)
3	**1e**	CH_3	CH_3O	8	98	75 (64:36)
4	**1j**	Cl	NO_2	4	95	85 (65:38)
5	**1g**	CH_3	NO_2	4	98	93 (70:30)
6	**1h**	CH_3O	NO_2	8	92	91 (67:33)

[a] Conversion based on **1**.
[b] Isolated yield based on **1**.
[c] Ratio determined by ^1H NMR spectra.

performed by repeated preparative thin plate chromatography. The results with different arylimines were listed in Table 2. The structures of compounds *cis*-**4a** and *trans*-**4a** were characterized by ^1H, ^{13}C and 2D NMR spectroscopy, MS and elemental analysis. The most diagnostic parameter for structural assignment of *cis*-**4a** and *trans*-**4a** is the scalar coupling constant between H-4 and H-3 and between H-2 and H-3. In *cis*-**4a**, the coupling constants of H-2 (d, $J=$ 11.6 Hz) and H-4 (dd, $J=6.6$, 11.6 Hz) obviously indicated the *anti* axial–axial orientation of $H\text{-}3_{axial}$ with H-2 and H-4. It could be deduced that the orientation of H-2 and H-4 was parallel. This orientation was also additionally supported by the appearance of one of the H-3 resonance at δ_H 2.82 ppm as a quartet ($J=12.3$ Hz). Only a *cis* configuration could give coupling constants of a similar magnitude between the two H-3 hydrogens and H-2 and H-4; for H-3a, the geminal coupling constant coincidently appeared to be equal to the vicinal coupling constants with H-2 and H-4. In *trans*-**4a**, the coupling constants of H-2 (dd, $J=3.6$, 7.5 Hz) and H-4 (t, $J=6.0$ Hz) were significantly smaller and typical for a gauche conformation. The configurations of *cis*-**4a** and *trans*-**4a** were further approved by NOESY experiment as shown in Figure 1: all reciprocal interaction was observed among H-4, H-3a, and H-2 in *cis*-**4a**. On the other hand, in the case of **trans-4a**, a strong reciprocal interaction was found between H-4 and H-3a, and a weak one between H-3e and H-2, but none between H-4 and H-2, all in accord with a *trans* configuration.

In addition, the reaction of 1,4-diaryl-1-azadienes **5** with **2a** or **2b** were studied under the same experimental conditions described above. The products obtained were 4-(2-oxo-pyrrolidin-1-yl)-2-arylvinyltetrahydroquinolines and 4-(carbazol-9-yl)-2-arylvinyltetrahydroquinolines instead of dihydropyridines as depicted in Schemes 3 and 4, respectively. The results showed that the reaction was an imino Diels–Alder reaction of 2-azadienes but not of 1-azadienes. This is probably due to the fact that the 2-azadienes usually have higher electron density than 1-azadienes.[3] Another reason for this regioselectivity might be attributed to the steric effect of the large phenyl group that inhibits the [4+2] cycloaddition of the 1-azadiene and directs the reaction toward the [4+2] cycloaddition of the 2-azadiene. Therefore, 1,4-diaryl-1-azadienes **5** behaved similarly to 1-arylimines (**1**). Analogous to the cases presented in Schemes 1 and 2, tetrahydroquinolines **6a** and **6b** were obtained as a single stereoisomer, but tetrahydroquinolines **7a** and **7c** were obtained as a mixture of *cis* and *trans* stereoisomers. The NMR spectral patterns of **6a–b** were similar to those of **3a–h**, hence compounds **6a**

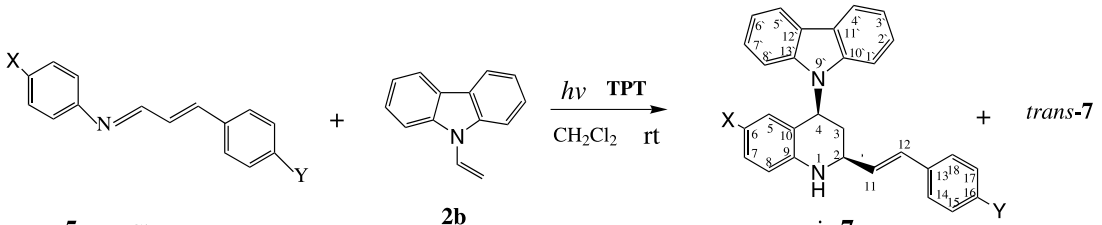


5a X=Cl, Y=H
5b X=CH_3O, Y=H

2a

cis-**6a**
cis-**6b**

Scheme 3.



5a X=Cl, Y=H
5c X=CH_3O, Y=NO_2

2b

cis-**7a**
cis-**7c**

Scheme 4.

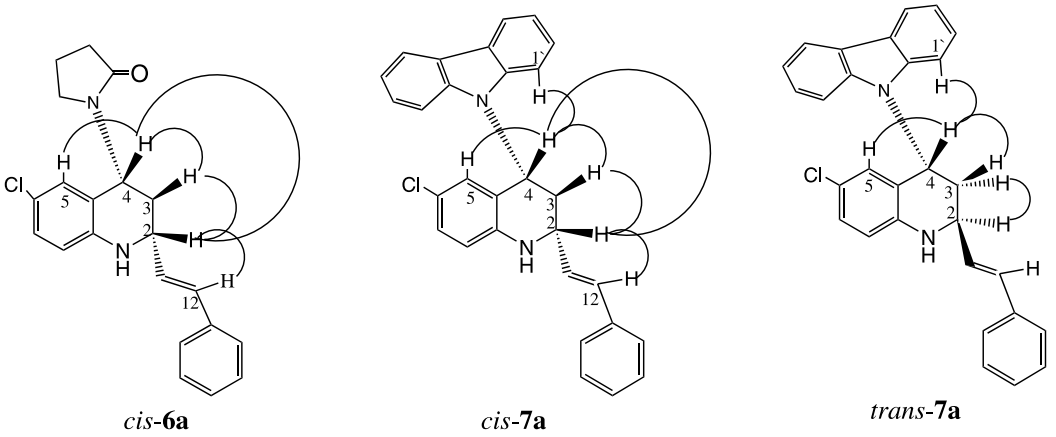
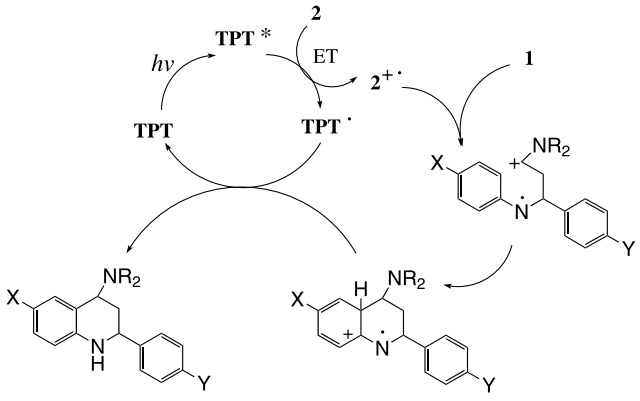


Figure 2. NOESY correlations of the *cis*-**6a**, *cis*-**7a** and *trans*-**7a**.



Scheme 5.

and **6b** were assigned as *cis* configuration. This assignment was further confirmed by the NOESY as depicted in Figure 2. Tetrahydroquinolines **7a** and **7c** showed similar NMR patterns to those of tetrahydroquinoline **4a–f** as mentioned above and the configuration assignments were supported by the NOESY as depicted in Figure 2.

Since no reaction took place between arylimines and **2b** or **2a** in the absence of **TPT** under the same condition for prolonged irradiation, the reaction might be rationalized as a **TPT**-catalyzed non-synchronous cation radical Diels–Alder reaction as shown in Scheme 5. This proposal is supported by separation of **2b** cyclodimer in **TPT**-catalyzed photocycloaddition reaction of arylimines with **2b**, which is the evidence for electron transfer from **2b** to excited electron acceptors and the formation of cation radical of **2b**[10] which usually lead to the formation of cyclodimer of **2b** by reaction with another **2b** (Table 3). **TPT** as reported[10e,f] could also catalyze the formation of cyclodimer and polymer of **2b** by photoinduced electron transfer process. We found these results appeared in photoreactions of both **2b** and **2a** with arylimines catalyzed by **TPT**, indicating the formation of cation radicals of **2b** and **2a**. The low oxidation potential of **2a** ($E^{ox}_{1/2}$ = 1.12 V vs SCE[11]) and **2b** ($E^{ox}_{1/2}$ = 1.30 V vs SCE[12]) relatively to arylimine ($E^{ox}_{1/2}$ = 1.55–1.87 V vs SCE[4b,13]) favores the preferential oxidation of **2b** and **2a** to their corresponding cation radicals by excited-state **TPT** to the oxidation of arylimines. The free energy change, ΔG, for the photoinduced electron transfer between **TPT** and **2b** and **2a** is calculated to be −29.5 and −25.3 Kcal mol^{-1}, respectively, by using the Rehm–Weller equation,[14] demonstrating that the reaction is thermdynamically feasible. Although Electron transfer between excited-state **TPT** and arylimines should be also possible, irradiation of **TPT** and arylimines in the absence of **2b** and **2a** produced nothing but small amounts of aldehydes and amines from decomposition of arylimines.

In conclusion, this work provides a convenient photochemical approach to preparation of 4-(2-oxopyrrolidin-yl)-2-aryltetrahydroquinolines and 4-(carbazol-9-yl)-2-aryltetrahydroquinolines in high yields by 2,4,6-triphenylpyrylium tetrafluoroborate (**TPT**) catalyzed imino Diels–Alder reaction of arylimines with *N*-vinyl-2-pyrrolidinone and *N*-vinylcarbazole under mild conditions.

3. Experimental

Melting points were determined on a Yanagimoto melting point apparatus and uncorrected. Elementary analyses were carried out on a PERKIN–ELMER 2400 II analyzer. ^{1}H and

Table 3. Preparation of 4-(2-oxopyrrolidin-yl)-2-arylvinyltetrahydroquinolines (**6**) and 4-(carbazol-9-yl)-2-arylvinyltetrahydroquinolines (**7**)

Entry	Arylimines			Olefin	*t* (h)	Conv.[a] (%)	Yield (%)[b]	
		X	Y				cis-**6**	**7** (*cis*/*trans*)[c]
1	**5a**	Cl	H	**2a**	8	88	85	
2	**5b**	CH_3O	H	**2a**	8	92	83	
3	**5a**	Cl	H	**2b**	8	95		85 (76:24)
4	**5c**	CH_3O	NO_2	**2b**	4	95		91 (72:28)

[a] Conversion based on **5**.
[b] Isolated yield based on **5**.
[c] Ratio determined by ^{1}H NMR spectra.

^{13}C NMR spectra were recorded on a Bruker AM-400 NMR or a Bruker DRX-300 NMR spectrometers in $CDCl_3$ with TMS as an internal standard. EI-MS were recorded with a HP 5988 A mass spectrometer.

3.1. General procedure for the photochemical reactions

To an anhydrous CH_2Cl_2 solution (50 ml) containing *N*-arylimine (**1**, 2.0 mmol) and *N*-vinylpyrrolidinoe (**2a**, 2.5 mmol), or *N*-vinylcarbazole (**2b**, 2.5 mmol) was added a catalytic amount of 2,4,6-triphenylpyrylium tetrafluoroborate (**TPT**, 8 mg, 0.02 mmol). The mixture was bubbled with argon for half an hour and irradiated with a 250 W high-pressure Hg lamp in a Pyrex bottle with stirring at ambient temperature. After completion of the reaction as monitored by TLC, the solvent was removed under reduced pressure and the products were separated by silica gel column chromatography eluted with hexane/acetone 10:1 (v/v) to afford *cis*-isomers of **3** or mixtures of *cis*- and *trans*-isomers of **4**. The solid was further purified by recrystallization from ethanol to give pure *cis*-isomer of **3a**–**h**. In the case of **4a**, **4e** and **4g**–**j**, further separation and purification were performed by preparative thin layer chromatography to give pure *cis*- and *trans*-isomers which were also recrystallized from ethanol.

3.1.1. *cis*-4-(2-Oxopyrrolidin-1-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline (*cis*-3a). Colorless needles, mp: 142–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.99–2.13 (m, 4H, H-3e, H-3′e, H-4′), 2.42–2.56 (m, 2H, H-3a, H-3′a), 3.19–3.25 (m, 2H, H-5′), 4.02 (br, 1H, N*H*), 4.60 (dd, 1H, J=10.2, 3.3 Hz, H-2), 5.73 (dd, 1H, J=11.1, 6.6 Hz, H-4), 6.58 (d, 1H, J=7.6 Hz, H-8,), 6.72 (t, 1H, J=7.8 Hz, H-6), 6.87 (d, 1H, J=7.8 Hz, H-5), 7.06 (t, 1H, J=7.8 Hz, H-7), 7.28–7.45 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C-4′), 31.4 (C-3′), 35.2 (C-3), 42.3 (C-5′), 48.4 (C-2), 56.3 (C-4), 114.9 (C-8), 118.1 (C-6), 118.8 (C-10), 126.4 (2C, C-12, C-16), 126.7 (C-7), 127.9 (C-5), 128.2 (C-14), 128.7 (2C, C-13, C-15), 143.0 (C-11), 145.9 (C-9), 175.8 (C-2′); MS *m*/*z* 292 (M^+, 77), 263 (17), 235 (14), 206 (100), 130 (77). Anal. Calcd for $C_{19}H_{20}N_2O$: C, 78.05; H, 6.89; N, 9.58. Found: C, 77.82; H, 6.88; N, 9.51%.

3.1.2. *cis*-6-Chloro-4-(2-oxopyrrolidin-1-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline (*cis*-3b). Colorless needles, mp: 175–177 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95–2.17 (m, 4H, H-3e, H-3′e, H-4′), 2.39–2.58 (m, 2H, H-3a, H-3′a), 3.20–3.26 (m, 2H, H-5′), 4.07 (br, 1H, N*H*), 4.57 (dd, 1H, J=10.5, 3.8 Hz, H-2), 5.23 (dd, 1H, J=11.4, 6.3 Hz, H-4), 6.51 (d, 1H, J=8.6 Hz, H-8), 6.82 (d, 1H, J=2.4 Hz, H-5), 7.01 (dd, 1H, J=8.2, 2.4 Hz, H-7), 7.30–7.42 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4 (C-4′), 31.5 (C-3′), 35.1 (C-3), 42.5 (C-5′), 48.5 (C-2), 56.6 (C-4), 116.3 (C-8), 120.7 (C-10), 123.0 (C-6), 126.5 (C-7), 126.7 (2C, C-12, C-16), 128.3 (C-14), 128.5 (C-5), 129.0 (2C, C-13, C-15), 142.8 (C-11), 144.7 (C-9), 176.1 (C-2′); MS *m*/*z* 328 ($M+2^+$, 17), 326 (M^+, 77), 26 (8) 255 (12), 240 (100), 164 (62). Anal. Calcd for $C_{19}H_{19}N_2OCl$: C, 69.83; H, 5.86; N, 8.57. Found: C, 69.67; H, 5.95; N, 8.48.

3.1.3. *cis*-6-Methoxy-4-(2-oxopyrrolidin-1-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline (*cis*-3c). Colorless needles, mp: 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.92–2.16 (m, 4H, H-3e, H-3′e, H-4′), 2.43–2.53 (m, 2H, H-3a, H-3′a), 3.18–3.26 (m, 2H, H-5′), 3.71 (s, 3H, OCH_3), 4.51 (dd, 1H, J=9.6, 3.2 Hz, H-2), 5.70 (dd, 1H, J=10.5, 6.8 Hz, H-4), 6.45 (d, 1H, J=8.8 Hz, H-8,), 6.57 (d, 1H, J=2.8 Hz, H-5), 7.01 (dd, 1H, J=8.8, 2.4 Hz, H-7), 7.27–7.44 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 (C-4′), 31.3 (C-3′), 35.2 (C-3), 42.3 (C-5′), 48.6 (C-2), 55.8 (OCH_3), 56.6 (C-4), 112.1 (C-8), 114.4 (C-7), 116.1 (C-5), 120.1 (C-10), 126.4 (2C, C-12, C-16), 127.8 (C-14), 128.6 (2C, C-13, C-15), 140.1 (C-9), 143.1 (C-11), 152.6 (C-6), 175.7 (C-2′); MS *m*/*z* 322 (M^+, 8), 260 (20), 236 (46), 192 (8), 174 (38), 160 (100). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.33; H, 7.01; N, 8.61.

3.1.4. *cis*-2-(*p*-Chlorophenyl)-6-methyl-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (*cis*-3d). Colorless needles, mp: 163–165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.07 (m, 4H, H-3e, H-3′e, H-4′), 2.22 (s, 3H, CH_3), 2.34–2.58 (m, 2H, H-3a, H-3′a), 3.18–3.24 (m, 2H, H-5′), 3.90 (br, 1H, N*H*), 4.52 (dd, 1H, J=10.2, 3.8 Hz, H-2), 5.68 (dd, 1H, J=11.4, 6.3 Hz, H-4), 6.52 (d, 1H, J=8.4 Hz, H-8), 6.67 (s, 1H, H-5), 6.88 (d, 1H, J=8.2 Hz, H-7), 7.34 (d, 4H, J=8.2 Hz, H-12, H-13, H-14, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (C-4′), 20.9 (*C*H_3), 31.6 (C-3′), 35.7 (C-3), 42.5 (C-5′), 48.6 (C-2), 56.2 (C-4), 115.5 (C-8), 119.1 (C-10), 127.3 (C-7), 128.1 (2C, C-12, C-16), 129.1 (2C, C-13, C-15), 129.2 (C-5), 133.7 (C-6), 141.9 (C-11), 143.6 (C-9), 176.1 (C-2′); MS *m*/*z* 340 (M^+, 7), 254 (61), 244 (18), 158 (38), 144 (100). Anal. Calcd for $C_{20}H_{21}N_2OCl$: C, 70.48; H, 6.21; N, 8.22. Found: C, 70.38; H, 6.30; N, 8.16.

3.1.5. *cis*-6-Methyl-2-(*p*-methoxyphenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (*cis*-3e). Colorless needles, mp: 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.09 (m, 4H, H-3e, H-3′e, H-4′), 2.22 (s, 3H, CH_3), 2.37–2.60 (m, 2H, H-3a, H-3′a), 3.22–3.44 (m, 2H, H-5′), 3.80 (s, 3H, OCH_3), 4.49 (dd, 1H, J=9.8, 3.6 Hz, H-2), 5.68 (dd, 1H, J=10.8, 6.6 Hz, H-4), 6.49 (d, 1H, J=8.0 Hz, H-8), 6.66 (s, 1H, H-5), 6.86 (d, 1H, J=8.0 Hz, H-7), 6.90 (d, 2H, J=8.0 Hz, H-13, H-15), 7.35 (d, 2H, J=8.0 Hz, H-12, H-16); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C-4′), 20.6 (*C*H_3), 31.4 (C-3′), 35.4 (C-3), 42.3 (C-5′), 48.6 (C-2), 55.9 (OCH_3), 57.2 (C-4), 114.0 (2C, C-13, C-15), 115.0 (C-8), 118.8 (C-10), 127.0 (C-7), 127.4 (C-6), 127.5 (2C, C-12, C-16), 129.9 (C-5), 135.2 (C-11), 143.7 (C-9), 159.1 (C-14), 175.8 (C-2′); MS *m*/*z* 336 (M^+, 7), 269 (5), 250 (70), 244 (43), 218 (78), 112 (100). Anal. Calcd for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 74.87; H, 7.12; N, 8.47.

3.1.6. *cis*-2-(*p*-Nitrophenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (*cis*-3f). Yellow needles, mp: 218–220 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.16 (m, 4H, H-3e, H-3′e, H-4′), 2.39–2.56 (m, 2H, H-3a, H-3′a), 3.22 (dd, 2H, J=7.2, 6.9 Hz, H-5′), 4.12 (br, 1H, N*H*), 4.71 (dd, 1H, J=10.5, 3.3 Hz, H-2), 5.72 (dd, 1H, J=11.7, 6.3 Hz, H-4), 6.65 (d, 1H, J=7.6 Hz, H-8), 6.76 (dd, 1H, J=7.6, 7.2 Hz, H-6), 6.88 (d, 1H, J=7.6 Hz, H-5), 7.09 (dd, 1H, J=7.6, 7.2 Hz, H-7), 7.35 (d, 2H, J=8.62 Hz, H-12, H-16), 8.22 (d, 2H, J=8.6 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.4 (C-4′), 31.6 (C-3′), 35.4 (C-3), 42.5 (C-5′), 48.4 (C-2), 56.2 (C-4), 115.6 (C-8), 119.1

(C-10), 119.0 (C-6), 124.3 (2C, C-13, C-15), 127.0 (C-7), 127.6 (2C, C-12, C-16), 128.7 (C-5), 145.5 (C-9), 147.8 (C-11), 150.7 (C-14), 176.2 (C-2′); MS *m*/*z* 337 (M^+,3), 251 (44), 205 (17), 130 (74). Anal. Calcd for $C_{19}H_{19}N_3O_3$: C, 67.64; H, 5.68; N, 12.45. Found: C, 67.77; H, 5.76; N, 12.48.

3.1.7. *cis*-6-Methyl-2-(*p*-nitrophenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (*cis*-3g). Yellow needles, mp: 187–189 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.95–2.16 (m, 4H, H-3e, H-3′e, H-4′), 2.23 (s, 3H, C*H*$_3$), 2.37–2.61 (m, 2H, H-3a, H-3′a), 3.21 (t, 2H, J=7.0 Hz, H-5′), 3.85 (br, 1H, N*H*), 4.68 (dd, 1H, J=10.0, 3.8 Hz, H-2), 5.71 (dd, 1H, J=10.8, 7.0 Hz, H-4), 6.56 (d, 1H, J=8.4 Hz, H-8), 6.76 (s, 1H, H-5), 6.90 (d, 1H, J=8.4 Hz, H-7), 7.63 (d, 2H, J=8.8 Hz, H-12, H-16), 8.23 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C-4′), 20.6 (*C*H$_3$), 31.3 (C-3′), 35.4 (C-3), 42.3 (C-5′), 48.4 (C-2), 56.2 (C-4), 115.5 (C-8), 119.0 (C-10), 124.0 (2C, C-13, C-15), 127.1 (C-7), 127.4 (2C, C-12, C-16), 128.4 (C-6), 129.1 (C-5), 142.9 (C-9), 147.7 (C-11), 150.6 (C-14), 175.9 (C-2′); MS *m*/*z* 351 (M^+, 11), 334 (48), 321 (2), 265 (100), 144 (68). Anal. Calcd for $C_{20}H_{21}N_3O_3$: C, 68.36; H, 6.02; N, 11.95. Found: C, 68.23; H, 6.11; N, 11.87.

3.1.8. *cis*-6-Methoxy-2-(*p*-nitrophenyl)-4-(2-oxopyrrolidin-1-yl)-1,2,3,4-tetrahydroquinoline (*cis*-3h). Yellow needles, mp: 240–242 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97–2.11 (m, 4H, H-3e, H-3′e, H-4′), 2.44–2.55 (m, 2H, H-3a, H-3′a), 3.22 (t, 2H, J=7.0 Hz, H-5′), 3.80 (s, 3H, OC*H*$_3$), 4.65 (dd, 1H, J=9.6, 3.2 Hz, H-2), 5.72 (dd, 1H, J=11.4, 6.8 Hz, H-4), 6.57 (d, 1H, J=8.4 Hz, H-8,), 6.63 (d, 1H, J=2.4 Hz, H-5), 6.72 (dd, 1H, J=8.4, 2.4 Hz, H-7), 7.63 (d, 2H, J=8.6 Hz, H-12, H-16), 8.22 (d, 2H, J=8.6 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.2 (C-4′), 31.3 (C-3′), 35.2 (C-3), 42.3 (C-5′), 48.4 (C-2), 55.8 (O*C*H$_3$), 56.2 (C-4), 112.1 (C-8), 114.5 (C-5), 116.5 (C-7), 112.0 (C-10), 124.0 (2C, C-13, C-15), 127.3 (2C, C-12, C-16), 139.3 (C-9), 147.5 (C-11), 150.5 (C-14), 175.9 (C-2′); MS *m*/*z* 367 (M^+, 3), 260 (29), 174 (52), 160 (100). Anal. Calcd for $C_{20}H_{21}N_3O_4$: C, 65.38; H, 5.76; N, 11.44. Found: C, 65.31; H, 5.84; N, 11.36.

3.1.9. *cis*-4-(Carbazol-9-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline (*cis*-4a). Colorless needles, mp: 196–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (ddd, 1H, J=12.6, 6.3, 2.8 Hz, 1H, H-3e), 2.81 (q, 1H, J=12.6 Hz, H-3a), 4.10 (br 1H, N*H*), 4.74 (dd, 1H, J=11.8, 1.5 Hz, H-2), 6.25 (dd, 1H, J=11.8, 6.2 Hz, H-4), 6.50 (t, 1H, J=7.6 Hz, H-6), 6.64 (d, 1H, J=7.8 Hz, H-5), 6.68 (d, 1H, J=7.8 Hz, H-8), 7.00 (m, 2H, H-7, H-14), 7.09–7.33 (m, 6H, H-1′, H-2′, H-3′, H-7′, H-12, H-16), 7.41–7.50 (m, 4H, H-8′, H-6′, H-13, H-15), 8.08 (t, 2H, J=7.2 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (C-3), 52.0 (C-4), 57.0 (C-2), 108.1 (C-1′), 112.5 (C-8′), 114.9 (C-8), 118.5 (C-6), 118.9 (C-4′); 119.1 (C-5′), 119.6 (C-10), 120.2 (C-3′), 120.4 (C-6′), 123.1 (C-11′), 123.9 (C-12′), 125.3 (C-2′), 125.7, (C-7′), 126.5 (2C, C-12, C-16), 127.7 (C-7), 128.0 (C-14), 127.5 (C-5), 128.7 (2C, C-13, C-15), 138.1 (C-10′), 141.3 (C-13′), 142.5 (C-11), 145.4 (C-9); MS *m*/*z* 374 (M^+, 11), 269 (2) 223 (6), 208 (100), 167 (41), 149 (86). Anal. Calcd for $C_{27}H_{22}N_2$: C, 86.58; H, 5.93; N, 7.48. Found: C, 86.47; H, 6.07; N, 7.56.

3.1.10. *trans*-4-(Carbazol-9-yl)-2-phenyl-1,2,3,4-tetrahydroquinoline (*trans*-4a). Colorless needles, mp: 171–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (ddd, 1H, J=11.7, 10.5, 2.4 Hz, 1H, H-3a), 2.80 (dt, 1H, J=11.7, 3.5 Hz, H-3e), 4.62 (dd, 1H, J=7.5, 3.6 Hz, H-2), 5.76 (t, 1H, J=6.0 Hz, H-4), 6.56 (t, 1H, J=8.2 Hz, H-6), 6.72–6.83 (m, 3H, H-5, H-1′, H-8), 7.08–7.45 (m, 10H, H-7, H-2′, H-3′, H-6′, H-7′, Ph), 7.49 (d, 1H, J=7.6 Hz, H-8′), 8.09 (t, 2H, J=7.8 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (C-3), 52.1 (C-4), 55.3 (C-2), 108.6 (C-1′), 112.4 (C-8′), 113.7 (C-8), 119.1 (C-6), 120.1 (C-10), 120.4 (C-3′), 120.6 (C-6′), 123.3 (C-11′), 124.0 (C-12′), 125.5 (C-2′), 125.9 (C-7′), 126.7 (2C, C-12, H-16), 127.6 (C-7), 128.4 (C-13, H-15), 128.7 (C-14), 129.1 (C-5), 139.6 (C-10′), 140.1 (C-13′), 142.4 (C-11), 146.1 (C-9); MS *m*/*z* 374 (M^+, 10), 312 (1), 279 (3), 223 (3), 208 (100), 167 (28), 149 (75). Anal. Calcd for $C_{27}H_{22}N_2$: C, 86.60; H, 5.92; N, 7.48. Found: C, 86.41; H, 6.17; N, 7.35.

3.1.11. *cis*-4-(Carbazol-9-yl)-2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (*cis*-4i). Colorless needles, mp: 165–166 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (dd, 1H, J=10.2, 6.3 Hz, H-3e), 2.85 (q, 1H, J=12.3 Hz, H-3a), 3.78 (s, 3H, OC*H*$_3$), 4.74 (d, 1H, J=10.5 Hz, H-2), 6.28 (dd, 1H, J=12.3, 6.6 Hz, H-4), 6.54 (t, 1H, J=7.8 Hz, H-6), 6.83 (d, 1H, J=7.8 Hz, H-8), 6.81–6.86 (m, 3H, H-5, H-13, H-15), 6.98 (d, 1H, J=8.4 Hz, H-1′), 7.08 (t, 1H, J=7.5 Hz, H-7), 7.14–7.28 (m, 3H, H-2′, H-3′, H-7′), 7.40 (d, 2H, J=8.6 Hz, H-12, H-16), 7.46–7.56 (m, 2H, H-6′, H-8′), 8.11 (dd, 2H, J=8.1, 7.8 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.4 (C-3), 52.1 (C-4), 55.3 (C-21, O*C*H$_3$) 56.5 (C-2), 108.0 (C-1′), 112.5 (C-8′), 114.0 (2C, C-13, C-15), 114.9 (C-8), 118.0 (C-6), 118.9 (C-5′), 119.1 (C-4′), 119.4 (C-10), 120.2 (C-3′), 120.4 (C-6′), 123.0 (C-11′), 123.8 (C-12′), 125.3 (C-2′), 125.7 (C-7′), 127.3 (C-7), 127.8 (2C, C-12, C-16), 128.5 (C-5), 129.1 (C-6), 133.2 (C-11), 138.2 (C-10′), 140.2 (C-13′), 146.2 (C-9), 158.9 (C-14); MS *m*/*z* 404 (M^+, 14), 238 (100). Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 82.97; H, 6.04; N, 6.85.

3.1.12. *trans*-4-(Carbazol-9-yl)-2-(*p*-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (*trans*-4i). Colorless needles, mp: 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (ddd, 1H, J=12.0, 10.6, 4.7 Hz, H-3a), 2.78 (dt, 1H, J=12.8, 3.3 Hz, H-3e), 3.75 (s, 3H, OC*H*$_3$), 4.46 (dd, 1H, J=7.5, 3.6 Hz, H-2), 5.76 (t, 1H, J=6.0 Hz, H-4), 6.58 (t, 1H, J=7.6 Hz, H-6), 6.67–6.71 (m, 2H, H-5, H-8), 6.81–6.86 (m, 3H, H-13, H-15, H-1′), 7.05–7.45 (m, 6H, H-7, H-12, H-16, H-2′, H-3′, H-7′), 7.50 (m, 2H, H-8′, H-6′), 8.11 (t, 2H, J=7.8 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 36.3 (C-3), 49.9 (C-4), 53.5 (C-2), 55.3 (C-21, O*C*H$_3$) 110.8 (C-1′), 112.5 (C-8′), 114.1 (2C, C-13, H-15), 114.8 (C-8), 118.1 (C-10), 119.1 (C-3′), 119.3 (C-6′), 120.4 (C-4′), 120.7 (C-5′), 123.4 (C-11′), 124.1 (C-12′), 125.6 (C-2′), 125.8 (C-7′), 127.6 (2C, C-12, H-16), 129.1 (C-6), 130.0 (C-7), 130.2 (C-5), 131.2 (C-11), 139.6 (C-10′), 141.1 (C-13′), 142.8 (C-9), 158.9 (C-14); MS *m*/*z* 404 (M^+, 11), 368 (3), 269 (2), 238 (100). Anal. Calcd for $C_{28}H_{24}N_2O$: C, 83.14; H, 5.98; N, 6.93. Found: C, 82.86; H, 6.11; N, 6.78.

3.1.13. *cis*-4-(Carbazol-9-yl)-2-(*p*-methoxyphenyl)-6-methyl-1,2,3,4-tetrahydroquinoline (*cis*-4e). Colorless needles, mp: 133–135 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.97 (s, 3H, C*H*$_3$), 2.29 (dd, 1H, J=12.8, 6.3 Hz, H-3e), 2.80 (q, 1H, J=11.7 Hz, H-3a), 3.75 (s, 3H, OC*H*$_3$), 4.67 (d,

1H, J=11.7 Hz, H-2), 6.48 (dd, 1H, J=11.7, 6.6 Hz, H-4), 6.56 (s, 1H, H-5), 6.59 (d, 1H, J=8.2 Hz, H-8), 6.70–6.86 (m, 3H, H-13, H-15, H-1′), 7.01 (d, 1H, J=8.2 Hz, H-7), 7.13–7.34 (m, 2H, H-1′, H-7′), 7.36 (d, 2H, J=8.6 Hz, H-12, H-16), 7.46–7.55 (m, 2H, H-6′, H-8′), 8.11 (dd, 2H, J=8.4, 7.8 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (CH_3), 35.9 (C-3), 52.4 (C-4), 55.5 (OCH_3), 56.9 (C-2), 108.2 (C-1′), 112.8 (C-8′), 114.3 (2C, C-13, C-15), 115.3 (C-8), 119.1 (C-3′); 119.3 (C-6′), 120.0 (C-10), 120.4 (C-4′), 120.6 (C-5′), 123.4 (C-11′), 124.1 (C-12′), 125.6 (C-2′), 125.9 (C-7′), 128.0 (2C, C-12, C-16), 128.2 (C-7), 129.1 (C-6), 129.5 (C-5), 135.1 (C-11), 138.5 (C-10′), 141.6 (C-13′), 143.5 (C-9), 159.6 (C-14); MS m/z 418 (M^+, 9), 252 (100). Anal. Calcd for $C_{29}H_{26}N_2O$: C, 83.22; H, 6.26; N, 6.69. Found: C, 83.17; H, 6.40; N, 6.43.

3.1.14. *trans*-4-(Carbazol-9-yl)-2-(*p*-methoxyphenyl)-6-methyl-1,2,3,4-tetrahydroquinoline (*trans*-4e). Colorless needles, mp: 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H, CH_3), 2.27 (ddd, 1H, J=13.5, 11.7, 3.6 Hz, H-3a), 2.69 (dt, 1H, J=13.5, 3.9 Hz, H-3e), 3.76 (s, 3H, OCH_3), 4.53 (dd, 1H, J=7.8, 3.3 Hz, H-2), 5.74 (t, 1H, J=5.7 Hz, H-4), 6.67 (s, 1H, H-5), 6.69 (d, 1H, J=7.8 Hz, H-8), 6.81–6.85 (m, 3H, H-7, H-12, H-16), 6.98 (d, 1H, J=8.0 Hz, H-7), 7.12–7.31 (m, 5H, H-13, H-15, H-2′, H-3′, H-7′), 7.37 (d, 2H, J=7.6 Hz, H-6′, H-8′), 8.09 (m, 2H, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.7 (CH_3), 36.2 (C-3), 50.0 (C-4), 53.2 (C-2), 55.6 (OCH_3), 108.6 (C-1′), 112.4 (C-8′), 114.3 (2C, C-13, C-15), 114.8 (C-8), 118.1 (C-10), 119.1 (C-3′), 119.3 (C-6′), 120.4 (C-4′), 120.7 (C-5′), 123.4 (C-11′), 124.1 (C-12′), 125.6 (C-2′), 125.8, (C-7′), 127.6 (2C, C-12, C-16), 129.1 (C-6), 130.0 (C-7), 130.2 (C-5), 131.2 (C-11), 139.6 (C-10′), 141.1 (C-13′), 142.8 (C-9), 158.9 (C-14); MS m/z 418 (M^+, 7), 252 (100). Anal. Calcd for $C_{29}H_{26}N_2O$: C, 83.22; H, 6.26; N, 6.69. Found: C, 83.11; H, 6.32; N, 6.57.

3.1.15. *cis*-4-(Carbazol-9-yl)-6-chloro-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*cis*-4j). Yellow needles, mp: 162–164 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.29 (ddd, 1H, J=16.5, 10.5, 4.8 Hz, H-3e), 2.85 (q, 1H, J=11.7 Hz, H-3a), 4.86 (d, 1H, J=11.7 Hz, H-2), 6.22 (dd, 1H, J=11.7, 6.3 Hz, H-4), 6.68 (d, 1H, J=8.0 Hz, H-8), 6.73 (s, 1H, H-5), 6.87 (d, 1H, J=8.0 Hz, H-1′), 7.07 (d, 1H, J=8.8 Hz, H-7), 7.17–7.32 (m, 3H, H-2′, H-3′, H-7′), 7.39 (d, 2H, J=4.5 Hz, H-8′, H-6′), 7.64 (d, 2H, J=8.8 Hz, H-12, H-16), 8.11 (dd, 2H, J=7.8, 7.6 Hz, H-4′, H-5′), 8.18 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.0 (C-3), 51.4 (C-4), 56.5 (C-2), 107.9 (C-1′), 112.0 (C-8′), 116.5 (C-8), 119.3 (C-3′), 119.5 (C-6′), 120.4 (C-4′), 120.5 (C-5′), 121.2 (C-10), 123.2 (C-11′), 124.0 (C-12′), 124.0 (2C, C-13, C-15), 125.5 (C-2′), 125.9 (C-7′), 127.2 (C-7), 127.4 (2C, C-12, C-16), 128.8 (C-5), 137.7 (C-10′), 141.0 (C-13′), 143.3 (C-9), 147.6 (C-14), 149.4 (C-11); MS m/z 455 (M^++2, 3), 453 (M^+, 9), 287 (30), 167 (100), 105 (83). Anal. Calcd for $C_{27}H_{20}N_3O_2Cl$: C, 71.44; H, 4.44; N, 9.26. Found: C, 71.43; H, 4.45; N, 9.26. Found: C, 71.32; H, 4.51; N, 9.18.

3.1.16. *trans*-4-(Carbazol-9-yl)-6-chloro-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*trans*-4j). Yellow needles, mp: 125–127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (ddd, 1H, J=11.7, 10.5, 2.8 Hz, H-3a), 2.67 (dt, 1H, J=11.7, 3.6 Hz, H-3e), 4.72 (dd, 1H, J=7.8, 3.9 Hz, H-2), 5.68 (t, 1H, J=5.7 Hz, H-4), 6.73 (s, 1H, H-5), 6.79 (d, 1H, J=8.0 Hz, H-8), 7.05 (d, 1H, J=8.8 Hz, H-7), 7.12–7.40 (m, 5H, H-1′, H-2′, H-3′, H-6′, H-7′), 7.51 (d, 1H, J=4.5 Hz, H-8′), 7.65 (d, 2H, J=8.8 Hz, H-12, H-16), 8.12 (dd, 2H, J=7.8, 7.6 Hz, H-4′, H-5′), 8.19 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.9 (C-3), 49.5 (C-4), 53.3 (C-2), 108.3 (C-1′), 111.6 (C-8′), 118.6 (C-8), 119.3 (C-3′); 119.5 (C-6′), 119.2 (C-10), 120.5 (C-4′), 120.7 (C-5′), 123.2 (C-11′), 124.0 (C-12′), 124.0 (2C, C-13, C-15), 125.5 (C-2′), 125.8 (C-7′), 127.2 (C-6), 127.4 (2C, C-12, C-16), 128.7 (C-5), 131.2 (C-7), 138.2 (C-10′), 141.3 (C-13′), 142.5 (C-9), 147.8 (C-14), 148.8 (C-11); MS m/z 455 (M^++2, 5), 453 (M^+, 12), 287 (25), 167 (100), 105 (78). Anal. Calcd for $C_{27}H_{20}N_3O_2Cl$: C, 71.44; H, 4.44; N, 9.26. Found: C, 71.32; H, 4.51; N, 9.18.

3.1.17. *cis*-4-(Carbazol-9-yl)-6-methyl-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*cis*-4g). Yellow needles, mp: 157–159 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.00 (s, 3H, CH_3), 2.29 (ddd, 1H, J=13.2, 6.4, 2.0 Hz, H-3e), 2.76 (q, 1H, J=12.4 Hz, H-3a), 4.86 (d, 1H, J=11.6 Hz, H-2), 6.27 (dd, 1H, J=11.6, 6.4 Hz, H-4), 6.60 (s, 1H, H-5), 6.68 (d, 1H, J=8.0 Hz, H-8), 6.93–6.97 (t, 2H, J=7.2 Hz, H-7, H-1′), 7.23 (t, 1H, J=7.8 Hz, H-3′), 7.26–7.29 (m, 2H, H-2′, H-7′), 7.49–7.56 (m, 2H, H-8′, H-6′), 7.67 (d, 2H, J=8.8 Hz, H-12, H-16), 8.09 (d, 1H, J=8.0 Hz, H-4′), 8.13 (d, 1H, J=8.0 Hz, H-5′), 8.18 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.4 (CH_3), 35.7 (C-3), 51.7 (C-4), 56.8 (C-2), 108.0 (C-1′), 112.3 (C-8′), 115.4 (C-8), 119.0 (C-3′), 119.2 (C-6′), 120.3 (C-10), 120.2 (C-4′), 120.4 (C-5′), 123.2 (C-11′), 124.0 (C-12′), 124.0 (2C, C-13, C-15), 125.4 (C-2′), 125.7 (C-7′), 127.4 (2C, C-12, C-16), 127.9 (C-7), 128.7 (C-6), 129.4 (C-5), 138.0 (C-10′), 141.2 (C-13′), 142.4 (C-9), 147.5 (C-14), 150.1 (C-11); MS m/z 433 (M^+, 8), 267 (100), 221 (18), 167 (17). Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.35; N, 9.69. Found: C, 77.64; H, 5.58; N, 9.75.

3.1.18. *trans*-4-(Carbazol-9-yl)-6-methyl-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*trans*-4g). Yellow needles, mp: 147–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.08 (s, 3H, CH_3), 2.29 (ddd, 1H, J=12.0, 10.5, 3.3 Hz, H-3a), 2.84 (dt, 1H, J=12.3, 3.6 Hz, H-3e), 4.44 (br, 1H, NH), 4.74 (dd, 1H, J=7.8, 4.2 Hz, H-2), 5.71 (t, 1H, J=5.4 Hz, H-4), 6.71 (s, 1H, H-5), 6.78 (d, 1H, J=8.2 Hz, H-8), 7.05 (d, 3H, J=8.8 Hz, H-7, H-1′, H-3′), 7.12–7.37 (m, 4H, H-2′, H-6′, H-7′, H-8′), 7.51 (d, 2H, J=8.6 Hz, H-12, H-16), 8.17 (dd, 2H, J=8.1, 7.8 Hz, H-4′, H-5′), 8.19 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3 (CH_3), 35.4 (C-3), 49.2 (C-4), 53.3 (C-2), 108.4 (C-1′), 112.0 (C-8′), 114.7 (C-8), 117.8 (C-10), 119.1 (C-3′), 119.3 (C-6′), 120.3 (C-4′), 120.5 (C-5′), 123.5 (C-11′), 124.0 (2C, C-13, C-15), 125.5 (C-2′), 125.7 (C-7′), 127.2 (2C, C-12, C-16), 127.9 (C-6), 129.6 (C-7), 130.2 (C-5), 139.6 (C-10′), 141.6 (C-13′), 141.8 (C-9), 147.4 (C-14), 151.3 (C-11); MS m/z 433 (M^+, 11), 267 (100), 221 (23), 167 (19). Anal. Calcd for $C_{28}H_{23}N_3O_2$: C, 77.58; H, 5.36; N, 9.69. Found: C, 77.44; H, 5.48; N, 9.55.

3.1.19. *cis*-4-(Carbazol-9-yl)-6-methoxy-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*cis*-4h). Yellow needles, mp: 172–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (ddd, 1H, J=12.9, 6.6, 2.4 Hz, H-3e), 2.74 (q, 1H, J=12.0 Hz, H-3a), 3.46 (s, 3H, OCH_3), 4.84 (dd, 1H, J=11.3, 2.4 Hz, H-2), 6.28 (dd, 1H, J=11.7, 6.6 Hz, H-4), 6.36 (s, 1H, H-5), 6.61 (d, 1H, J=8.2 Hz, H-8), 6.75 (d, 1H, J=

7.6 Hz, H-7), 6.97 (d, 1H, J=7.6 Hz, H-1′), 7.18–7.31 (m, 3H, H-2′, H-3′, H-7′), 7.48–7.54 (m, 2H, H-6′, H-8′), 7.67 (d, 2H, J=8.4 Hz, H-12, H-16), 8.09 (d, 1H, J=7.8 Hz, H-4′), 8.13 (d, 1H, J=7.8 Hz, H-5′), 8.18 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.6 (C-3), 51.8 (C-4), 55.6 (O*C*H$_3$), 56.9 (C-2), 108.0 (C-1′), 112.3 (C-8′), 112.5 (C-8), 115.3 (C-7), 116.6 (C-5), 119.1 (C-3′), 119.3 (C-6′), 120.3 (C-4′), 120.5 (C-5′), 123.3 (C-10), 123.7 (C-12′), 124.0 (2C, C-13, C-15), 125.4 (C-2′), 125.7 (C-7′), 127.5 (2C, C-12, C-16), 138.0 (C-10′), 138.7 (C-9), 141.5 (C-13′), 147.5 (C-14), 150.1 (C-11), 153.3 (C-6); MS m/z 449 (M^+, 26), 419 (9), 283 (100), 253 (21), 237 (22), 167 (36). Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.69; H, 5.35; N, 9.41.

3.1.20. *trans*-4-(Carbazol-9-yl)-6-methoxy-2-(*p*-nitrophenyl)-1,2,3,4-tetrahydroquinoline (*trans*-4h). Yellow needles, mp: 146–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (dd, 1H, J=11.7, 10.8 Hz, H-3e), 2.67 (dt, 1H, J=13.2, 3.6 Hz, H-3a), 3.50 (s, 3H, OC*H*$_3$), 4.70 (dd, 1H, J=7.8, 4.0 Hz, H-2), 5.70 (t, 1H, J=6.0 Hz, H-4), 6.47 (d, 1H, J=2.8 Hz, H-5), 6.54 (d, 1H, J=8.2 Hz, H-8), 6.77 (dd, 1H, J=8.2, 2.8 Hz, H-7), 7.15–7.31 (m, 3H, H-1′, H-3′,H-6′), 7.39–7.44 (m, 2H, H-2′, H-7′), 7.50 (d, 1H, J=7.6 Hz, H-8′), 7.65 (d, 2H, J=8.4 Hz, H-12, H-16), 8.13 (dd, 2H, J=8.2, 7.8 Hz, H-4′, H-5′), 8.19 (d, 2H, J=8.8 Hz, H-13, H-15); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5 (C-3), 49.8 (C-4), 53.3 (C-2), 55.6 (O*C*H$_3$), 109.1 (C-1′), 111.9 (C-8′), 113.6 (C-8), 116.0 (C-5), 117.0 (C-7), 119.1 (C-3′); 119.3 (C-6′), 120.3 (C-4′), 120.5 (C-5′), 121.5 (C-10), 123.7 (C-11′, C-12′), 124.1 (2C, C-13, C-15), 125.4 (C-2′), 125.7 (C-7′), 127.5 (2C, C-12, C-16), 139.2 (C-9), 141.5 (C-13′), 147.9 (C-14), 149.6 (C-11), 152.8 (C-6); MS m/z 449 (M^+, 18), 419 (6), 283 (100), 253 (28), 167 (46). Anal. Calcd for $C_{28}H_{23}N_3O_3$: C, 74.82; H, 5.16; N, 9.35. Found: C, 74.71; H, 5.28; N, 9.18.

3.1.21. *cis*-6-Chloro-4-(2-oxopyrrolidin-1-yl)-2-(2-phenylvinyl)-1,2,3,4-tetrahydroquinoline (*cis*-6a). Colorless needles, mp: 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.82–2.10 (m, 4H, H-3e, H-3′e, H-4′), 2.31–2.41 (q, 1H, J=10.2 Hz, H-3a), 2.50 (dt, 1H, J=8.0, 3.8 Hz, H-3′a), 3.12–3.26 (m, 2H, H-5′), 4.39 (ddd, 1H, J=11.4, 6.4, 2.2 Hz, H-2), 5.56 (dd, 1H, J=11.6, 6.6 Hz, H-4), 6.17 (dd, 1H, J=15.6, 6.4 Hz, H-11), 6.51 (d, 1H, J=8.4 Hz, H-8), 6.63 (d, 1H, J=15.6 Hz, H-12), 6.78 (d, 1H, J=2.4 Hz, H-5), 6.98 (d, 1H, J=8.6 Hz, H-7), 7.10 (t, 1H, J=8.0 Hz, H-16), 7.25–7.40 (m, 4H, H-14, H-15, H-17, H-18); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.0 (C-4′), 31.1 (C-3′), 35.1 (C-3), 42.1 (C-5′), 47.5 (C-2), 55.9 (C-4), 116.0 (C-8), 120.2 (C-10), 122.3 (C-6), 126.3 (2C, C-14, C-18), 127.8 (16), 128.5 (C-7), 128.9 (2C, C-15, C-17), 130.1 (C-5), 131.3 (C-12), 136.1 (C-13), 143.7 (C-9), 175.7 (C-2′); MS m/z 352 (M^+, 2), 266 (3), 238 (4), 154 (5), 112 (100). Anal. Calcd for $C_{21}H_{21}N_2OCl$: C, 71.48; H, 6.00; N, 7.94. Found: C, 71.38; H, 6.06; N, 8.08.

3.1.22. *cis*-6-Methoxy-4-(2-oxopyrrolidin-1-yl)-2-(2-phenylvinyl)-1,2,3,4-tetrahydroquinoline (*cis*-6b). Colorless needles, mp: 153–155 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.87–2.15 (m, 4H, H-3e, H-3′e, H-4′), 2.47–2.54 (m, 2H, H-3a, H-3′a), 3.16–3.28 (m, 2H, H-5′), 3.71 (s, 3H, OC*H*$_3$), 4.51 (ddd, 1H, J=11.0, 6.8, 2.7 Hz, H-2), 5.70 (dd, 1H, J=11.1, 6.9 Hz, H-4), 6.22 (dd, 1H, J=15.6, 6.8 Hz, H-11), 6.45 (d, 1H, J=8.2 Hz, H-8,), 6.55 (d, 1H, J=15.6 Hz, H-12), 6.62 (d, 1H, J=2.7 Hz, H-5), 6.68 (dd, 1H, J=8.8, 2.7 Hz, H-7), 7.25–7.40 (m, 5H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.5 (C-4′), 31.6 (C-3′), 33.0 (C-3), 42.6 (C-5′), 48.3 (C-2), 54.7 (O*C*H$_3$), 56.1 (C-4), 112.4 (C-8), 114.7 (C-7), 116.5 (C-5), 120.7 (C-10), 126.7 (2C, 15, C-17), 128.0 (16), 128.9 (2C, C-14, C-18), 131.0 (C-11), 131.3 (C-12), 136.7 (C-13), 139.7 (C-9), 152.9 (C-6), 176.1 (C-2′); MS m/z 348 (M^+, 15), 262 (100), 260 (85), 160 (82). Anal. Calcd for $C_{22}H_{24}N_2O_2$: C, 75.83; H, 6.94; N, 8.04. Found: C, 75.52; H, 7.13; N, 8.07.

3.1.23. *cis*-4-(Carbazol-9-yl)-6-chloro-2-(2-phenylvinyl)-1,2,3,4-tetrahydroquinoline (*cis*-7a). Colorless needles, mp: 161–163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.17 (ddd, 1H, J=12.4, 5.6, 2.0 Hz, H-3e), 2.63 (q, 1H, J=12.4 Hz, H-3a), 4.30 (ddd, 1H, J=11.2, 8.0, 2.0 Hz, H-2), 6.09 (dd, 1H, J=11.4, 6.6 Hz, H-4), 6.18 (dd, 1H, J=16.0, 7.8 Hz, H-11), 6.59 (d, 1H, J=8.4 Hz, H-8), 6.65 (d, 1H, J=15.6 Hz, H-12), 6.67 (s, 1H, H-5), 6.96 (d, 1H, J=8.2 Hz, H-1′), 7.01 (dd, 1H, J=8.4, 2.0 Hz, H-7), 7.17–7.44 (m, 8H, H-2′, H-3′, H-7′, Ph), 7.51 (m, 2H, H-6′, H-8′), 8.10 (d, 1H, J=8.0 Hz, H-4′), 8.14 (d, 1H, J=8.0 Hz, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.8 (C-3), 51.1 (C-4), 54.8 (C-2), 108.0 (C-1′), 112.3 (C-8′), 116.0 (C-8), 119.2 (C-3′), 119.4 (C-6′), 120.3 (C-4′), 120.5 (C-5′), 121.1 (C-10), 123.1 (C-6), 123.2 (C-11′), 124.0 (C-12′), 125.4 (C-2′), 126.4 (2C, C-14, C-18), 127.2 (C-5), 128.0 (16), 128.5 (C-7), 128.6 (2C, C-15, C-17), 129.9 (C-11), 131.8 (C-12), 136.3 (C-13), 137.9 (C-10′), 141.0 (C-13′), 143.3 (C-9). MS m/z 436 (M^++2, 3), 434 (M^+, 9), 268 (100). Anal. Calcd for $C_{29}H_{23}N_2Cl$: C, 80.08; H, 5.33; N, 6.44. Found: C, 79.82; H, 5.46; N, 6.32.

3.1.24. *trans*-4-(Carbazol-9-yl)-6-chloro-2-(phenylvinyl)-1,2,3,4-tetrahydroquinoline (*trans*-7a). Colorless needles, mp: 147–149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.14 (dt, 1H, J=12.9, 6.0 Hz, H-3a), 2.74 (ddd, 1H, J=12.9, 8.7, 4.8 Hz, H-3e), 4.22 (dd, 1H, J=7.5, 6.0 Hz, H-2), 5.89 (dd, 1H, J=8.4, 6.0 Hz, H-4), 6.31 (dd, 1H, J=15.9, 6.6 Hz, H-11), 6.54 (d, 1H, J=15.9 Hz, H-12), 6.60 (d, 2H, J=8.7 Hz, H-8, H-1′), 6.68 (d, 1H, J=8.7 Hz, H-7), 6.79 (d, 1H, J=2.4 Hz, H-5), 7.07–7.11 (m, 3H, H-14, H-18, H-3′), 7.20–7.41 (m, 8H, H-2′, H-6′, H-7′, Ph), 7.44 (b, 1H, H-8′), 8.11 (t, 2H, J=8.0 Hz, H-4′, H-5′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.2 (C-3), 48.9 (C-4), 51.8 (C-2), 108.4 (C-1′), 112.5 (C-8′), 115.8 (C-8), 116.3 (2C, C-15, C-17), 119.3 (C-3′), 119.4 (C-6′), 119.7 (C-10), 120.4 (2C, C-4′,C-5′), 122.5 (C-6), 123.4 (C-11′), 123.8 (C-12′), 125.4 (C-2′), 126.5 (C-5), 128.5 (16), 128.7 (C-7), 129.2 (2C, C-14, C-18), 130.2 (C-11), 131.5 (C-12), 136.5 (C-13), 138.2 (C-10′), 140.1 (C-13′), 142.8 (C-9). MS m/z 436 (M^++2, 2), 434 (M^+, 5), 346 (7), 268 (61), 194 (22), 194 (100). Anal. Calcd for $C_{29}H_{23}N_2Cl$: C, 80.08; H, 5.33; N, 6.44. Found: C, 79.82; H, 5.47; N, 6.35.

3.1.25. *cis*-4-(Carbazol-9-yl)-6-methoxy-2-(*p*-nitrophenylvinyl)-1,2,3,4-tetrahydroquinoline (*cis*-7b). Yellow needles, mp: 182–183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.25 (ddd, 1H, J=12.7, 5.6, 2.4 Hz, H-3e), 2.64 (q, 1H, J=11.7 Hz, H-3a), 3.46 (s, 3H, OC*H*$_3$), 4.32 (ddd, 1H, J=10.5, 6.0, 2.4 Hz, H-2), 6.20 (dd, 1H, J=11.7, 6.6 Hz, H-4), 6.37 (s, 1H, H-5), 6.39 (dd, 1H, J=15.6, 7.6 Hz, H-11), 6.53 (dd, 1H, J=7.6, 2.8 Hz, H-7), 6.60–6.78

(m, 2H, H-8, H-12), 6.98 (d, 1H, J=7.8 Hz, H-1′), 7.23 (t, 2H, J=7.8 Hz, H-2′, H-3′), 7.33 (t, 1H, J=7.8 Hz, H-7′), 7.41 (d, 2H, J=8.8 Hz, H-14, H-18), 7.56 (m, 2H, H-6′, H-8′), 8.12–8.19 (m, 4H, H-4′, H-5′, H-15, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.9 (C-3), 51.3 (C-4), 54.6 (O*C*H$_3$), 55.5 (C-2), 108.0 (C-1′), 112.3 (C-8′), 112.4 (C-8), 115.0 (C-7), 116.3 (C-5), 118.8 (C-3′), 119.1 (C-6′), 120.2 (C-4′), 120.4 (C-5′), 120.7 (C-10), 123.1 (C-11′), 123.8 (C-12′), 123.9 (2C, C-15, C-17), 125.3 (C-2′), 125.7 (C-7′), 126.7 (2C, C-14, C-18), 128.7 (C-11), 135.4 (C-12), 138.0 (C-9), 138.5 (C-10′), 141.2 (C-13′), 142.8 (C-9), 146.8 (C-16), 152.9 (C-6); MS m/z 475 (M^+, 4), 445 (2), 305 (30), 259 (14), 167 (100). Anal. Calcd for $C_{30}H_{25}N_3O_3$: C, 75.77; H, 5.30; N, 8.84. Found: C, 75.65; H, 5.39; N, 8.73.

3.1.26. *trans*-4-(Carbazol-9-yl)-6-methoxy-2-(*p*-nitrophenylvinyl)-1,2,3,4-tetrahydroquinoline (*trans*-7b). Yellow needles, mp 156–158 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (dd, 1H, J=8.2, 5.6 Hz, H-3e), 2.71 (dt, 1H, J=11.7, 6.6 Hz, H-3a), 3.50 (s, 3H, OC*H*$_3$), 4.19 (dd, 1H, J=7.5, 5.6 Hz, H-2), 5.96 (t, 1H, J=6.3 Hz, H-4), 6.45 (dd, 1H, J=15.6, 7.6 Hz, H-11), 6.53 (d, 1H, J=2.8 Hz, H-5), 6.59 (dd, 1H, J=7.6, 2.8 Hz, H-7), 6.65–6.80 (m, 2H, H-8, H-12), 6.86 (d, 1H, J=7.8 Hz, H-1′), 7.19–7.35 (m, 4H, H-2′, H-3′, H-6′, H-7′), 7.42 (d, 2H, J=8.6 Hz, H-14, H-18), 7.54 (b, 1H, H-8′), 8.15–8.22 (m, 4H, H-4′, 5′, H-15, H-17). ^{13}C NMR (75 MHz, $CDCl_3$) δ 32.3 (C-3), 49.5 (C-4), 51.6 (C-2), 55.5 (O*C*H$_3$), 108.3 (C-1′), 112.2 (C-8′), 113.5 (C-8), 116.0 (C-7), 116.4 (C-5), 118.7 (C-10), 119.1 (C-3′), 119.2 (C-6′), 120.3 (C-4′), 120.4 (C-5′), 123.2 (C-11′), 123.8 (2C, C-15, C-17), 125.4 (C-2′), 125.6 (C-7′), 126.8 (2C, C-14, C-18), 128.8 (C-11), 135.7 (C-12), 138.4 (C-9), 139.6 (C-10′), 140.8 (C-13′), 143.0 (C-9), 146.9 (C-16), 152.3 (C-6); MS m/z 475 (M^+, 2), 305 (27), 259 (36), 167 (100). Anal. Calcd for $C_{30}H_{25}N_3O_3$: C, 75.77; H, 5.30; N, 8.84. Found: C, 75.58; H, 5.52; N, 8.68.

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Studies on the diastereoselective reductive alkylation of (*R*)-phenylglycinol derived phthalimide: observation of stereoelectronic effects

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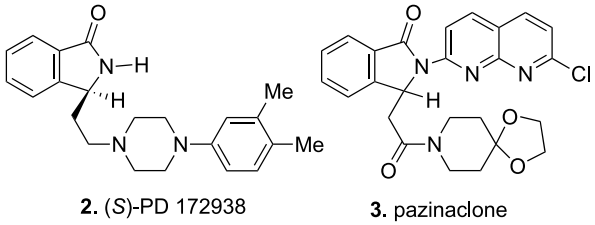
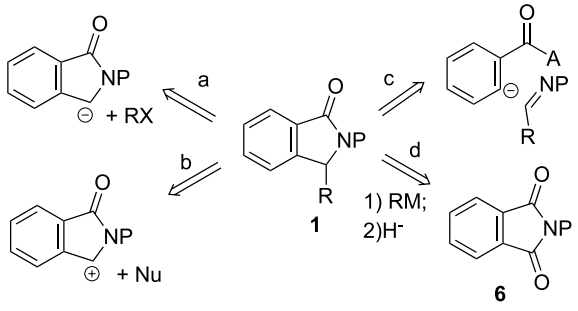
Abstract—Full details of a flexible approach to *N*-protected (*R*)-3-alkyl-isoindolin-1-ones **13** via diastereoselective reductive-alkylation are described, with emphasis on the stereochemical outcome of the key diastereoselective reactions. Additional experiments allowed finding remarkable stereoelectronic effects on the reductive ring-opening reactions.

1. Introduction

3-Substituted isoindolin-1-one (2,3-dihydro-1*H*-isoindolin-1-one) is a key structural feature found in many pharmaceutically interesting molecules and natural products. For example, PD-172938 (*S*-**2**) was shown to have affinity for the dopamine D_4 receptor;[1] pazinaclone **3** is an anxiolytic drug candidate;[2] (*S*)-pagoclone **4** is a licensed compound under development for the treatment of general anxiety disorder and panic disorder[3] and chlorthalidone **5** is a diuretic and antihypertensive drug.[4] while lennoxamine,[5] nuevamine, and chilenine are alkaloids isolated from various barberry species. Moreover, (*R*) and (*S*)-3-methyl-1*H*-isodindolin-1-ones have been shown to be valuable chiral auxiliaries.[6] Consequently, the chemistry of 3-alkyl-isoindolin-1-ones has attracted much attention, and a number of synthetic methods have been developed.[1,3,5–13] Among them, the most flexible and straightforward ones are those where the alkyl groups at the C-3 position are introduced directly. This has been achieved either by the reaction of 3-metalated isoindolin-1-ones with electrophiles (Scheme 1, path a);[9] by the reaction of an *N*-acyliminium equivalent with nucleophiles (path b);[10] by the reaction of methyl *o*-lithiobenzoate to imines (path c);[11] or by organometallic reagents addition to phthalimide followed





Scheme 1.

Keywords: Isoindolin-1-one; Phenylglycinol; Reductive alkylation; Diastereoselective reaction; Stereoelectronic effects.
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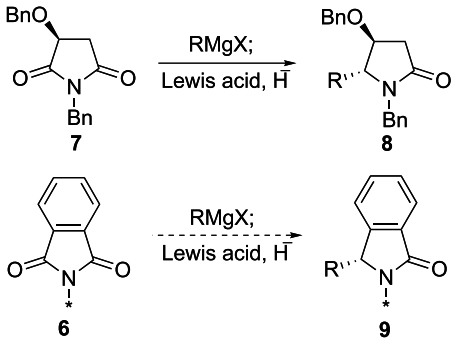
by reductive deoxygenation (path d).[12,13] However, few flexible methods are available for the asymmetric synthesis of simple 3-alkyl-isoindolin-1-ones in high enantiomeric excess.[6,8,9c,10,12d] Accordingly, development of flexible method for the asymmetric synthesis of 3-alkyl-isoindolin-1-ones is highly desirable. In a previous communication,[13a] we reported a flexible approach to *N*-protected optically active 3-alkyl-isoindolin-1-ones. Herein, we provide a complete account of our work in this area as well as the studies undertaken to gain an insight into the stereochemical outcome of the key reactions.

2. Results and discussion

In recent years, we have been engaged in the development of a synthetic methodology based on the highly regio- and diastereo-selective reductive alkylation of (*S*)-malimide (Scheme 2, **7**→**8**).[14] As an extension of this work, we began, in 1998, to explore the similar reductive alkylation for a flexible approach to optically active 3-alkyl-isoindolin-1-ones (**6**→**9**).[15,16] Central to our approach was the asymmetric induction. For this purpose, (*R*)-phenylglycinol[17] was selected as the chiral auxiliary, which was expected to display an exo-cyclic 1,3-asymmetric induction.



Scheme 2.

Thus, the requisite (*R*)-phthalimide derivative **11** was prepared by heating a mixture of phthalic anhydride and (*R*)-phenylglycinol under solvent free conditions.[18] Treatment of the phthalimide derivative (*R*)-**11** with an excess of methyl magnesium iodide yielded diastereomeric *N*,*O*-acetal **12a** (R=Me), which was subjected to boron trifluoride etherate mediated triethylsilane reduction[14,19] to afford **13a** as the major diastereomer. The diastereomeric ratio of **13a/14a** was 87:13 according to the chromatographic separation. Extension of this procedure to other Grignard reagents (RMgX, b: R=Et, c: *n*-Bu, d: *i*-Bu, e: *n*-C_7H_{15}, f: Bn, g: Ph) led to the corresponding products **13b**–**13g** and **14b**–**14g** in diastereoselectivities ranged from 71:29 to 91:9. The stereochemistries of the major diastereomers **13** were determined by single-crystal X-ray crystallographic analysis of compounds (3*R*,1′*R*)-**13c**[13a] and (3*R*,1′*R*)-**13g** (Fig. 1). The stereochemistries of the major diastereomers **13a**, **13b** and **13d**–**13f** were ascertained by comparing the spectroscopic data with those of **13c** and **13g**, and were shown in the general structure **13**.

To improve the diastereoselectivity of the reductive alkylation, a modified approach using tricyclic lactams[7j,8,19e,19f,20]

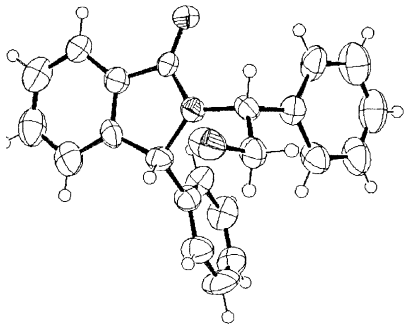


Figure 1. (3*R*,1′*R*)-**13g**.

16 or **17** as the key intermediates was considered. This required the transformation of aza-carbinols **12** to tricyclic lactams. The literature precedents show that such a conversion is, in some cases,[18] difficult to accomplish. Indeed, when we stirred a methanolic solution of **12a** under acidic conditions, no cyclized product was isolated, we obtained instead compound **15** (stereochemistry no determined) as the sole diastereomer in 84% yield. Gratefully, it was found that the desired transformation could be achieved simply by stirring, at room temperature, the aza-carbinol **12a** in dichloromethane in the presence of a catalytic amount of *p*-toluenesulfonic acid (Scheme 4). Thus, tricyclic lactam **16a** was formed in excellent diastereoselectivity (Table 1, entry 1).

Noteworthy is that the acid catalyzed cyclisation of the diastereomeric mixture of aza-carbinol **12a** at either room temperature or refluxing conditions led to the same major diastereoisomer **16a** (R=Me), which was also the same as that obtained by an alternative method.[8] This allowed us to assume that the isolated tricyclic lactam **16a** was the thermodynamically more stable diastereoisomer. The observed stereochemical preference during the formation of **16** can be understood by comparing the structure of **16** with that of **17**. In **16**, the phenyl group is situated in the convex face of the tricyclic system, while that of **17** is in the concave face of the tricyclic system, which suffers from severe steric interaction. The formation of other homologous (**16c**, **16g** and **16f**) proceeded similarly in excellent diastereoselectivity (Table 1, entries 2, 4, 5). Mention should also be made that in the case of **16e/17e**, the diastereoselectivity was only 81:19 (vide infra).

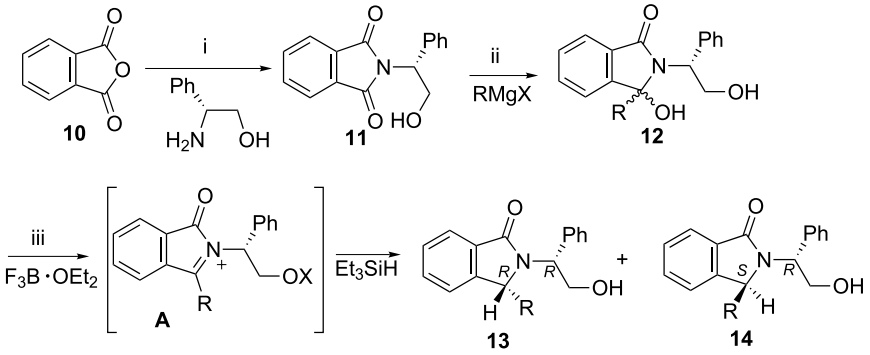
The reductive ring opening of **16a** under the standard conditions ($TiCl_4$, Et_3SiH, CH_2Cl_2, −78 °C)[8,19e,19f] afforded, as anticipated, **13a** and **14a** in excellent diastereoselectivity (**13a**:**14a**=95:5, Table 1, entry 1). Similarly, the reductive ring opening of compounds **16c**, **16e** and **16g** afforded, respectively **13c**, **13e** and **13g** in diastereoselectivities ranged from 91:9 to 97:3. Thus, the two variations depicted, respectively in Schemes 3 and 4 are complementary in view of chemical yield and stereoselectivity.

Since compound **18** is a commercially available cheap product, we also explored the possibility to use it as a starting material for the preparation of **19**, which was considered as a precursor of **16f**. Thus, heating a neat mixture of **18** and (*R*)-phenylglycinol led to the desired **19a** and its geometric isomer **19b** in 92:8 ratio and in a combined

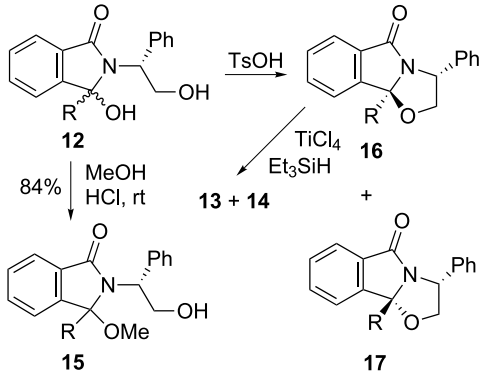
Table 1. Preparation of 3-substituted isoindolin-1-ones **13** via reductive ring-opening of the tricyclic lactams **16**

Entry	Starting compound (*R*)	Cyclic ethers (yield, %)[a]	Diastereo-selectivity[b]	Products (yield, %)[a]	Diastereo-selectivity[b]
1	**12a** (Me)	**16a**+**17a** (92)	96:4	**13a**+**14a** (90)	95:5
2	**12c** (*n*-Bu)	**16c**+**17c** (94)	95:5	**13c**+**14c** (78)	97:3
3	**12e** (*n*-C_7H_{15})	**16e**+**17e** (83)	81:19	**13e**+**14e** (72)[c]	91:9
4	**12g** (Ph)	**16g**+**17g** (86)	≥99:1	**13g**+**14g** (88)	96:4
5	**19** (Bn)	**16f** (40)[d]	ca.100:0	**13f**+**14f** (97)	92:8

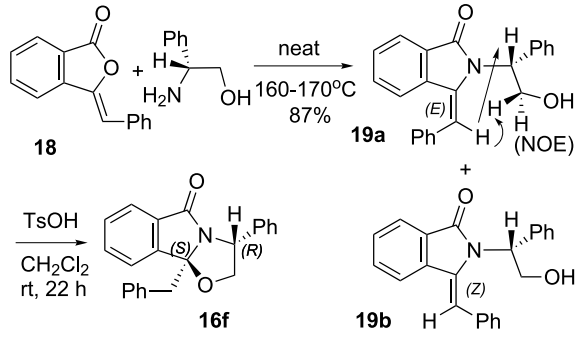
[a] Isolated yield.
[b] Ratio determined by chromatographic separation.
[c] The reaction used a diastereomeric mixture of **16e** and **17e** (81:19) as the starting material.
[d] 37% of the starting material **19** was recovered (vide infra).



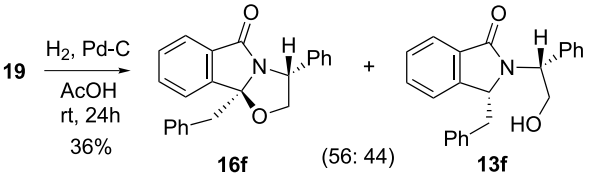
Scheme 3. Reagents and conditions: (i) neat, 160–170 °C, 96%; (ii) RMgX (a, R=Me, 87%; b, R=Et, 96%; c, R=*n*-Bu, 87%; d, R=*i*-Bu, 91%; e, R=*n*-C_7H_{15}, 88%; f, R=Bn, 96%; g, R=Ph, 90%), THF, −15 °C; (iii) Et_3SiH, $F_3B\cdot OEt_2$, CH_2Cl_2, −78 °C (diastereoselectivity, **13**:**14**/combined yields: a, 87:13/92%; b, 85:15/95%; c, 84:16/98%; d, 91:9/85%; e, 77:23/61%; f, 81:19/97%; g, 71:29/90%).



Scheme 4.



Scheme 5.



Scheme 6.

yield of 87% (Scheme 5). In contrast to the *N*-unsubstituted analogues,[22a,22b] the NOESY experiments showed that the major geometric isomer **19a** exists in (*E*)-form.[22c,22d] Stirring a solution of the inseparable mixture of **19a** and **19b** in the presence of a catalytic amount of TsOH afforded **16f** as the only observable diastereomer in 40% yield. In addition, 37% of the starting material **19** was recovered.

Attempting to form **13f** directly by catalytic hydrogenation of **19** under acidic conditions yielded **13f** and **16f** in 44:56 ratio, and in a disappointing combined yield of 36% (Scheme 6).

Next, we addressed the problem of the stereochemical outcome of the key reactions. The high diastereoselectivity for the $TiCl_4$ mediated reductive ring-opening of the tricyclic lactams **16**/**17** can be rationalized on the basis of both allylic 1,3-interaction[23] and Felkin–Anh model,[24] originally proposed by Meyers and co-workers for a related system,[19e,19f] which was adopted recently by Allin et al. (**B** and **C**)[8] and Decroix et al.[22c,22d] to explain the observed high diastereoselectivity during the formation of the diastereomers **13a**, **13g**[8] and related compounds.[22c,22d] Namely, the predominant formation of the chelation stabilized *N*-acyliminium[21] conformer **C** ensures the facile approach of the hydride from the less hindered β-face, leading to **13** as the predominant diastereomer (Fig. 2). In the case of $BF_3\cdot OEt_2$ mediated reductive deoxygenation of *N*,*O*-acetals **12**, being unable to form a chelating

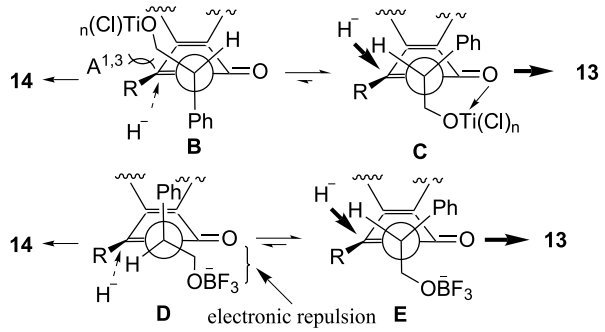
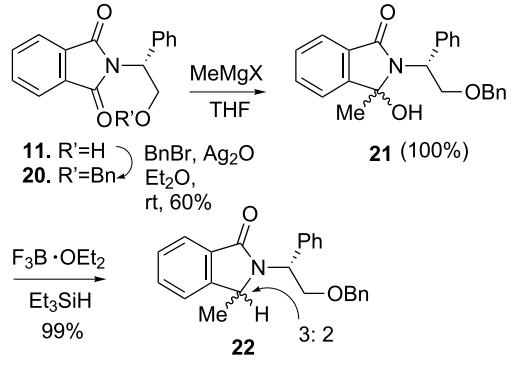


Figure 2.

intermediate like **C**, **D** and **E** will co-exist in the medium, with the later being predominant. Thus the approach of hydride from the β-face of **E** and from the α-face of **D** will lead, respectively, to **13** or **14**.

Noteworthy is that the reductive deoxygenation of *O*-protected carbinol **21** led to **22** in 3:2 diastereomeric ratio (Scheme 7).



Scheme 7.

To gain an insight into the lower chemical yield observed during the formation of **13e/14e** from **16e/17e** (Table 1, entry 3), the following experiments were performed. Starting with a 81:19 diastereomeric mixture of **16e/17e**, the reductive ring opening ($TiCl_4$, Et_3SiH) gave **13e** and **14e** in 91:9 ratio and in a combined yield of 72% (Table 1, entry 3 and Table 2, entry 1). Higher diastereomeric ratio (86:14) of the starting material (**16e/17e**) gave similar diastereoselectivity, but in higher yield (Table 2, entry 2). Pure diastereomer **16e** provided the deoxygenative products **13e** and **14e** in 95:5 diastereoselectivity and in 91% yield (Table 2, entry 3). Unexpectedly, when starting with pure diastereomer **17e**, no desired deoxygenative products **13e/14e** were obtained. In this case, we observed instead partial epimerization of **16e** to **17e**, which gave a mixture of **16e** and **17e** in ca. 1:1 ratio. These results suggested that the yields of **13e/14e** depended only on the content of the diastereomer **16e** in the starting diastereomeric mixture (**16e/17e**), namely, only the diastereomer **16e** was convertible to **13e/14e**.

These surprising phenomena can be explained in terms of stereoelectronic effect[25] in the *N*-acyliminium formation step. For the diastereomer **16**, the stereoelectronically-favored pathway involves the chelation between an oxygen lone lobe with Lewis acid from the convex face of the ring system (Fig. 3, **F**). For diastereomer **17**, the stereoelectronic effect requires the chelation of the Lewis acid with the lone pair lobe located in the concave of the ring system (**G**), which is unfavored due to severe steric interaction.

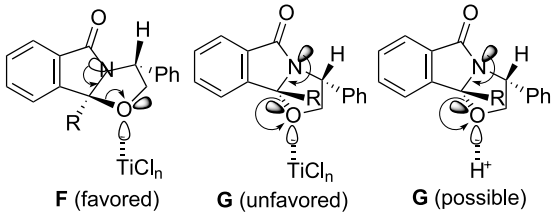


Figure 3.

The fact that **17e** can be epimerized to **16e** (Table 2, entry 4), while the later could not be converted to the reductive ring-opening product, might implicate that the epimerization occurred during work-up procedure (Brønsted acidic conditions), where proton being a small 'acid' is capable of forming the *N*-acyliminium intermediate via **G**.

3. Conclusion

In summary, we have developed a versatile and flexible approach to *N*-protected (*R*)-3-alkyl-isoindolin-1-ones **13** via highly diastereoselective reductive-alkylation procedure (**11**→**13**) and a complementary cyclisation-reductive ring-opening protocol (**12**→**16**→**13**). This approach is versatile in scope, since various C-3 substituents can be introduced easily by Grignard reaction. Detailed studies on the diastereoselective reactions allowed us to reveal that the steric and stereoelectronic effects operated in the selective reactions.

Table 2. Influence of diastereomeric ratio of tricyclic lactams **16e/17e** on the yields and diastereomeric ratio of products **13e/14e**

Entry	Starting cyclic ether (diastereomeric ratio)	Products **13e/14e** (Yield, %)[a]/diastereomeric ratio[b] (**13e**:**14e**)
1	**16e/17e** (81:19)	72/91:9
2	**16e/17e** (86:14)	77/92:8
3	(±)-**16e** (100:0)	91/95:5
4	(±)-**17e** (0:100)	—[c]

[a] Isolated yield.
[b] Ratio determined by chromatographic separation.
[c] No desired product was obtained, some epimerized product was isolated in 47% combined yield (56% conversion), the diastereomeric ratio of the final products (±)-**16e**:(±)-**17e** was about 1:1.

4. Experimental

4.1. General

All melting points were determined on a Yanaco MP-500 micro melting point apparatus and were uncorrected. Infrared spectra were measured with a Nicolet Avatar 360 FT-IR spectrometer using film KBr pellet techniques. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Varian unity + 500 spectrometer with tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) units downfield from TMS. Mass spectra were recorded on a Finnigan MAT-GCQ (direct injection, EI). Optical rotations were measured with Perkin–Elmer 341 automatic polarimeter. Flash column chromatography was carried out with silica gel (200–300 mesh). THF was distilled over sodium. Dichloromethane was distilled over P_2O_5.

CCDC-253349 contains the supplementary crystallographic data for this paper (compound **13g**). These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ,UK; fax: +44 1223 336 033; or e-mail: deposit@ccdc.cam.ac.uk).

4.1.1. 2-[(1*R*)-2-Hydroxy-1-phenylethyl]-isoindolin-1,3-dione (11). A mixture of phthalic anhydride (437 mg, 2.95 mmol) and (*R*)-(−)-phenylglycinol (386 mg, 2.81 mmol) was heated to 160–170 °C and stirred for 7 h. The reaction mixture was cooled, and then CH_2Cl_2 was added to dissolve the product. The solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel to give **11** (740 mg, yield 98%) as pale yellow oil, which crystallized upon standing at low temperature. R_f: 0.55 (AcOEt/P.E.=1:2). Mp 59–60 °C. $[\alpha]_D^{20}=+42.4$ (*c* 1.3, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3462, 1772, 1708, 1467, 1390, 1367, 1334, 1189, 1067 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.69 (brs, 1H, OH), 4.22 (dd, J=5.2, 11.6 Hz, 1H, C*H*$_2$OH), 4.65 (dd, J=9.0, 11.6 Hz, 1H, C*H*$_2$OH), 5.47 (dd, J=5.2, 9.0 Hz, 1H, PhCHN), 7.23–7.88 (m, 9H, Ar) ppm. HRFABMS calcd for $[C_{16}H_{13}O_3N+H]^+$: 268.0974. Found: 268.0969.

4.2. General procedure for the reductive alkylation of (*R*)-phthalimide derivative (11)

A solution of phthalimide **11** (0.72 mmol) in anhydrous THF (5 mL) was cooled to −15 °C under argon atmosphere, a Grignard reagent (3.61 mmol) in diethyl ether was added dropwise. After stirred at −15 °C for 1.5 h, the reaction was quenched with a saturated aqueous solution of ammonium chloride and extracted with dichloromethane (3×15 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuum. Column chromatography separation (eluent: ethyl acetate–petroleum ether, 60:40) yielded a mixture of two diastereomers (3*R*/*S*,1′*R*)-**12**, which without further separation, was used in the next step.

A mixture of diastereomers (3*R*/*S*,1′*R*)-**12** (0.53 mmol) was dissolved in dry dichloromethane (10 mL) under argon atmosphere. The solution was cooled to −78 °C, to which triethylsilane (5.33 mmol) and boron trifluoride etherate (1.71 mmol) were added. After stirred at −78 °C for 6 h, the mixture was allowed to warm up. The reaction was quenched by a saturated aqueous sodium bicarbonate and extracted with dichloromethane (3×20 mL). The combined extracts were dried ($MgSO_4$) and concentrated in vacuum. The crude was chromatographied on a column of silica gel eluting with ethyl acetate–petroleum ether (bp 60–90 °C) (60:40) to give separable diastereomers (3*R*,1′*R*)-**13** and (3*S*,1′*R*)-**14**

4.2.1. (3*R*) and (3*S*)-3-Methyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13a) and (3*S*,1′*R*-14a). Diastereomeric ratio: 87:13, combined yield: 92%. Less polar diastereomer (3*R*,1′*R*)-**13a**: white viscous oil. R_f: 0.41 (AcOEt/P.E.=1:2). $[\alpha]_D^{20}=+88.6$ (*c* 2.3, CH_2Cl_2); $[\alpha]_D^{20}=+87.9$ (*c* 1.0, $CHCl_3$); [Lit.[8] $[\alpha]_D^{20}=+21.3$ (*c* 2.34, CH_2Cl_2). Lit.[9c] $[\alpha]_D^{20}=+84$ (*c* 0.9, CH_2Cl_2)]. IR (film) ν_{max}: 3390, 3083, 3053, 3027, 2971, 2930, 2868, 1664, 1470, 1406, 1355, 1214, 1066 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.46 (d, J=6.8 Hz, 3H, CH_3), 4.12 (dd, J=3.4, 12.4 Hz, 1H, C*H*$_2$OH), 4.35 (q, J=6.8 Hz, 1H, CH_3C*H*), 4.49 (dd, J=8.0, 12.4 Hz, 1H, C*H*$_2$OH), 4.78 (dd, J=3.4, 8.0 Hz, 1H, PhCHN), 7.27–7.88 (m, 9H, Ar) ppm. MS (ESI, *m*/*z*): 268 ($M+H^+$, 25), 148 (100). HRFABMS calcd for $[C_{17}H_{17}O_2N+H]^+$: 268.1338. Found: 268.1331.

More polar diastereomer (3*S*,1′*R*)-**14a**: white solid. R_f: 0.30 (AcOEt/P.E.=1:2). mp 109–111 °C. $[\alpha]_D^{20}=+41.8$ (*c* 0.6, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3280, 2971, 2926, 2858, 1665, 1619, 1455, 1429, 1361, 1173, 1102, 1072, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.32 (d, J=6.7 Hz, 3H, CH_3), 4.24 (dd, J=3.8, 11.7 Hz, 1H, C*H*$_2$OH), 4.43 (dd, J=7.6, 11.7 Hz, 1H, C*H*$_2$OH), 4.54 (q, J=6.7 Hz, 1H, CH_3C*H*), 5.13 (dd, J=3.8, 7.6 Hz, 1H, PhCHN), 7.27–7.88 (m, 9H, Ar) ppm. MS (ESI, *m*/*z*): 268 ($M+H^+$, 27), 148 (100). HRFABMS calcd for $[C_{17}H_{17}O_2N+H]^+$: 268.1338. Found: 268.1327.

4.2.2. (3*R*) and (3*S*)-3-Ethyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13b) and (3*S*,1′*R*-14b). Diastereomeric ratio: 85:15, combined yield: 95%. Less polar diastereomer (3*R*,1′*R*)-**13b**: white viscous oil. R_f: 0.50 (AcOEt/P.E.=1:1.5). $[\alpha]_D^{20}=+98.0$ (*c* 1.0, $CHCl_3$). IR (film) ν_{max}: 3366, 3083, 3058, 3027, 2967, 2934, 2878, 1664, 1616, 1491, 1469, 1454, 1421, 1361, 1332, 1301, 1066, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.56 (t, J=7.5 Hz, 3H, CH_3), 1.92–2.00 (m, 1H, CH_2), 2.02–2.11 (m, 1H, CH_2), 4.11 (dd, J=3.4, 12.5 Hz, 1H, C*H*$_2$OH), 4.41 (dd, J=2.5, 5.0 Hz, 1H, C*H*CH_2), 4.50 (dd, J=8.0, 12.5 Hz, 1H, C*H*$_2$OH), 4.63 (dd, J=3.4, 8.0 Hz, 1H, PhCHN), 7.22–7.39 (m, 6H, Ar), 7.46–7.60 (m, 2H, Ar), 7.90 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, *m*/*z*): 282 ($M+H^+$, 18), 585 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{18}H_{19}O_2N+H]^+$: 282.1494. Found: 282.1487.

More polar diastereomer (3*S*,1′*R*)-**14b**: white solid. R_f: 0.39 (AcOEt/P.E.=1:1.5). mp 133–134 °C. $[\alpha]_D^{20}=+66.9$ (*c* 1.0, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3255, 3073, 3048, 2966, 2926, 2868, 1662, 1614, 1470, 1440, 1378, 1055, 1030 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.39 (t, J=7.3 Hz, 3H, CH_3), 1.76–1.86 (m, 1H, CH_2), 1.88–1.96 (m, 1H, CH_2), 4.22 (dd, J=4.0, 11.6 Hz, 1H, C*H*$_2$OH), 4.45 (dd, J=8.0,

11.6 Hz, 1H, CH_2OH), 4.57 (dd, J=4.3, 4.8 Hz, 1H, CHCH$_2$), 4.98 (dd, J=4.0, 8.0 Hz, PhCHN), 7.28–7.40 (m, 4H, Ar), 7.43–7.60 (m, 4H, Ar), 7.89 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, m/z): 282 ($M+H^+$, 15), 585 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{18}H_{19}O_2N+H]^+$: 282.1494. Found: 282.1486.

4.2.3. (3*R*) and (3*S*)-3-*n*-Butyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13c) and (3*S*,1′*R*-14c). Diastereomeric ratio: 86:14, combined yield: 98%. Less polar diastereomer (3*R*,1′*R*)-**13c**: white solid. R_f: 0.52 (AcOEt/P.E.=1:1). mp 130–132 °C. $[\alpha]_D^{20}=+61.8$ (c 1.0, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3361, 1716, 1652, 1614, 1470, 1408 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.64–0.74 (m, 1H, CH$_2$CH_2CH$_2$), 0.80 (t, J=7.3 Hz, 3H, CH$_3$), 1.06–1.16 (m, 1H, CH$_2$CH_2CH$_2$), 1.16–1.28 (m, 2H, CH$_2$CH_2CH$_3$), 1.86–2.01 (m, 2H, CH_2CH_2-CH$_2$), 4.11 (dd, J=3.2, 12.4 Hz, 1H, CH_2OH), 4.39 (dd, J=2.9, 5.2 Hz, 1H, CHCH$_2$), 4.48 (dd, J=8.0, 12.4 Hz, 1H, CH_2OH), 4.66 (dd, J=3.2, 8.0 Hz, 1H, PhCHN), 7.24–7.40 (m, 6H, Ar), 7.50 (t, J=7.5 Hz, 1H, Ar), 7.56 (dt, J=1.1, 7.5 Hz, 1H, Ar), 7.88 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, m/z): 310 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53. Found: C 77.34, H 7.47, N 4.53.

More polar diastereomer (3*S*,1′*R*)-**14c**: white solid. R_f: 0.41 (AcOEt:P.E.=1:1). mp 139–140 °C. $[\alpha]_D^{20}=+84.1$ (c 0.5, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3373, 1653, 1619, 1465, 1455, 1429 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.54 (t, J=7.1 Hz, 3H, CH$_3$), 0.56–0.66 (m, 1H, CH$_2$CH_2CH$_2$), 0.70–0.80 (m, 2H, CH$_2$CH_2CH_2), 0.86–0.98 (m, 1H, CH$_2$CH_2CH$_2$), 1.64–1.78 (m, 1H, CHCH_2CH$_2$), 1.82–1.94 (m, 1H, CHCH_2CH$_2$), 4.19 (dd, J=4.0, 11.6 Hz, 1H, CH_2OH), 4.46 (dd, J=7.8, 11.6 Hz, 1H, CH_2OH), 4.59 (t, J=4.0 Hz, 1H, CHCH$_2$), 4.90 (dd, J=4.0, 7.8 Hz, 1H, PhCHN), 7.28–7.38 (m, 4 H, Ar), 7.45 (t, J=7.5 Hz, 3H, Ar), 7.53 (t, J=7.5 Hz, 1H, Ar), 7.85 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, m/z): 310 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{23}NO_2$: C 77.64, H 7.49, N 4.53. Found: C 77.40, H 7.56, N 4.80.

4.2.4. (3*R*) and (3*S*)-3-*iso*-Butyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13d) and (3*S*,1′*R*-14d). Diastereomeric ratio: 91:9, combined yield: 85%. Less polar diastereomer (3*R*,1′*R*)-**13d**: white solid. R_f: 0.48 (AcOEt/P.E.=1:1). mp 54–56 °C. $[\alpha]_D^{20}=+44.7$ (c 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3352, 3053, 2950, 2930, 2868, 1662, 1469, 1434, 1387, 1230, 1153 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.69 (d, J=6.3 Hz, 3H, CH$_3$), 0.92 (d, J=6.3 Hz, 3H, CH$_3$), 1.62–1.78 (m, 2H, CH$_2$CH), 1.80–1.92 (m, 1H, CH$_2$CH), 4.13 (dd, J=2.9, 11.7 Hz, 1H, CH_2OH), 4.33 (dd, J=3.1, 7.0 Hz, 1H, CHCH$_2$), 4.48 (dd, J=7.8, 11.7 Hz, 1H, CH_2OH), 4.72 (dd, J=2.9, 7.8 Hz, 1H, PhCHN), 7.22–7.60 (m, 8H, Ar), 7.88 (m, 1H, Ar) ppm. MS (ESI, m/z): 310 ($M+H^+$, 4), 641 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{20}H_{23}O_2N+H]^+$: 310.1807. Found: 310.1804.

More polar diastereomer (3*S*,1′*R*)-**14d**: white solid. R_f: 0.31 (AcOEt/P.E.=1:1). mp 154–155 °C. $[\alpha]_D^{20}=+93.9$ (c 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3356, 3088, 3027, 2979, 2949, 2925, 2868, 2848, 1662, 1613, 1470, 1465, 1436 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.70 (d, J=6.3 Hz, 3H, CH$_3$), 0.71 (d, J=6.3 Hz, 3H, CH$_3$), 1.40–1.50 (m, 1H, CH$_2$CH), 1.60–1.80 (m, 2H, CH$_2$CH), 4.20 (dd, J=4.0, 11.7 Hz, 1H, CH_2OH), 4.47 (dd, J=8.0, 11.7 Hz, 1H, CH_2OH), 4.53 (dd, J=3.8, 8.5 Hz, 1H, CHCH$_2$), 4.95 (dd, J=4.0, 8.0 Hz, 1H, PhCHN), 7.21–7.57 (m, 8H, Ar), 7.86 (d, J=7.6 Hz, 1H, Ar) ppm. MS (ESI, m/z): 310 ($M+H^+$, 4), 641 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{20}H_{23}O_2N+H]^+$: 310.1807. Found: 310.1796.

4.2.5. (3*R*) and (3*S*)-3-*n*-Heptyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13e) and (3*S*,1′*R*-14e). Diastereomeric ratio: 77:23, combined yield: 61%. Less polar diastereomer (3*R*,1′*R*)-**13e**: colorless viscous oil. R_f: 0.46 (AcOEt/P.E.=1:1). $[\alpha]_D^{20}=+41.1$ (c 0.7, $CHCl_3$). IR (film) ν_{max}: 3337, 3083, 3058, 3027, 2955, 2927, 2856, 1668, 1614, 1468, 1455, 1414, 1362 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.60–0.78 (m, 1H, C_6H_{12}), 0.84 (t, J=7.0 Hz, 3H, CH$_3$), 1.09–1.32 (m, 9H, C_6H_{12}), 1.83–2.02 (m, 2H, C_6H_{12}), 4.11 (dd, J=3.5, 12.5 Hz, 1H, CH_2OH), 4.38 (dd, J=3.0, 5.0 Hz, 1H, CHCH$_2$), 4.47 (dd, J=8.0, 12.5 Hz, 1H, CH_2OH), 4.65 (dd, J=3.5, 8.0 Hz, PhCHN), 7.23–7.27 (m, 1H, Ar), 7.28–7.36 (m, 4H, Ar), 7.49 (t, J=7.5 Hz, 1H, Ar), 7.53–7.58 (m, 1H, Ar), 7.52–7.59 (m, 1H, Ar), 7.88 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, m/z): 352 ($M+H^+$, 30), 725 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{23}H_{29}O_2N+H]^+$: 352.2277. Found: 352.2268.

More polar diastereomer (3*S*,1′*R*)-**14e**: white solid. R_f: 0.36 (AcOEt/P.E.=1:1). mp 91–92 °C. $[\alpha]_D^{20}=+93.0$ (c 1.0, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3357, 3083, 3063, 3030, 2985, 2954, 2925, 2869, 2854, 1665, 1618, 1470, 1454, 1432, 1360, 1219 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.51–0.64 (m, 1H, C_7H_{15}), 0.66–0.77 (m, 2H, C_7H_{15}), 0.80 (t, J=7.0 Hz, 3H, CH$_3$), 0.86–0.96 (m, 3H, C_7H_{15}), 0.96–1.07 (m, 2H, C_7H_{15}), 1.09–1.20 (m, 2H, C_7H_{15}), 1.64–1.78 (m, 1H, C_7H_{15}), 1.80–1.92 (m, 1H, C_7H_{15}), 4.19 (dd, J=4.1, 11.7 Hz, 1H, CH_2OH), 4.45 (dd, J=7.8, 11.7 Hz, 1H, CH_2OH), 4.60 (t, J=4.3 Hz, CHCH$_2$), 4.88 (dd, J=4.1, 7.8 Hz, 1H, PhCHN), 7.27–7.38 (m, 4H, Ar), 7.44–7.48 (m, 3H, Ar), 7.53 (t, J=7.5 Hz, 1H, Ar), 7.85 (d, J=7.5 Hz, 1H, Ar) ppm. MS (ESI, m/z): 352 ($M+H^+$, 16), 725 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{23}H_{29}O_2N+H]^+$: 352.2277. Found: 352.2272.

4.2.6. (3*R*) and (3*S*)-3-Benzyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13f) and (3*S*,1′*R*-14f). Diastereomeric ratio: 81:19, combined yield: 97%. Less polar diastereomer (3*R*,1′*R*)-**13f**: white solid. R_f: 0.36 (AcOEt/P.E.=1:2). mp 165–167 °C (lit.[9c] mp 167 °C). $[\alpha]_D^{20}=+54$ (c 1.1, $CHCl_3$) [Lit.[9c] $[\alpha]_D^{20}=+66$ (c 0.5, CH_2Cl_2)]. IR (KBr, Pellet) ν_{max}: 3435, 3083, 3063, 3027, 2950, 2922, 2851, 1666, 1618, 1496, 1470, 1450, 1424, 1219 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.88 (dd, J=7.9, 13.9 Hz, 1H, PhCH_2CH), 3.38 (dd, J=4.4, 13.9 Hz, 1H, PhCH_2CH), 4.10 (dd, J=3.3, 12.6 Hz, 1H, CH_2OH), 4.46 (dd, J=8.0, 12.6 Hz, 1H, CH_2OH), 4.55 (dd, J=4.4, 7.9 Hz, CHBn), 4.87 (dd, J=3.3, 8.0 Hz, 1H, PhCHN), 6.82–6.90 (m, 1H, Ar), 6.90–7.00 (m, 2H, Ar), 7.14–7.45 (m, 10H, Ar), 7.81 (d, J=7.6 Hz, 1H, Ar) ppm. MS (ESI, m/z): 344 ($M+H^+$, 30), 709 [$(2M+Na)^+$, 100]. Anal Calcd for $C_{23}H_{21}O_2N$: C 80.44, H 6.16, N 4.08. Found: C 80.16, H 6.22, N 4.12.

More polar diastereomer (3*S*,1′*R*)-**14f**: white solid. R_f: 0.21 (AcOEt/P.E.=1:2). mp 134–135 °C. $[\alpha]_D^{20}=+111.5$ (*c* 1.1, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3435, 3083, 3063, 2958, 2922, 2851, 1668, 1616, 1496, 1460, 1429, 1255 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 2.43 (dd, $J=10.4$, 13.5 Hz, 1H, PhCH_2CH), 3.44 (dd, $J=4.5$, 13.5 Hz, 1H, PhCH_2CH), 4.31 (dd, $J=4.2$, 11.6 Hz, 1H, CH_2OH), 4.58 (dd, $J=7.9$, 11.6 Hz, 1H, CH_2OH), 4.76 (dd, $J=4.5$, 10.4 Hz, CHBn), 5.18 (dd, $J=4.2$, 7.9 Hz, 1H, PhCHN), 6.49 (d, $J=7.6$ Hz, 1H, Ar), 6.93–7.03 (m, 2H, Ar), 7.24–7.59 (m, 10H, Ar), 7.89 (d, $J=7.6$ Hz, 1H, Ar) ppm. MS (ESI, *m/z*): 344 ($M+H^+$, 14), 709 [$(2M+Na)^+$, 93], 1052 [$(3M+Na)^+$, 100]. HRFABMS calcd for $[C_{23}H_{21}O_2N+H]^+$: 344.1641. Found: 344.1640.

4.2.7. (3*R*) and (3*S*)-3-Phenyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R*,1′*R*-13g) and (3*S*,1′*R*-14g). Diastereomeric ratio: 71:29, combined yield: 90%. Less polar diastereomer (3*R*,1′*R*)-**13g**: white soild. R_f: 0.52 (AcOEt/P.E.=1:1). mp 134–135 °C (Lit.[8] mp 115–116 °C). $[\alpha]_D^{20}=-75$ (*c* 2.6, CH_2Cl_2); $[\alpha]_D^{20}=-69$ (*c* 1.0, $CHCl_3$) [Lit.[8] $[\alpha]_D^{20}=+84.8$ (*c* 3.28, CH_2Cl_2) for antipode]. IR (KBr, Pellet) ν_{max}: 3459, 3088, 3063, 3027, 2935, 2873, 1711, 1666, 1614, 1465, 1395, 1358, 1245 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.06 (dd, $J=8.0$, 15.0 Hz, 1H, CH_2OH), 4.30–4.38 (m, 2H, CH_2OH +PhC*H*N), 5.21 (s, 1H, PhCH), 7.00–7.58 (m, 13H, Ar), 7.92–8.00 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 330 ($M+H^+$, 10), 681 [$(2M+Na)^+$, 100]. Anal Calcd for $C_{22}H_{19}O_2N$: C 80.22, H 5.81, N 4.25. Found: C 80.04, H 5.93, N 4.23.

More polar diastereomer (3*S*,1′*R*)-**14g**: white solid. R_f: 0.38 (AcOEt/P.E.=1:1). mp 172–173 °C. $[\alpha]_D^{20}=+48.6$ (*c* 0.9, $CHCl_3$). IR (KBr, Pellet) ν_{max}: 3412, 3088, 3058, 3032, 2926, 2879, 2848, 1666, 1612, 1495, 1468, 1429, 1356, 1222 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.87 (dd, $J=5.6$, 11.2 Hz, 1H, CH_2OH), 3.95 (dd, $J=8.6$, 11.2 Hz, 1H, CH_2OH), 5.21 (s, 1H, PhCH), 5.40 (dd, $J=5.6$, 8.6 Hz, PhCHN), 7.05–7.50 (m, 13H, Ar), 7.92–7.98 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 330 ($M+H^+$, 13), 681 [$(2M+Na)^+$, 59], 1010 [$(3M+Na)^+$, 100]. Anal. Calcd for $C_{22}H_{19}O_2N$: C 80.22, H 5.81, N 4.25. Found: C 80.34, H 6.02, N 4.30.

4.2.8. (3*R*) or (3*S*)-3-Methoxy-3-methyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (3*R* or 3*S*,1′*R*-15). To a methanolic solution of **12a** (45 mg, 0.16 mmol) (5 mL) was added 1 M HCl solution until pH 1. The resulting solution was stirred at room temperature for 4 h. The mixture was neutralized with a saturated solution of K_2CO_3. The resulting mixture was extracted with dichloromethane. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuum. The crude was purified by flash column chromatography on silica gel to give diastereomerically pure **15** (38 mg, yield 84%) as white crystal. mp 95–97 °C. $[\alpha]_D^{20}=+61.5$ (*c* 0.89, CH_2Cl_2). IR (KBr, Pellet) ν_{max}: 3357, 3063, 2981, 2930, 2904, 2858, 2822, 1669, 1603, 1496, 1468, 1421, 1363, 1158, 1136, 1081, 1062, 1021 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.75 (s, 3H, CCH_3), 3.47 (s, 3H, OCH_3), 4.37 (dd, $J=7.2$, 8.6 Hz, 1H, CH_2OH), 4.84 (dd, $J=8.0$, 8.6 Hz, 1H, CH_2OH), 5.32 (dd, $J=7.2$, 8.0 Hz, 1H, PhCHN), 7.19–7.43 (m, 5H, Ar), 7.46–7.67 (m, 3H, Ar), 7.82 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 298 ($M+H^+$, 100). HRFABMS calcd for $[C_{18}H_{19}O_3N+Na]^+$: 320.1259. Found: 320.1265.

4.3. Representative procedure for the preparation of (3*R*,9b*S*)-9b-alkyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (16)

A solution of **12a** (80 mg, 0.28 mmol) and *p*-toluenesulfonic acid monohydrate (8 mg, 0.05 mmol) in dichloromethane (15 mL) was stirred at room temperature for 22 h. To the mixture was added K_2CO_3. The resulting mixture was extracted with dichloromethane (3×15 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuum. The crude was purified by flash column chromatography on silica gel to give **16a** (69 mg) and **17a** (3 mg) (diastereomeric ratio=96:4) in a combined yield of 92%.

4.3.1. (3*R*,9b*S*)-9b-Methyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (3*R*,9b*S*-16a). Diastereomeric ratio: 96:4, combined yield: 92%. Faster eluting (major) diastereomer **16a**: white crystal. R_f: 0.66 (AcOEt-P.E.=1:2). mp 128–130 °C. [Lit.[8] 119–122 °C]. $[\alpha]_D^{20}=-112.1$ (*c* 0.9, $CHCl_3$) {Lit.[8] $[\alpha]_D=-123.7$ (*c* 3.07, CH_2Cl_2)}. IR (KBr, Pellet) ν_{max}: 2983, 2884, 1710, 1612, 1494, 1465, 1350, 1319, 1224, 1165, 1119 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 1.75 (s, 3H, CH_3), 4.38 (dd, $J=7.3$, 8.6 Hz, 1H, CH_2O), 4.83 (dd, $J=7.6$, 8.6 Hz, 1H, CH_2O), 5.32 (dd, $J=7.3$, 7.6 Hz, 1H, C*H*CH_2), 7.28–7.42 (m, 5H, Ar), 7.54–7.67 (m, 4H, Ar) ppm. MS (ESI, *m/z*): 266 ($M+H^+$, 100). HRFABMS calcd for $[C_{17}H_{15}NO_2+H]^+$: 266.1181. Found: 266.1177.

4.3.2. (3*R*,9b*S*)-9b-*n*-Butyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (3*R*,9b*S*-16c). Diastereomeric ratio: 95:5, combined yield: 94%. Faster eluting (major) diastereomer **16c**: white viscous oil. R_f: 0.75 (AcOEt/P.E.=1:3). $[\alpha]_D^{20}=-111.6$ (*c* 0.9, $CHCl_3$). IR (film) ν_{max}: 3060, 3030, 2956, 2872, 1718, 1465, 1357, 1320, 1300, 1156 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.84 (t, $J=7.3$ Hz, 3H, CH_3), 0.91–1.20 (m, 4H, CH_2-CH_2C$H_2$$CH_3$), 1.94–2.08 (m, 2H, C$H_2$$CH_2CH_2CH_3$), 4.41 (dd, $J=7.1$, 8.6 Hz, 1H, CH_2O), 4.82 (dd, $J=7.4$, 8.6 Hz, 1H, CH_2O), 5.33 (dd, $J=7.1$, 7.4 Hz, 1H, C*H*CH_2), 7.20–7.40 (m, 5H, Ar), 7.50–7.90 (m, 4H, Ar) ppm. HRFABMS calcd for $[C_{20}H_{21}O_2N+H]^+$: 308.1651. Found: 308.1649.

4.3.3. (3*R*,9b*S*)-9b-*n*-Heptyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (3*R*,9b*S*-16e). Diastereomeric ratio: 81:19, combined yield: 92%. Faster eluting (major) diastereomer **16e**: white viscous oil. R_f: 0.72 (AcOEt/P.E.=1:2). $[\alpha]_D^{20}=-109.4$ (*c* 1.1, $CHCl_3$). IR (film) ν_{max}: 3057, 2925, 2854, 1651, 1540, 1458, 1360, 1268, 1122, 1025 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.82 (t, $J=7.2$ Hz, 3H, CH_3), 1.11–1.34 (m, 10H, CH_2 (C_5H_{10})CH_3), 1.90–2.11 (m, 2H, CH_2(C_5H_{10})CH_3), 4.41 (dd, $J=7.1$, 8.6 Hz, 1H, CH_2O), 4.81 (dd, $J=8.0$, 8.6 Hz, 1H, CH_2O), 5.27 (dd, $J=7.1$, 8.0 Hz, 1H, C*H*CH_2), 7.28–7.42 (m, 5H, Ar), 7.45–7.67 (m, 3H, Ar), 7.85 (m, 1H, Ar) ppm. HRFABMS calcd for $[C_{23}H_{27}NO_2+H]^+$: 350.2120. Found: 350.2110.

Slower eluting (minor) diastereomer **17e**: white viscous oil.

R_f 0.44 (AcOEt/P.E.=1:2). $[\alpha]_D^{20}=+62.2$ (*c* 0.8, $CHCl_3$). IR (film) ν_{max}: 3062, 3031, 2953, 2927, 2856, 1708, 1467, 1387, 1371, 1332, 1074 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 0.84 (t, $J=7.2$ Hz, 3H, CH_3), 1.18–1.38 (m, 10H, $CH_2(C_5H_{10})CH_3$), 1.90–2.12 (m, 2H, $CH_2(C_5H_{10})CH_3$), 4.41 (dd, $J=7.1$, 8.5 Hz, 1H, CH_2O), 4.81 (dd, $J=7.8$, 8.5 Hz, 1H, CH_2O), 5.34 (dd, $J=7.1$, 7.8 Hz, 1H, $CHCH_2$), 7.28–7.42 (m, 5H, Ar), 7.45–7.67 (m, 3H, Ar), 7.85 (m, 1H, Ar) ppm. HRFABMS calcd for $[C_{23}H_{27}NO_2+H]^+$: 350.2115. Found: 350.2115.

4.3.4. (3*R*,9b*S*)-3,9b-Diphenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (3*R*,9b*S*-16g). Only one diastereomer **16g** was isolated, yield 86%. White solid. R_f: 0.67 (AcOEt/P.E.=1:1). mp 100–102 °C {Lit.[8] (3*S*,9b*R*)-**16g**: 104–106 °C}. $[\alpha]_D^{20}=-240.5$ (*c* 1.8, CH_2Cl_2) {Lit.[8] $[\alpha]_D=+282.0$ (*c* 1.9, CH_2Cl_2)}. IR (KBr, Pellet) ν_{max}: 3062, 3021, 2924, 2878, 1720, 1608, 1465, 1447, 1337, 1308, 1237 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.20 (dd, $J=8.3$, 8.8 Hz, 1H, CH_2O), 4.92 (dd, $J=8.4$, 8.8 Hz, 1H, CH_2O), 5.28 (dd, $J=8.3$, 8.4 Hz, 1H, $CHCH_2$), 7.15–7.42 (m, 9H, Ar), 7.50–7.70 (m, 4H, Ar), 7.82–7.88 (m, 1H, Ar) ppm. HRFABMS Calcd for $[C_{22}H_{22}O_2N+H]^+$: 328.1338. Found: 328.1328.

4.4. Representative procedure for the reductive ring-opening of (3*R*,9b*S*)-9b-alkyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (16)

To a cooled (−78 °C) solution of less polar diastereomer **16** (716 mg, 2.7 mmol) in dry dichloromethane (15 mL) was added dropwise titanium tetrachloride (0.44 mL, 4.05 mmol) followed by triethylsilane (0.64 mL, 4.05 mmol) under nitrogen atmosphere. After stirred at −78 °C for 1 h, the mixture was allowed to react at room temperature and stirred until the completion of the reaction. The reaction was quenched by saturated aqueous sodium bicarbonate at 0 °C and extracted with dichloromethane (3×15 mL). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4 then concentrated in vacuum. The crude was purified by flash column chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:2) to give (3*R*,1′*R*)-**13a** and its diastereomer **14a** in 95:5 ratio (combined yield: 90%, 649 mg).

4.4.1. (3*R*)-3-Methyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (13a and 14a). Diastereomeric ratio=95:5 (combined yield: 90%).

4.4.2. (3*R*)-3-*n*-Butyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (13c and 14c). Diastereomeric ratio=97:3 (combined yield: 78%).

4.4.3. (3*R*)-3-*n*-Heptyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (13e and 14e). Diastereomeric ratio=91:9 (combined yield: 72%).

4.4.4. (3*R*)-3-Benzyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (13f and 14f). Diastereomeric ratio=92:8 (combined yield: 97%).

4.4.5. (3*R*)-3-Phenyl-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (13g and 14g). Diastereomeric ratio=96:4 (combined yield: 88%).

4.4.6. (*E*) and (*Z*)-Benzylidene-2-[(1*R*)-2-hydroxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindol-1-one (19). A mixture of 2-benzylidenephthalide **18** (437 mg, 2.95 mmol) and (*R*)-(−)-phenylglycinol (151 mg, 1.10 mmol) was heated to 160–170 °C and stirred for 23 h. The reaction mixture was cooled, to which CH_2Cl_2 was added. The solution was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel to give a geometric mixture of **19** (326 mg, **19a**:**19b**=92:8, combined yield 87%) as a white solid. R_f: 0.43 (AcOEt/P.E.=1:7). mp 182–184 °C. $[\alpha]_D^{20}=+96.8$ (*c* 1.1, CH_2Cl_2). IR (KBr, Pellet) ν_{max}: 3433, 3058, 3027, 2930, 2879, 1679, 1640, 1491, 1470, 1445, 1401, 1312, 1265, 1178 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) data of *E*-**19** δ: 4.33 (dd, $J=3.6$, 12.3 Hz, 1H, CH_2OH), 4.62 (dd, $J=7.8$, 12.3 Hz, 1H, CH_2OH), 5.35 (dd, $J=3.6$, 7.8 Hz, 1H, PhCHN), 6.50 (s, 1H, PhCH=C), 7.10–7.50 (m, 13H, Ar), 7.90–7.96 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 342 ($M+H^+$, 4), 705 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{23}H_{19}O_2N+H]^+$: 342.1485. Found: 342.1494.

4.4.7. (3*R*,9b*S*)-9b-Benzyl-3-phenyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-*a*]-isoindol-5-one (3*R*,9b*S*-16f). A solution of **19** (238 mg, 0.70 mmol) and *p*-toluenesulfonic acid monohydrate (23 mg, 0.12 mmol) in dichloromethane (5 mL) was stirred at rt for 22 h. To the mixture was added $NaHCO_3$. After filtration and concentration, the crude was purified by flash column chromatography on silica gel eluting with ethyl acetate–petroleum ether to give **16f** (98 mg, yield: 40%). R_f: 0.52 (AcOEt/P.E.=1:3). $[\alpha]_D^{20}=-130.9$ (*c* 0.9, CH_2Cl_2). IR (KBr, Pellet) ν_{max}: 3078, 3063, 3022, 2996, 2945, 2925, 2879, 2848, 1726, 1614, 1598, 1496, 1465, 1450, 1359, 1301, 1224, 1137 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 3.03 (d, $J=14.1$ Hz, 1H, $PhCH_2$), 3.51 (d, $J=14.1$ Hz, 1H, $PhCH_2$), 4.67 (dd, $J=6.9$, 8.8 Hz, 1H, CH_2OH), 4.92 (dd, $J=8.2$, 8.8 Hz, 1H, CH_2OH), 5.37 (dd, $J=6.9$, 8.2 Hz, 1H, PhCHN), 6.96–7.52 (m, 13H, Ar), 7.76 (m, 1H, Ar) ppm. MS (ESI, *m/z*): 705 [$(2M+Na)^+$, 100]. HRFABMS calcd for $[C_{23}H_{19}O_2N+H]^+$: 342.1485. Found: 342.1491.

4.4.8. 2-[(1*R*)-2-Benzyloxy-1-phenylethy]-isoindolin-1,3-dione (20). To a solution of **11** (112 mg, 0.42 mmol) in diethyl ether was added Ag_2O (286 mg, 1.23 mmol) and a solution of benzyl bromide (0.3 mL, 2.52 mmol) in diethyl ether. The suspension was stirred at room temperature for 16 days in dark. After filtration through Celite and concentration in vacuo, the crude was flash chromatographed to afford **20** (90 mg, 60%) as a white viscous oil. $[\alpha]_D^{20}=+2.7$ (*c* 0.93, $CHCl_3$). IR (film) ν_{max}: 3058, 3027, 2925, 2858, 1772, 1712, 1496, 1470, 1455, 1387, 1368, 1132, 1107, 1020 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ: 4.03 (dd, $J=5.5$, 9.9 Hz, 1H, PhCHN), 4.58 (s, 2H, $PhCH_2O$), 4.63 (dd, $J=9.9$, 10.2 Hz, 1H, CH_2OBn), 5.62 (dd, $J=5.5$, 10.2 Hz, 1H, CH_2OBn), 7.22–7.88 (m, 14H, Ar) ppm. MS (ESI, *m/z*): 358 ($M+H^+$, 16), 376 ($M+Na^+$, 100). HRFABMS calcd for $[C_{23}H_{19}O_3N+H]^+$: 358.1434. Found: 358.1439.

4.4.9. (3*R*/*S*,1′*R*)-3-Methyl-2-[2-benzyloxy-1-phenylethyl]-2,3-dihydro-1*H*-isoindolin-1-one (3*R*/*S*,1′*R*-22). To

a cooled (−10 °C) solution of **20** (189 mg, 0.53 mmol) in anhydrous tetrahydrofuran (4 mL) was added dropwise a solution of MeMgI (2.0 mmol/mL, 5.3 mL, 2.64 mmol) in diethyl ether under nitrogen atmosphere. After stirred at the same temperature for 4 h, the reaction was quenched with saturated aqueous solution of ammonium chloride (6 mL) and extracted with dichloromethane (3×30 mL). The combined extracts were dried with anhydrous Na_2SO_4 and concentrated in vacuum. Filtration with a short pad of column eluting with ethyl acetate–petroleum ether (1:1) yielded a mixture of two diastereomers (3*R*,1′*R*)-**21a** and (3*R*,1′*S*)-**21b** (203 mg, yield: 100%).

To a cooled (−78 °C) solution of diastereomer mixture **21a**,**b** (117 mg, 0.31 mmol) in dry dichloromethane (10 mL) was added dropwise triethylsilane (0.49 mL, 3.13 mmol) and boron trifluoride etherate (0.12 mL, 0.94 mmol) under nitrogen atmosphere. After stirred at −78 °C for 6 h, the mixture was allowed to react at room temperature and stirred overnight. The reaction was quenched by saturated aqueous sodium bicarbonate and extracted with dichloromethane. The combined extracts were washed with brine and dried over anhydrous Na_2SO_4, then concentrated under vacuum. The crude was purified by flash column chromatography on silica gel eluting with ethyl acetate–petroleum ether (1:2) to give unseparable (3*R*,1′*R*)-**22** and (3*S*,1′*R*)-**22** (111 mg, yield 99%) as a white viscous oil, which is a 3:2 diastereomeric mixture as indicated by ^{1}H NMR analysis. R_f: 0.52 (AcOEt/P.E.=1:1.5). IR (film) ν_{max}: 3462, 3350, 3061, 3030, 2973, 2928, 2867, 1683, 1616, 1496, 1360, 1218, 1101 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$), major diastereomer δ: 1.38 (d, J=6.8 Hz, 3H, CH_3), 4.12 (dd, J=6.8, 10.0 Hz, 1H, NCHCH_2), 4.42 (dd, J=8.0, 10.0 Hz, 1H, NCHCH_2), 4.48 (q, J=6.8 Hz, 1H, CHCH$_3$), 4.62 (s, 2H, OCH_2Ph), 5.33 (dd, J=6.8, 8.0 Hz, 1H, NPhCH), 7.20–7.80 (m, 14H, Ar) ppm. Minor diastereomer δ: 1.26 (d, J=6.6 Hz, 3H, CH_3), 4.23 (dd, J=5.7, 10.2 Hz, 1H, NCHCH_2), 4.48 (dd, J=8.0, 10.2 Hz, 1H, NCHCH_2), 4.61 (s, 2H, OCH_2Ph), 4.64 (q, J=6.6 Hz, 1H, CHCH$_3$), 5.42 (dd, J=5.7, 8.0 Hz, 1H, NPhCH), 7.20–7.80 (m, 14H, Ar) ppm. MS (ESI, *m*/*z*): 250 (79), 358 (M+H$^+$, 85), 148 (100). HRFABMS calcd for $[C_{24}H_{23}O_2N+H]^+$: 358.1807. Found: 358.1804.

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Novel taxane diterpenes from *Taxus sumatrana* with the first C-21 taxane ester

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Abstract—Phytochemical investigation of the taxane diterpenes content of an acetone extract of the leaves and twigs of *Taxus sumatrana* (Taxaceae) has resulted in the isolation of five new taxane diterpenes esters, tasumatrols H–L (**1**–**5**) together with 13 known taxanes (**11**–**23**). Compound **5** is the first 21-carbon taxane ester to be isolated from a natural source. The structures of these taxanes as well as their derivatives were established on the basis of spectral analyses, especially MS as well as 1-and 2D NMR. Compounds **2** and **4** showed significant activity against human liver carcinoma (Hepa59T/VGH), human large cell carcinoma of the lungs (NCI), human cervical epitheloid carcinoma (Hela), human colon adenocarcinoma (DLD-1) and human medulloblastoma (Med) cell lines.

1. Introduction

Taxoids are highly oxygenated diterpenes generally containing 6/8/6-membered skeleton isolated from different species of yew trees (family Taxaceae).[1,2] They have received considerable attention after the discovery of the clinical efficacy of paclitaxel against different cancers due to its remarkable inhibition of microtubules polymerization leading to apoptosis of cancer cells.[3,4] As part of our search for biorenewable and cytotoxic taxoids,[5,6] we studied the taxane diterpenoidal content of *Taxus sumatrana* (Taxaceae) growing in Taiwan. A phytochemical investigation of an acetone extract of the leaves and young twigs *T. sumatrana* (Taxaceae) has resulted in the isolation of five novel taxane diterpenes esters, tasumatrols H–L (**1**–**5**), together with 13 known taxanes (**11**–**23**). Compound **5** is the first 21-carbon taxane ester to be isolated from a natural source. The known compounds were identified as 10-deacetyl-13-oxobaccatin III (**11**),[7] 10-deacetylbaccatin III (**12**),[8] taxacin (**13**),[9] yunnanxane (**14**),[10] 5α-hydroxy-2α,7β,9α,10β,13α-tetraacetoxy-4(20),11-taxadiene (**15**),[11] taxuspine F (**16**),[12] baccatin IV (**17**),[13] wallifoliol (**18**),[14] 20-deacetyltaxachitriene A (**19**),[15] taxinin M (**20**),[16] 7-*epi*−10-deacetyltaxol (**21**),[17] Taxol (**22**),[18] and baccatin III (**23**).[19] The structures of the isolated taxanes were established on the basis of spectral analyses, especially MS as well as 1-and 2D NMR. The cytotoxic activity of the isolated new compounds was tested against human liver carcinoma (Hepa59T/VGH), human large cell carcinoma of the lungs (NCI), human cervical epitheloid carcinoma (Hela), human colon adenocarcinoma (DLD-1) and human medulloblastoma (Med) cell lines.

2. Results and discussion

Solvent fractionation and multiple chromatographic separation over NP and RP-18 silica gel of an acetone extract of the leaves and young twigs of *T. sumatrana* afforded taxanes **1**–**5** in addition to 13 known taxoids.

2.1. Structure of compound 1

Compound **1** was isolated as a white powder with $[\alpha]_D = -27.2°$ (*c* 0.1, MeOH). The molecular formula $C_{29}H_{36}O_{11}$ was established by NMR and FAB-MS, which showed quasi-molecular ion peaks at *m/z* 561 $[M+H]^+$ and at *m/z* 583 $[M+Na]^+$ corresponding to 12° of unsaturation. The IR spectrum displayed absorption bands diagnostic of hydroxyl (3418 cm^{-1}) and ester (1733 cm^{-1}) group(s). Both ^1H and ^{13}C NMR spectral data (Tables 1 and 2)

Keywords: *Taxus sumatrana*; Taxaceae; Taxane diterpenes; Cytotoxic activity.
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Table 1. ^{1}H NMR spectral data of **1–5** in $CDCl_3$ (δ in ppm, multiplicities, J in Hz)[a]

Position	1	2	3	4	5
1				1.87 d (1.5)	2.43 s
2	5.74 d (12.0)	5.90 d (12.0)	5.82 d (12.0)	5.36 dd (6.1, 1.5)	6.21 d (9.9)
3	2.85 d (12.0)	2.74 d (12.0)	2.69 d (12.0)	2.69 d (6.1)	3.77 br s
4					
5	5.10 br s	3.76 br s	4.85 d (9.0)	4.19 m	4.47 br s
6	1.97 m	2.36 m	2.71 m	2.18 m	2.18 m (α)
	1.95 m	1.80 m	2.67 m	1.74 m	1.72 m (β)
7	4.25 m	4.35 m	4.31 br s	1.20 m	5.49 m
				1.15 m	
9				2.28 m	5.42 br s
				1.61 m	
10				6.11 dd (5.3, 1.5)	5.32 s
13	4.54 m	2.57 m	2.43 m	2.81 m	
		2.54 m	2.39 m	2.41 m	
14	2.46 dd (14.8, 6.6)	1.65 m	2.40 m	5.08 m	3.01 br s
	2.22 dd (14.8, 7.5)	1.51 m	2.36 m		
16	1.27 s	1.84 s	1.32 s	1.66 s	3.63 d (8.1)
					4.00 d (8.1)
17	1.24 s	1.33 s	1.26 s	1.12 s	1.28 s
18	1.24 s	2.04 s	2.04 s	2.09 s	1.16 s
19	2.08 s	1.20 s	1.60 s	0.81 s	5.10 d (12.3)
					4.38 d (12.3)
20	3.73 br s	4.50 d (12.4)	4.68 d (9.0)	5.12 s	5.41 s
	3.81 br s	4.24 d (12.4)	4.24 d (9.0)	4.75 s	4.69 s
21					3.79 br d (8.0) (2H)
OCOPh					
o-	8.01 d (6.9)	8.03 d (6.8)	7.97 d (7.1)		8.16 d (7.2)
m-	7.46 t (6.9)	7.48 t (6.8)	7.47 t (7.1)		7.52 t (7.2)
p-	7.57 t (6.9)	7.60 t (6.8)	7.61 t (7.1)		7.61 t (7.2)
Ac-2				2.03 s	2.05 s
Ac-4			1.76 s		
Ac-5	2.02 s				
Ac-7					2.16 s
Ac-9					2.03 s
Ac-10				2.06 s	2.11 s
Ac-20		2.02 s			
2′				2.36 m	
3′				3.85 m	
4′				1.22 d (6.3)	
5′				1.15 d (7.2)	

[a] Assignments were made using HMQC and HMBC techniques.

indicated the presence of one acetyl ester at δ_H 2.02 (3H, s) and δ_C 21.5 and 169.9 along with a benzoyl ester at δ_C 165.4, 131.3, 130.3, 128.4, 133.0 and δ_H 8.01 (d, J= 6.9 Hz), 7.46 (t, J=6.9 Hz) and 7.57 (t, J=6.9 Hz). Considering the empirical formula, 12° of unsaturation and subtracting carbons attributable to a benzoate and an acetate esters depicted a diterpene with four rings and two double bonds as verified by two olefinic quaternaries at δ_C 131.0 (C-11) and 139.9 (C-12) and a carbonyl at δ_C 172.8. The four methyl singlets at δ_H 1.27 (3H), 1.24 (6H), and 2.08 (3H) and their corresponding carbon signals at δ_C 22.1, 24.6, 10.3 and 11.6 together with the two quaternaries at δ_C 61.0 (C-1) and 88.2 (C-15) were in agreement with 11(15→1)-*abeo*-taxane skeleton.[20–22] The ^{1}H NMR spectrum revealed four oxygenated methines at δ 5.74 (d, J= 12.0 Hz, H-2), 5.10 (br s, H-5), 4.25 (m, H-7), 4.54 (m, H-13) with the apparent absence of signals assignable to H-9 and H-10 (normally found between δ_H 6.0–6.50). The relative low field chemical shift of the first two protons implied their acylation that was supported by their HMBC correlations with the respective carbonyls of the attached ester (Fig. 1). The COSY experiment displayed connectivities between H-13/H-14, H-2/H-3 and H-5/H-6/H-7. The low field quaternary carbon at δ 74.6 (C-4) was attributed to its attachment to a hydroxyl group and further supported by its HMBC correlations to H-2, H-5 and H-6. The oxygenated methylene protons at δ 3.81 and 3.73 had HMBC correlations with C-4 and C-5 and were assigned to H-20. The downfield shift of C-15 (δ 88.2) suggested its unusual oxygenation and its correlations to H-16, H-17 and H-2 in addition to a correlation between H-16/C-1 suggested the presence of 11(15→1)-*abeo*-taxane skeleton. Another deshielded quaternary oxygenated carbon observed at δ_C 84.3 was assigned to C-9 on the basis of its correlation to H-19. In order to account for 12° of unsaturations and the unusual deshielding of C-9 and C-15, it was proposed that C-15, C-1, C-11, C-9 and C-10 were involved in a 10,15-lactone ring allowing possible assignment of the carbonyl at δ 172.8 to C-10. This was supported by absence of HMBC three bond correlations with the carbonyl implying its attachment to the quaternary carbons at both ends as well as comparison of the data of **1** with the corresponding data of wallifoliol and its analogues.[14] Upon acetylation compound **1** yielded **6**, which showed four acetyl singlets at δ 2.17, 2.07, 2.02 and 1.97, and the oxygenated methine protons at δ 5.33 (H-7) and δ 5.58 (H-13), together with the oxygenated methylene protons at δ 4.57 and 4.32 (H-20), respectively. The relative stereochemistry of **1** was determined from its

Table 2. ^{13}C NMR spectral data of **1–5** in $CDCl_3$[a]

Carbon	1	2	3	4	5
1	61.0 s	64.4 s	62.8 s	59.2 d	50.5 d
2	68.8 d	70.0 d	68.9 d	70.6 d	70.6 d
3	45.9 d	45.4 d	43.7 d	40.0 d	39.4 d
4	74.6 s	75.2 s	80.6 s	147.6 s	145.0 s
5	72.2 d	69.1 d	84.4 d	76.2 d	72.7 d
6	32.5 t	33.0 t	37.4 t	30.9 t	39.0 t
7	68.2 d	67.7 d	71.1 d	33.0 t	69.1 d
8	48.5 s	48.8 s	48.2 s	39.3 s	49.4 s
9	84.3 s	85.3 s	85.8 s	43.8 t	70.0 d
10	172.8 s	175.2 s	175.1 s	70.1 d	64.4 d
11	131.0 s	130.0 s	127.7 s	134.6 s	80.3 s
12	139.9 s	138.7 s	138.8 s	135.8 s	90.8 d
13	79.0 d	39.3 t	39.2 t	39.2 t	204.2 s
14	36.3 t	25.4 t	25.5 t	70.8 d	48.7 d
15	88.2 s	91.1 s	91.4 s	37.3 s	50.2 s
16	22.1 q	20.7 q	22.2 q	25.4 q	81.5 t
17	24.6 q	22.5 q	24.4 q	31.8 q	15.4 q
18	10.3 q	14.0 q	14.1 q	21.5 q	12.6 q
19	11.6 q	11.7 q	10.2 q	22.2 q	61.4 t
20	61.9 t	64.0 t	74.3 t	113.5 t	113.1 t
21					68.7 t
OCOPh	165.4 s	165.2 s	164.7 s		166.8 s
i-	131.3 s	130.5 s	130.1 s		129.2 s
o-	130.3 d	129.8 d	129.5 d		130.1 d
m-	128.4 d	128.7 d	128.3 d		128.7 d
p-	133.0 d	133.7 d	133.5 d		133.6 d
Ac-2				170.2 s	169.2 s
				21.5 q	21.4 q
Ac-4			169.5 s		
			21.5 q		
OAc-5	169.9 s				
	21.5 q				
Ac-7					172.8 s
					20.9
C-9					168.4 s
					21.0
Ac-10				169.9 s	170.0 s
				21.5	21.4 q
Ac-20		170.8 s			
		21.5 q			
1′				175.1 s	
2′				46.9 d	
3′				69.5 d	
4′				20.8 q	
5′				14.0 q	

[a] Assignments were aided by HMQC, HMBC and DEPT techniques.

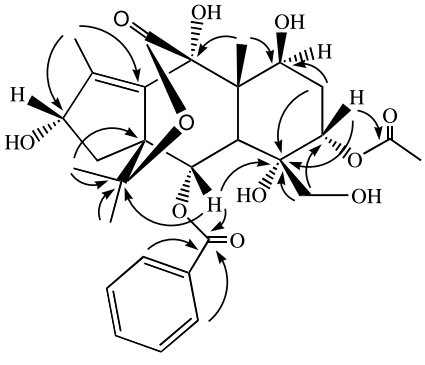


Figure 1. Selected HMBC correlations of **1**.

NOESY spectrum that showed correlations between H-2/H-19β, H-20; H-20/H-5; H-5/H-19; H-7/H-6α; H-13/H-16. Consequently, the structure of **1** was established as tasumatrol H (Fig. 2).

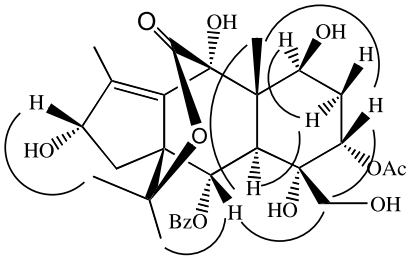


Figure 2. Selected NOESY correlations of **1**.

2.2. Structure of compound 2

Compound **2** was isolated as a white powder with $[\alpha]_D = -25.6°$ (*c* 0.1, MeOH). The molecular formula $C_{29}H_{36}O_{10}$ was deduced from NMR and FAB-MS, indicating one oxygen atom less than the case of **1**. The IR spectrum proved the existence of hydroxyl and ester and both ^1H and ^{13}C

NMR spectral data (Tables 1 and 2) disclosed the same key structural features of **1**, including the same 11(15→1)-*abeo*-taxane skeleton with two esters, with significant differences in the chemical shift values at C-5, C-13, C-14 and C-20. The DEPT experiment indicated the presence of three non-oxygenated methylenes instead of two in case of **1** that was associated with the absence of ^{1}H and ^{13}C NMR signals of one oxygenated methine (C-13). The CH_2 signal at δ_C 39.3 was directly attached (from HMQC experiment) to two protons multiplets centered at δ_H 2.57 and 2.54. The latter protons showed HMBC correlation to the methyl carbon at δ_C 14.0 (C-18) in addition to COSY correlations to the high field-shifted two protons at δ_H 1.65 and 1.51 that were assigned to H-14. The NMR data of **2** revealed the absence of any substitution with a hydroxyl or acyl group at either C-13 or C-14. The chemical shift of the oxygenated methine proton at δ_H 3.76 (br s, H-5) implied that C-5 is attached to a hydroxyl group. On the other hand, the relative downfield-shifted signals assigned to the two AB protons of H-20 (δ_H 4.50 and 4.24) and their HMBC correlations to the acetyl carbonyl at δ_C 170.8 located the only acetate group at C-20. The benzoyloxy group was found to be attached to C-2 as evidenced by the HMBC correlation between H-2 (5.90 d, $J=12$ Hz) and the benzoyl carbonyl at δ_C 165.2. The proposed structure was further confirmed by HMBC correlations between H-16/C-15; H-17/C-15; H-5/C-7; H-7/C-19; H-19/C-9 and H-18/C-11,C-13. Acetylation of **2** gave **7**, which showed three acetyl singlets at δ 2.06, 2.05 and 1.95, and the oxygenated methine protons at δ 5.06 (H-5) and δ 5.30 (H-7). The relative stereochemistry at the chiral centers was determined through NOESY correlations, especially between H-19/H-2, H-5,H-20, H-3/H-7 as well as H-5/H-20. Based on the previous discussion, compound **2** was identified as tasumatrol I.

2.3. Structure of compound 3

Compound **3** was isolated as a white powder with $[\alpha]_D=-21.8°$ (*c* 0.1, MeOH). The molecular formula $C_{29}H_{34}O_9$ was determined by NMR and EI-MS through revealing a molecular ion peak at *m/z* 526 $[M]^+$. The ^{1}H and ^{13}C NMR spectral data (Tables 1 and 2) proved the presence the same 11(15→1)-*abeo*-taxane skeleton of **2** having a six-membered lactone with a benzoyloxy and an acetyloxy groups. However, the signal assigned to H-5 was observed as a doublet, not as a broad singlet as in the case of **1** and **2**, at δ 4.85 and did not show any HMBC correlation to either ester carbonyl. On the other hand, the *gem*-coupled protons at δ_H 4.68, 4.24 were assigned to the CH_2-20 (each d, $J=9$ Hz) which was consistent with the formation of a 4-membered oxetane ring commonly present in taxane diterpenes[23] thus satisfying 13° of unsaturation. The relative low field quaternary at δ_C 80.6 was assigned to C-4 indicating its connection to an acetyloxy group since the benzoyloxy group was already decided to be connected to C-2 as a result of δ_H 5.82/δ_C 164.7 HMBC correlation. The HMBC demonstrated correlations between H-20/C-3, C-4,C-5; H-5/C-3, C-4 verifying the presence of an oxetane ring. Other key HMBC correlations were observed between H-16/C-1,C-15; H-2/C-1,C-3,C-15; H-7/C-5,C-8; H-19/C-3,C-9; OH-9 (δ_H 4.40)/C-10,C-11 and H-18/C-11,C-13. Compound **3** was acetylated to yield **8**, which exhibited two acetyl singlets at δ 2.01 and 1.68. Moreover, the signal of H-7 was shifted down-field to δ 5.29. The NOESY correlations between H-20 (δ_H 4.68)/H-2; H-19/H-2,H-17; H-7/H-3, H-5,CH_3-Ac in addition to *o*-benzoyl protons (δ_H 7.97)/ H-14 (δ_H 2.40) determined the relative stereochemistry at the chiral centers and confirmed the structure of **3**. Accordingly, **3** was characterized as tasumatrol J. It is notable that the lack of oxygenation at C-13 in compounds having the taxane skeleton of **2** and **3** is quite rare.[1]

2.4. Structure of compound 4

Compound **4** was isolated as a white powder with $[\alpha]_D=+19.3°$ (*c* 0.1, MeOH). The molecular formula $C_{29}H_{44}O_8$ together with 8° of unsaturation were derived from NMR and FAB-MS that revealed a quasi-molecular ion peak at *m/z* 543 $[M+Na]^+$. The ^{1}H NMR spectrum (Table 1) showed the four methyl singlets distinctive of a normal taxane skeleton at δ_H 1.66, 1.12, 2.09 and 0.81 assigned to H-16, H-17, H-18 and H-19, respectively. The ^{13}C NMR (Table 2) proved the presence of four methyl signals (δ_C 25.4, 31.8, 21.5, 22.2), two quaternary olefinic (δ_C 134.6, 135.8; C-11 and C-12), three ester carbonyls (δ_C 170.2, 169.9 and 175.1) and two acetyl methyls at (δ_C 21.5 double intensity). The ^{1}H NMR revealed the two methyl singlets (δ 2.03, 2.06) of two acetyloxy groups in addition to two methyl doublets at δ_H 1.22 and 1.15. The COSY spectrum displayed connectivities between the methyl doublet at δ_H 1.22 and an oxygenated CH at δ_H 3.85 (m, H-3′); the methyl doublet at δ_H 1.15 and CH at δ_H 2.36 (br s, H-2′) along with a correlation between the two methines at δ_H 2.36 and 3.85. These data together with the carbon signals at δ_C 175.1 (C=O), 46.9 (CH), 69.5 (CH), 20.8 (CH_3) and 14.0 (CH_3) was in agreement with the presence of 2-methyl-3-hydroxybutanoyloxy ester of a related taxane.[24] The two olefinic singlets at δ_H 5.12 and 4.75 together with the CH_2 signal at δ_C 113.5 was in accordance with 4(20) double bond. The ^{1}H NMR revealed four oxygenated methines at δ_H 5.36, 4.19, 6.11 and 5.08 in addition to that belonging to the fore-mentioned 2-methyl-3-hydroxybutanoate ester at δ_H 3.85 (m, H-3′). The two acetyl carbonyls at δ_C 170.2, 169.9 had HMBC correlations with the proton signals at δ_H 5.36 (H-2) and 6.11 (H-10), respectively, while the carbonyl at δ_C 175.1 showed correlations with both δ_H 3.85 (H-3′) and 5.08 (H-14). The DEPT experiment revealed the presence of four methylenes suggesting the absence of oxygenation at neither C-7 nor C-9 which was supported by COSY correlations between H-6/H-7 and H-9/H-10 and HMBC correlations between H-19/C-7,C-9. Other COSY correlations were observed between H-1/H-2, H-2/H-3, H-5/H-6, H-6/H-7, H-13/H-14 proving the attachment of two acetyloxy at each of C-2 and C-10 along with the 2-methyl-3-hydroxybutanoyloxy at C-14. The HMBC spectrum displayed correlation between H-5/C-3,C-20; H-10/C-12 and H-2/C-1,C-14; H-14/C-12,C-15; H-20/C-3. The NOESY experiment displayed correlations between H-1/H-16; H-2/H-19β; H-3α/H-14; H-5/H-6β; H-6β/H-19; H-19/H-9; H-9/H-10 which pointed out to configuration at these positions. The data of **4** were closely similar to those reported for taiwanxan-type taxoid (oxygenation at C-14) previously isolated from Taxus x media Rehd. cv. Hicksii that differed only in acetylation pattern with almost identical data for the 2-methyl-3-hydroxybutanoyloxy group.[10] Acetylation of **4** yielded **9**, which showed identical spectral

data with those of the acetylated product of **14**. From all the above data, the structure of **4** was established and designated as tasumatrol K.

2.5. Structure of compound 5

Compound **5** was isolated as a white powder with $[\alpha]_D = -30.8°$ (*c* 0.1, MeOH). The molecular formula $C_{36}H_{44}O_{15}$ and 15° of unsaturation were derived from NMR and FAB-MS that revealed two quasi-molecular ion peaks at *m/z* 717 $[M+H]^+$ and 739 $[M+Na]^+$. The NMR data (Tables 1 and 2) demonstrated four acetyloxy (8 C-atoms) and one benzoyloxy (7 C-atoms) substitutions in a taxane diterpene which left one carbon atom unaccounted for in the molecular formula. The carbonyl at δ_C 204.2 was assigned to C-13 owing to its HMBC correlation with the methyl singlet at δ_H 1.16 (H-18) while the *C*H_2 signal at δ_C 113.1 and the two olefinic singlets at δ_H 5.41, 4.69 were typical values for 4(20)-double bond and these protons showed HMBC correlations to δ_C 39.4 (C-3) and 72.7 (C-5). The ^{13}C NMR spectra displayed the presence of three oxymethylenes at δ_C 81.5, 61.4 and 68.7 which required extensive study of the 2-D spectra to locate them together with the five acyl groups. The acetate carbonyls at δ_C 169.2, 172.8, 168.4 and 170.0 demonstrated HMBC correlations with methyl singlets at δ_H 2.05, 2.16, 2.03 and 2.11 as well as with the oxygenated C*H* signals at δ_H 6.21, 5.49, 5.42, 5.32 that were assigned for H-2, H-7, H-9 and H-10, respectively. On the other hand, the benzoyl carbonyl at δ_C 166.8 revealed correlations with the oxymethylene at δ_H 5.10, 4.38 (each d, $J=12.3$ Hz) which in turn had correlations with δ_C 69.1 (C-7) and 70.0 (C-9). Consequently, the four acetyloxy groups were connected to C-2, C-7, C-9 and C-10 while the benzoyl group was attached to the oxymethylene of C-19. The second oxymethylene protons at δ_H 4.00 and 3.63 (each d, $J=8.1$ Hz) revealed HMBC correlations to carbons at δ_C 80.3 (C-11), 90.8 (C-12) and 50.2 (C-15). The low field shift of C-12 (90.8) suggested its oxygenation as a part of 12(16)-epoxy ring that accounted for the number of rings in the molecular formula as well as explained the change in configuration that led to the unusually very small coupling constants of $J_{9,10}$. The third oxygenated methylene could only be depicted as attached to C-14 as a result of HMBC correlations between its signal at δ_H 3.79 (2H, br d, $J=8$ Hz) with C-1, C-13 and C-14 as well as the COSY correlations between H-14/H-1; H-1/H-2 and H-2/H-3. The NOESY correlations between H-3/H-7,H-10; H-3/H-20,H-14 determined the α-orientation of H-3, H-14, H-10 and H-7 (Fig. 3). On the other hand, NOESY correlations between H-1/H-2,H-16; H-19/H-2,H-9 and H-9/H-2,H-17 were consistent with the β-orientation of H-1, H-2, H-9 and H-19. Correlations of H-7/H-6α and H-6β/H-5 agreed with the β-orientation of H-5. The unusual hydroxymethyl (C-21) group was thus located at β-disposition of C-14. Acetylation of **5** yielded a diacetate (**10**), which showed two additional acetyl singlets (δ_H 2.27, 2.14) in the ^{1}H NMR spectrum. The chemical shifts of H-5 and H-21 were shifted down-field from δ_H 4.47 and 3.79 (2H, brd, $J=8.0$ Hz) in **5** to δ_H 5.31, 4.43 (dd, $J=5.4$ Hz, 10.5 Hz) and 4.20 (dd, $J=2.4$ Hz, 10.5 Hz), respectively, in **10**. The COSY and NOESY (Fig. 3) spectra of **10** established further the structure of **5**. It is worthy to note that one carbon transfer is biosynthetically feasible usually through *S*-adenosyl-L-methionine.[24] As far as we know, this is the first report of the isolation of a 21-carbon taxane ester from any natural source.

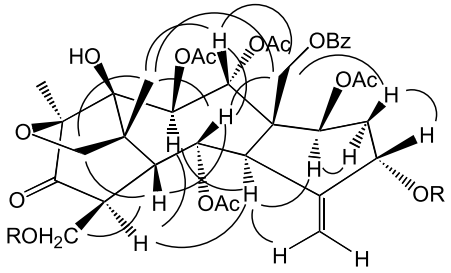
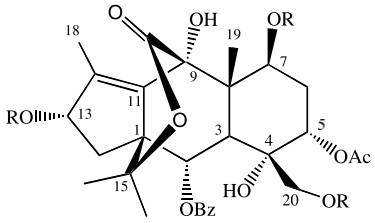


Figure 3. NOESY correlations and steric conformation of **5** and **10**.



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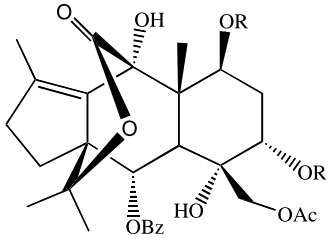
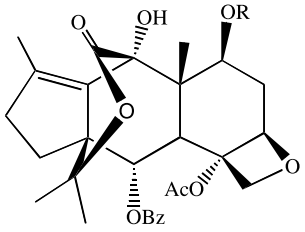
6 R = Ac



2 R = H
7 R = Ac

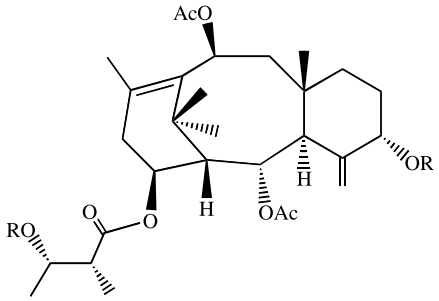


3 R = H
8 R = Ac

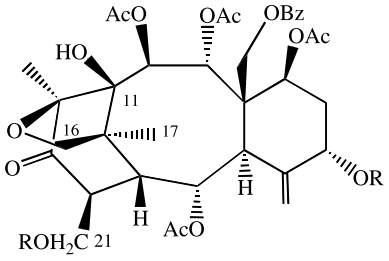
Table 3. Results of cytotoxic activity, expressed as ED_{50} (μg/mL), of the new taxanes against Hepa59, NCI, Hela, DLD-1 and Med cell lines[a]

Name	Hepa59 T/VGH	NCI	Hela	DLD-1	Med
Tasumatrol H	(—)	(—)	(—)	(—)	(—)
Tasumatrol I	6.26	2.45	2.73	3.40	5.12
Tasumatrol J	16.93	13.72	12.69	11.26	10.80
Tasumatrol K	8.57	7.28	7.88	6.57	8.03
Tasumatrol L	(—)	(—)	(—)	(—)	(—)

[a] Hepa59T/VGH, human liver carcinoma; NCI, human large cell carcinoma of lungs; Hela, human cervical epitheloid carcinoma; DLD-1, human colon adenocarcinoma; Med, human medulloblastoma. (—) = ED_{50} > 20 μg/mL. Values for mitomycin, used as standard, were: 0.18 (Hepa59T/VGH), 0.19 (NCI), 0.18 (Hela), 0.11 (DLD-1) and 0.24 (Med).



4 R = H
9 R = Ac



5 R = H
10 R = Ac

2.6. Results of cytotoxic activity

The cytotoxic activity of the isolated new compounds was tested against human liver carcinoma (Hepa59T/VGH), human large cell carcinoma of the lungs (NCI), human cervical epitheloid carcinoma (Hela), human colon adenocarcinoma (DLD-1) and human medulloblastoma (Med) cell lines. As demonstrated in Table 3, compounds **2** and **4** exhibited significant activity against all the tested cell lines.

3. Experimental

3.1. General

Optical rotations were recorded on a JASCO DIP-1000 polarimeter. IR and UV spectra were measured on Hitachi T-2001 and Hitachi U-3210 spectrophotometers, respectively. Low-resolution EIMS and FABMS spectra were recorded on a VG Quattro 5022 mass spectrometer. High-resolution ESIMS spectra were measured on a JEOL HX 110 mass spectrometer. The ^{1}H, ^{13}C NMR, COSY, HMQC, HMBC, and NOESY spectra were recorded on a Bruker FT-300 spectrometer or on a Varian Unity INOVA 500 FT-NMR at 500 MHz for ^{1}H and 125 MHz for ^{13}C, respectively, using TMS as internal standard. The chemical shifts are given in δ (ppm) and coupling constants in Hz. Silica gel 60 (Merck) was used for column chromatography (CC), and pre-coated silica gel plates (Merck, Kieselgel 60 F-254, 1 mm) were used for preparative TLC. Sephadex LH-20 (Amersham Pharmacia Biotech AB, Sweden) was used for either purification and/or separation.

3.2. Plant material

The leaves and twigs of seven years old trees of *T. sumatrana* (Miq.) de Laub. were collected from Kaohsiung county, Taiwan at an altitude of 1000 m in March 2002. A voucher specimen (TPG 8-7) was kept in the Institute of Marine Resources, National Sun Yat-sen University, Kaohsiung, Taiwan.

3.3. Extraction and isolation

Dried leaves and twigs (15.5 kg) were grounded and extracted thrice with acetone at room temperature. The combined extracts were filtered and concentrated under vacuum to obtain a crude extract (3.05 kg). The extract was stirred twice with water (2×3.5 L) and the resulting emulsion was separated from the residue (Res) and partitioned between EtOAc/water (1:1) to produce EtOAc extract (173 g). The EtOAc extract was fractionated on Sephadex LH-20 using MeOH for elution into fraction A (60 g) and B (86 g). Fraction A was chromatographed on a NP-silica gel column using *n*-hexane/CH_2Cl_2/MeOH (100:100:1 to 1:1:1) to yield 10 fractions F-1 to F-10. Fraction F-9 (7.5 g) was subjected to reversed phase preparative TLC using a gradient of H_2O/MeOH/CH_3CN (70:25:5, 60:35:5, 50:45:5, 40:55:5, 30:65:5, 20:75:5 each 500 mL) to yield six fractions F-9-1 to F-9-6. Fraction F-9-4 was separated on NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (8:8:1) to yield 10-deacetyl-13-oxobaccatin III (**11**, 15 mg), **1** (10 mg) and 10-deacetylbaccatin III (**12**, 11 mg). The residue (Res) was partitioned between *n*-hexane/MeOH/H_2O (4:3:1) to produce a *n*-hexane and hydromethanolic layers. The latter was concentrated under vacuum and then partitioned between water and ethyl acetate. The resultant ethyl acetate extract was concentrated to 250 g and then fractionated on Sephadex LH-20 using MeOH for elution to yield seven fractions Tax-A to Tax-G. Tax-B (32 g) was separated on silica gel column using a gradient of *n*-hexane/CH_2Cl_2/MeOH (100:100:1 to 0:1:1) to furnish eight fractions Tax-B-a to Tax-B-h. Tax-B-a (2.45 g) was separated on silica gel column using a gradient of *n*-hexane/acetone followed by purification on preparative silica gel TLC using *n*-hexane/acetone (2:1) to produce **2** (8 mg). Tax-B-b (370 mg) was separated on NP-HPLC

using *n*-hexane/acetone (2:1) to produce five fractions Tax-B-b-1 to Tax-B-b-5. Tax-B-b-3 was further fractionated on NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (20:20:1) to yield taxacin (**13**, 15 mg) and yunnanxane (**14**, 9 mg). Treatment of Tax-B-b-4 in the same previous manner furnished 5α-hydroxy-2α,7β,9α,10β,13α,tetraacetoxy-4(20),11-taxadiene (**15**, 16 mg) and taxuspin F (**16**, 21 mg) whereas a similar treatment of Tax-B-b-5 gave baccatin IV (**17**, 21 mg). Fractionation of Tax-B-c (342 mg) using NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (10:10:1) to give three fractions Tax-B-c-1 to Tax-B-c-3. Tax-B-c-2 was fractionated on RP-HPLC using MeOH/H_2O (70:3) to give wallifoliol (**18**, 34 mg). Further fractionation of Tax-B-c-3 using NP HPLC and *n*-hexane/EtOAc (2:1) furnished **3** (11 mg). Tax-B-e (510 mg) was fractionated by NP-HPLC using *n*-hexane/CH_2Cl_2/MeOH (15:15:1) to yield three fractions, Tax-B-e-1 to Tax-B-e-3. Separation of Tax-B-e-1 by RP-HPLC using MeOH/H_2O/CH_3CN (50:45:5) to give 20-deacetyltaxachitriene A (**19**, 9 mg) and a mixture that was fractionated by NP HPLC using *n*-hexane/CH_2Cl_2/MeOH (10:10:1) to produce taxinine M (**20**, 13 mg) and **4** (9 mg). Fraction Tax-B-f (294 mg) was subjected to RP HPLC using MeOH/H_2O/CH_3CN (55:45:5) then further purified by NP HPLC using *n*-hexane/CH_2Cl_2/MeOH (8:8:1) to yield 7-*epi*−10-deacetyl taxol (**21**, 17 mg). Fraction Tax-B-g (3.39 g) was chromatographed on a silica gel column using *n*-hexane/acetone (5:1) then fractionated by NP HPLC using *n*-hexane/CH_2Cl_2/MeOH (10:10:1) to give, after purification on NP-PTLC using *n*-hexane/EtOAc (2:3), taxol (**22**, 6 mg), baccatin III (**23**, 12 mg) and, after purification on NP-PTLC using n-hexane/acetone (4:1), **5** (8 mg).

3.3.1. Compound 1. Colorless powder. $[\alpha]_D^{25}=-27.2°$ (*c* 0.1, MeOH); UV λ_{max} (log ε) (MeOH) 229 (4.10) nm; IR (CH_2Cl_2) ν_{max} 3418 (OH), 1733, 1715, 1703 (C=O), 1278, 714 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Tables 1 and 2; EIMS: *m/z* 542 $[M-H_2O]^+$, 524 $[M-2H_2O]^+$, 480 $[M-HOAc]^+$, 376, 331, 298, 283, 273, 271, 255, 229, 227, 219, 213, 201, 77, 43; FABMS: *m/z* 583 $[M+Na]^+$, 561 $[M+H]^+$; HRESIMS *m/z* 583.2153 $[M+Na]^+$ (calcd for $C_{29}H_{36}O_{11}Na$, 583.2155).

3.3.2. Compound 2. Colorless powder. $[\alpha]_D^{25}=-25.6°$ (*c* 0.1, MeOH); UV λ_{max} (log ε) (MeOH) 228 (4.05) nm; IR (CH_2Cl_2) ν_{max} 3419 (OH), 1714, 1703 (C=O), 1635 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Tables 1 and 2; FABMS: *m/z* 567 $[M+Na]^+$, 545 $[M+H]^+$; EIMS: *m/z* 341, 327, 229, 214, 187, 161, 149, 105, 77; HRESIMS *m/z* 567.2205 $[M+Na]^+$ (calcd for $C_{29}H_{36}O_{10}Na$, 567.2207).

3.3.3. Compound 3. Colorless powder. $[\alpha]_D^{25}=-21.8°$ (*c* 0.1, MeOH); UV λ_{max} (log ε) (MeOH) 225 (4.03) nm; IR (CH_2Cl_2) ν_{max} 3415 (OH), 1733, 1729, 1718 (C=O), 1647, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Tables 1 and 2; FABMS: *m/z* 549 $[M+Na]^+$, 527 $[M+H]^+$; EIMS: *m/z* 526 $[M]^+$, 448, 437, 149, 121, 105, 77; HRESIMS *m/z* 527.2283 $[M+Na]^+$ (calcd for $C_{29}H_{34}O_9Na$, 527.2281).

3.3.4. Compound 4. Colorless powder. $[\alpha]_D^{25}=+19.3°$ (*c* 0.1, MeOH); UV λ_{max} (log ε) (MeOH) 218 (3.96) nm; IR (CH_2Cl_2) ν_{max} 3445 (OH), 1733 (C=O), 1246 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Tables 1 and 2; FABMS: *m/z* 543 $[M+Na]^+$; HRESIMS *m/z* 543.2932 $[M+Na]^+$ (calcd for $C_{29}H_{44}O_8Na$, 543.2935).

3.3.5. Compound 5. Colorless powder. $[\alpha]_D^{25}=-30.8°$ (*c* 0.1, MeOH); UV λ_{max} (log ε) (MeOH) 227 (4.08) nm; IR (CH_2Cl_2) ν_{max} 3440 (OH), 1733, 1716 (C=O), 1218 (C–O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) Tables 1 and 2; FABMS: *m/z* 739 $[M+Na]^+$, 717 $[M+1]^+$; EIMS: *m/z* 686 $[M-CH_2O]^+$, 669, 668, 626, 4113, 371, 341, 325, 311, 296, 283, 281, 253, 239, 223, 197, 185, 175, 159, 77; HRESIMS *m/z* 739.2575 $[M+Na]^+$ (calcd for $C_{36}H_{44}O_{15}Na$, 739.2578).

3.3.6. Compound 6. Compound **1** (3 mg) was acetylated (Ac_2O/py, each 0.3 mL) at room temperature for 16 h. After the usual work up of the reaction product gave **6** (2.1 mg). $[\alpha]_D^{25}=-23.4°$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.80 (d, *J*=12 Hz, H-2), 2.80 (d, *J*=12 Hz, H-3), 5.05 (br s, H-5), 1.90 (m, H-6), 2.22 (m, H-6), 5.33 (dd, *J*=5.1, 10.5 Hz, H-7), 5.58 (m, H-13), 2.40 (m, H-14), 1.36, 1.34, 1.26, 0.90 (s, Me-16, -17, -18, -19), 4.56 (d, *J*=10.8 Hz, H-20), 4.32 (d, *J*=10.8 Hz, H-20), 1.97, 2.02, 2.07, 2.17 (each $COCH_3$, s), 7.98 (d, *J*=7.2 Hz, *o*-COPh), 7.57 (t, *J*=7.2 Hz, *p*-COPh), 7.46 (t, *J*=7.2 Hz, *m*-COPh); EIMS: *m/z* 668 $[M-H_2O]^+$, 608, 566, 504, 444, 429, 402, 147, 105, 77; HRESIMS *m/z* 709.2476 $[M+Na]^+$ (calcd for $C_{35}H_{42}O_{14}Na$, 709.2473).

3.3.7. Compound 7. Compound **2** (3 mg) was acetylated using Ac_2O/py (1:1) at room temperature for 16 h. After the usual work up of the reaction product gave **7** (2.0 mg). $[\alpha]_D^{25}=-10.2°$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.81 (d, *J*=12 Hz, H-2), 2.70 (d, *J*=12 Hz, H-3), 5.06 (br s, H-5), 1.85 (m, H-6), 2.20 (m, H-6), 5.30 (m, H-7), 2.30–2.50 (m, H-13), 1.67 (m, H-14), 1.33, 1.32, 1.26, 0.93 (s, Me-16, -17, -18, -19), 4.50 (d, *J*=10.5 Hz, H-20), 4.30 (d, *J*=10.5 Hz, H-20), 1.95, 2.05, 2.06 (each $COCH_3$, s), 8.04 (d, *J*=7.5 Hz, *o*-COPh), 7.60 (t, *J*=7.5 Hz, *p*-COPh), 7.46 (t, *J*=7.5 Hz, *m*-COPh); EIMS: *m/z* 628 $[M]^+$, 611, 446, 300, 167, 149, 121, 105, 77; HRESIMS *m/z* 651.2415 $[M+Na]^+$ (calcd for $C_{33}H_{40}O_{12}Na$, 651.2417).

3.3.8. Compound 8. Compound **3** (2 mg) was acetylated (Ac_2O/py, each 0.3 mL) at room temperature for 16 h. After the usual work up of the reaction product gave **8** (1.8 mg). $[\alpha]_D^{25}=-4.5°$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.78 (d, *J*=11.7 Hz, H-2), 2.79 (d, *J*=11.7 Hz, H-3), 4.81 (d, *J*=6 Hz, H-5), 2.98 (m, H-6), 5.29 (dd, *J*=5.4, 9.3 Hz, H-7), 2.40–2.50 (m, H-13), 1.67 (m, H-14), 2.18, 1.33, 1.30, 1.26 (s, Me-16, -17, -18, -19), 4.73 (d, *J*=8.4 Hz, H-20), 4.29 (d, *J*=8.4 Hz, H-20), 2.01, 1.68 (each $COCH_3$, s), 7.97 (d, *J*=7.8 Hz, *o*-COPh), 7.61 (t, *J*=7.8 Hz, *p*-COPh), 7.47 (t, *J*=7.8 Hz, *m*-COPh); EIMS: *m/z* 568 $[M]^+$, 404, 360, 149, 131, 105, 77; HRESIMS *m/z* 591.2206 $[M+Na]^+$ (calcd for $C_{31}H_{36}O_{10}Na$, 591.2206).

3.3.9. Compound 9. Compound **4** (2 mg) was acetylated using Ac_2O/py (1:1) at room temperature for 16 h. After the usual work up of the reaction product gave **9** (1.6 mg).

$[\alpha]_D^{25} = +11.3°$ (*c* 0.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 5.34 (overlap, H-2), 2.93 (d, $J=5.7$ Hz, H-3), 5.28 (t, $J=7.2$ Hz, H-5), 1.85 (m, H-6), 2.25 (m, H-6), 1.65 (m, H-9), 6.05 (dd, $J=10$, 3 Hz, H-10), 2.50–2.60 (m, H-13), 5.08 (m, H-14), 2.18, 1.67, 1.23, 1.13 (s, Me-16, -17, -18, -19), 5.28 (s, H-20), 4.85 (s, H-20), 2.01, 2.04, 2.06, 2.10 (each $COCH_3$, s), 5.06 (m, H-4′); EIMS: *m/z* 444, 429, 384, 264, 249, 135, 105, 91, 83; HRESIMS *m/z* 627.3145 $[M+Na]^+$ (calcd for $C_{33}H_{48}O_{10}Na$, 627.3146).

3.3.10. Compound 10. Compound **5** (2 mg) was acetylated using Ac_2O/py (1:1) at room temperature for 15 h. After the usual work up of the reaction product gave **10** (1.5 mg). $[\alpha]_D^{25} = -28.1°$ (*c* 0.4, $CHCl_3$);^1H NMR (300 MHz, $CDCl_3$): δ 2.27 (overlap, H-1), 6.20 (d, $J=11$ Hz, H-2), 3.51 (d, $J=11$ Hz, H-3), 5.31 (br s, H-5), 2.27 (overlap, H-6), 1.75 (m, H-6), 5.45 (dd, $J=6.3$, 10.5 Hz, H-7), 5.31 (d, $J=3.5$ Hz, H-9), 5.39 (d, $J=3.5$ Hz, H-10), 2.95 (m, H-14), 4.05 (d, $J=8.1$ Hz, H-16), 3.54 (d, $J=8.1$ Hz, H-16), 1.19 (s, Me-17), 1.26 (s, Me-18), 5.12 (d, $J=12.3$ Hz, H-19), 4.39 (d, $J=12.3$ Hz, H-19), 5.53 (s, H-20), 4.81 (s, H-20), 4.43 (dd, $J=5.4$, 10.5 Hz, H-21), 4.20 (dd, $J=2.4$, 10.5 Hz, H-21), 2.03, 2.05, 2.08, 2.14, 2.16, 2.27 (each CH_3, s), 8.15 (d, $J=$ 7.2 Hz, *o*-COPh), 7.62 (t, $J=7.2$ Hz, *p*-COPh), 7.52 (t, $J=$ 7.2 Hz, *m*-COPh); EIMS: *m/z* 800 $[M]^+$, 740, 680, 638, 516, 253, 151, 133, 105, 77; HRESIMS *m/z* 823.2786 $[M+Na]^+$ (calcd for $C_{40}H_{48}O_{17}Na$, 823.2789).

3.3.11. Compound 14. The title compound (3 mg) was acetylated using Ac_2O/py (1:1) at room temperature for 16 h. After the usual work up of the reaction product gave a compound (2 mg) identical with **9**.

3.4. Cytotoxicity assay

The cells for assay were cultured in RPMI-1640 medium supplemented with a 5% CO_2 incubator at 37 °C. The cytotoxicity assay depends on the binding of methylene blue to fixed monolayers of cells at pH 8.5, washing the monolayer, and releasing the dye by lowering the pH value. Samples and control standard drugs were prepared at a concentration of 1, 10, 40, and 100 μg/mL. After seeding 2880 cells/well in a 96-well microplate for 3 h, 20 μL of sample or standard agent was placed in each well and incubated at 37 °C for 3 days. After removing the medium from the microplates, the cells were fixed with 10% formaldehyde in 0.9% saline for 30 min, then dyed with 1% (w/v) methylene blue in 0.01 M borate-buffer (100 μL/well) for 30 min. the 96-well plate was dipped into a 0.01 M borate-buffer solution four times in order to remove the dye. Then, 100 μL/well of EtOH–0.1 M HCl (1:1) was added as a dye eluting solvent, and the absorbance was measured on a microtiter plate reader (Dynatech, MR 7000) at a wavelength of 650 nm. The ED_{50} value was defined by a comparison with the untreated cells as the concentration of test sample resulting in 50% reduction of absorbance.

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New '2-phenylnaphthalene'-mediated synthesis of benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones and 6-oxa-benzo[*a*]anthracene-5,7,12-triones: first total synthesis of 6-oxa-benzo[*a*]anthracen-5-ones

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Abstract—We describe here a novel synthesis of benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones based on the heteroannulation of 2-(2-bromophenyl)-3-hydroxy-1,4-naphthoquinones. The naphthoquinones were prepared from 3-(2-bromophenyl)naphthalen-2-ols, which were obtained by intramolecular aldol condensation of 2-[3-(2-bromophenyl)-2-oxo-propyl]benzaldehydes. Alternatively, benzo[*b*]naphtho[2,3-*d*]furan-6,11-diones were obtained more directly and efficiently by cyclization of 3-(2-bromophenyl)naphthalen-2-ols to benzo[*b*]-naphtho[2,3-*d*]furans and oxidation of the resulting compounds. Furthermore, the first 6-oxabenzo[*a*]anthracen-5-one described was similarly obtained from 2-[3-(2-formylphenyl)-2-oxopropyl]benzoic acid and oxidized to 6-oxa-benzo[*a*]anthracene-5,7,12-trione.

A tricyclic structural pattern, consisting of a either a phenyl ring attached to position 2 of a naphthalene nucleus or composed of various heterocyclic ring units with similar molecular structural arrangements, is present in a large number of biologically and pharmacologically active compounds.[1] Examples include benzo[*a*]pyrene and 7,12-dimethylbenz[*a*]anthracene (carcinogenic); coralyne and nitidine (antileukemic); chartreusin and rabelomycin (antibacterial, cytotoxic); camptothecin, streptonigrin, and ellipticine (antineoplastic); WS-5995A (anticoccidial); genistein (estrogenic); methaqualone (sedative, hypnotic, anticonvulsive); and gossypol (antioxidant, male contraceptive), among others.[1] The structural pattern per se may not be sufficient to provide biological activity. Nevertheless, by attachment of the appropriate groups or substituents to specific positions on both ring units, it is believed that compounds with the desired biological actions can be designed.

Among compounds possessing this structural pattern, it is evident that many antineoplastic agents assume a coplanar conformation. The coplanarity of the two ring systems can be achieved either by hydrogen-bond formation between the two ring units, as in streptonigrin, or through a condensed structure, such as camptothecin or ellipticine.[1]

On the basis of the concept outlined above, a search for suitable chemical structures to fulfil the requirements for drug design has been undertaken in recent years. For instance, it was found that 5*H*-benzo[*d*]naphtho[2,3-*b*]pyran-5,7,12-triones (**4**) include compounds like the antibiotic WS-5995 A,[2] which is produced by a new strain of Streptomyces designated *S. auranticolor*. In addition, two recently described synthetic analogues, *o*-quinone J1 and model *p*-quinone J7,[3] were shown to be antitumour agents that inhibit macromolecule synthesis, block nucleoside transport, induce DNA fragmentation, and decrease the growth and viability of L1210 leukemic cells more effectively than ellagic acid and genistein in vitro.

Closely related benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione **3** belongs to another family of compounds selected as suitable starting structures for drug design. These compounds also possess the characteristic '2-phenylnaphthalene-type' structural pattern, with the presence of the ether linkage connecting the rings making the structure planar. It was found that although this compound did not exhibit anticancer properties itself, compounds of type **3** bearing substituents at specific positions proved to be promising antitumoural agents.[4]

Keywords: Quinones; Heterocycles; Ketoacids; Ullman reaction.
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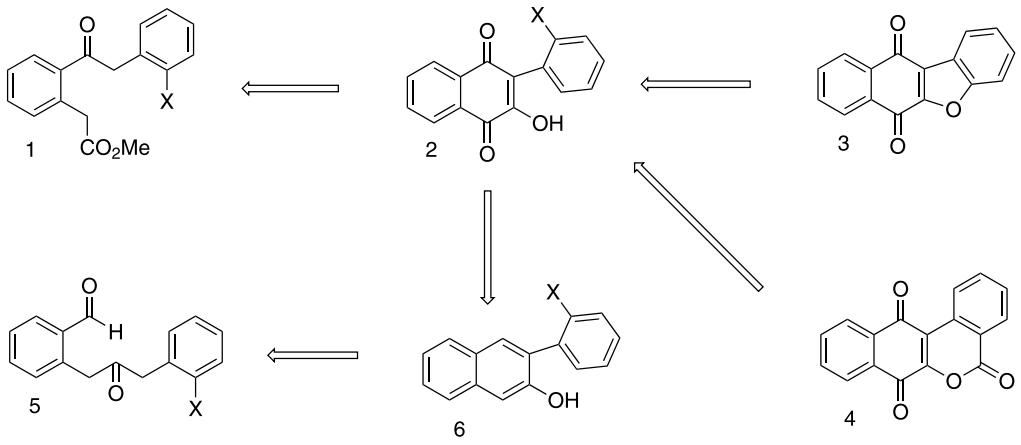
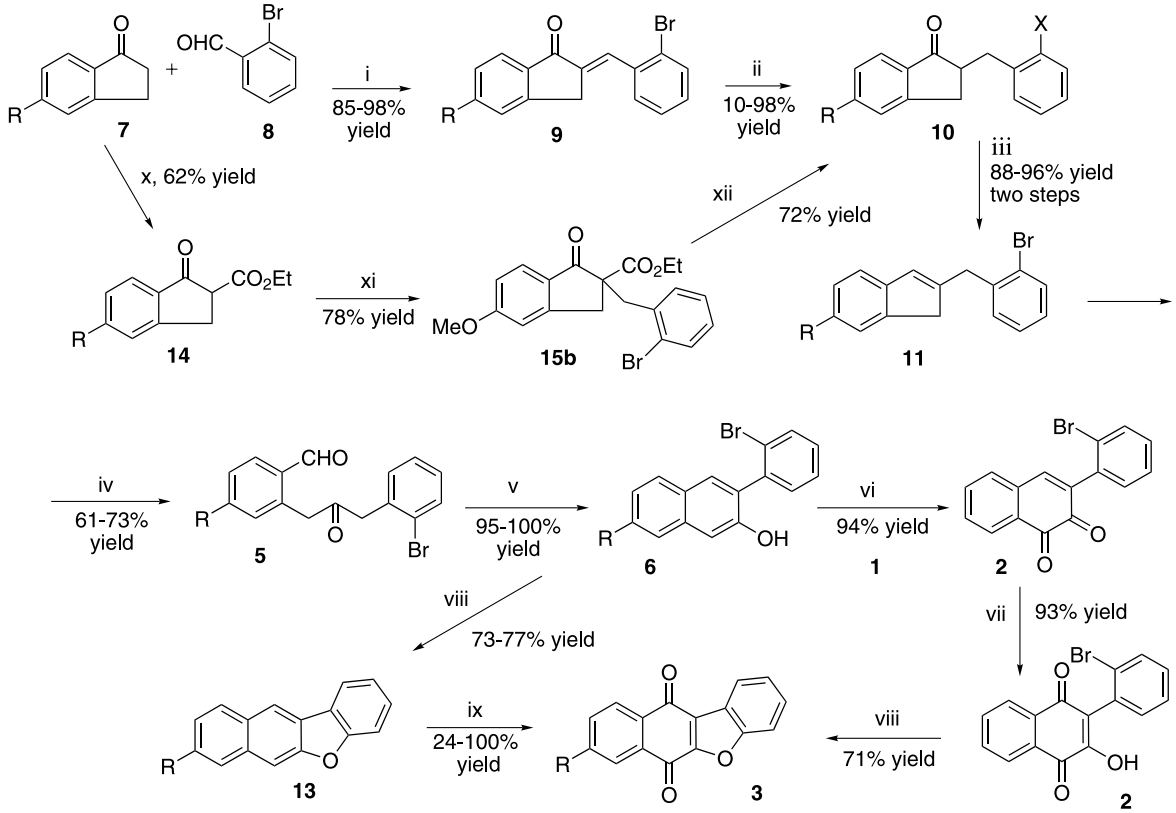


Scheme 1. X=Br, $CONEt_2$.

Previous syntheses of benzofuronaphthoquinones **3**,[5] benzopyronaphthoquinones **4**[6] and related compounds include a common 2-phenylnaphthalene-type strategy for the synthesis of these targets. This method is based on the heteroannulation of appropriate 2-phenyl-1,4-naphthoquinones **2** (Scheme 1) obtained by mixed intramolecular Claisen condensation of phenylacetylphenylacetic acids **1**.[5a,d,6h] However, this simple and efficient method is of limited scope due to the lack of availability of starting materials **1**.

We describe a novel, yet closely related, '2-phenylnaphthalene'-based synthesis of benzofuronaphthoquinones **3** and benzopyronaphthoquinones **4** that does not suffer from the limitations outlined above. This method also involves heteroannulation of 2-hydroxy-3-phenyl-1,4-naphthoquinones **2**, which can be obtained by intramolecular aldol cyclization of ketobenzaldehydes **5** followed by oxidation of the resulting 3-phenyl-2-naphthols **6**.[7]

This new route to naphthoquinones **2** was first applied to the synthesis of unsubstituted benzofuronaphthoquinone **3a**. The starting bromophenylketopropylbenzaldehyde **5a** was obtained as follows (Scheme 2): condensation of 1-indanone **7a** with *o*-bromobenzaldehyde (**8**) in basic conditions gave



Scheme 2. 3, **5**, **6**, **7**, **9**, **11**, **13**, **14**: (a) R=H; (b) R=OMe; **10**: (a) R=H, X=Br, (b) R=X=H; (c) R=OMe, X=Br; (d) R=OMe, X=H. Conditions. (i) NaMeO/MeOH, rt, 15–27 h. (ii) H_2, Pd/C, AcOEt, 1 atm, 75–210 min. (iii) (a) $NaBH_4$, MeOH, rt, 60–90 min; (b) H_2SO_4, reflux, 1–2 h. (iv) (a) O_3, −78 °C, 3–6 min; (b) Me_2S, −78 °C (4–7 h), rt (13 h). (v) NaOH aq, rt, 1.5–2 h. (vi) Fremy's salt, K_2HPO_4, acetone, rt, 1–4 h. (vii) H_2SO_4, MeOH, reflux, 29 h. (viii) CuO, K_2CO_3, pyr, reflux, 1.5–4 h. (ix) CrO_3, AcOH, reflux, 10 min. (x) NaH, $CO(OEt)_2$, benzene, reflux, 0.5 h. (xi) NaH, 2-bromobenzyl bromide, DMF, 60 °C, 44.5 h. (xii) 48% HBr. 96% AcOH, 120 °C, 1.5 h.

the bromobenzylideneindanone **9a** (98% yield),[8] which when subjected to controlled catalytic hydrogenation furnished the expected bromobenzylindanone **10a**[9] (98% yield) without the formation of compound **10b** through simultaneous hydrogenolysis of the C–Br bond. Subsequent reduction of indanone **10a** with $NaBH_4$ gave a mixture of indanols,[10] which was directly converted into bromobenzylindene **11a**[11] by refluxing with concentrated sulfuric acid for an hour. Finally, indene **11a** was transformed into the desired ketoaldehyde **5a** by ozonolysis.[12] This key intermediate was easily identified from spectroscopic and analytical data. The mass spectrum showed the molecular ion peaks at *m/z* 318 and *m/z* 316, with the typical isotope pattern expected for bromo compounds. The ^1H NMR spectrum contained a singlet at 10.01 ppm due to the aldehyde proton. Several representative signals in the ^{13}C NMR include a signal at 125.2 ppm, due to the carbon bearing the bromo- substituent, and two signals at 193.3 and 203.2 ppm, due to the ketone and aldehyde carbonyls, respectively.

Intramolecular aldol condensation of ketoaldehyde **5a** readily gave a quantitative yield of the expected bromophenylnaphthol **6a**.[13] Treatment of this compound with Fremy's salt yielded bromophenylnaphthoquinone **12a** in 94% yield[14] and this was reacted with sodium hydroxide in methanol at rt for 15 min to give bromophenylhydroxynaphthoquinone **2** in only 7% yield.[15] However, the yield of this reaction was improved to 93% when it was carried out under acidic conditions (H_2SO_4, MeOH, reflux).[16] Finally, when compound **2** was subjected to previously described Ullman reaction conditions,[15] the expected benzofuronaphthoquinone **3a** was obtained in 71% yield.

Alternatively, when 3-bromophenyl-2-naphthol **6a** was submitted to the Ullman reaction conditions,[15] 73% yield of the benzonaphthofuran **13a** was obtained. Oxidation of **13a** with CrO_3 in acetic acid[17] gave the target **3a** in quantitative yield. The molecular formula of compound **13a** ($C_{16}H_{10}O$) was confirmed by mass spectrometry. The ^1H NMR contained signals between 7.35 and 8.42 ppm due to the ten aromatic protons. Two characteristic signals in the ^{13}C NMR were observed at 154.8 and 157.6 ppm due to the carbons of the ethereal bridge.

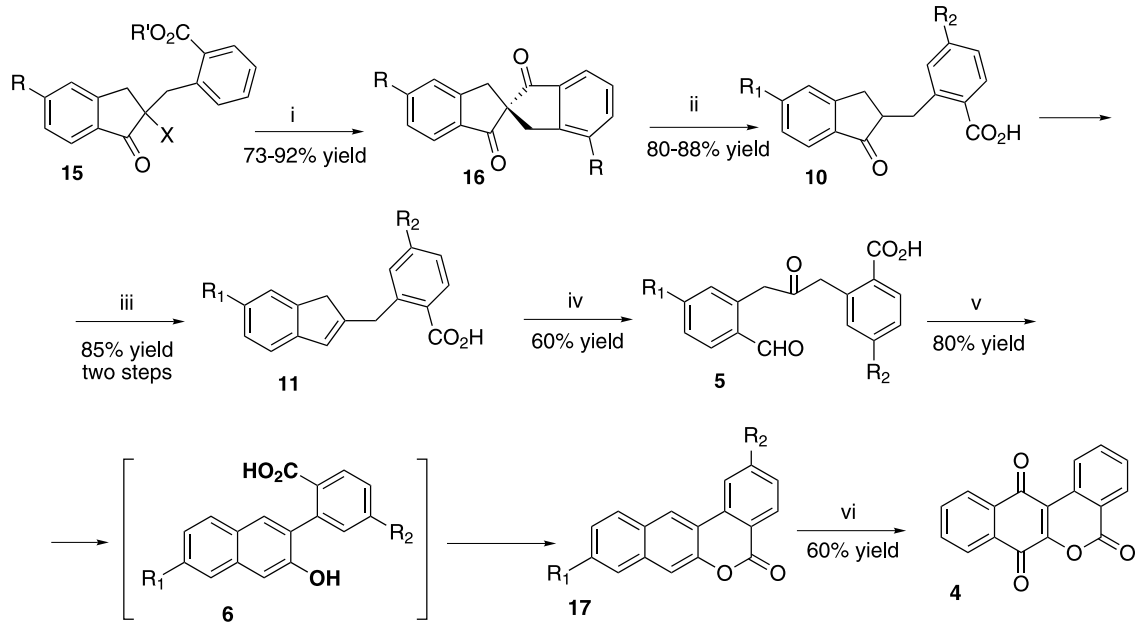
This alternative synthesis of **3a** is clearly more convenient than the route via hydroxyphenylnaphthoquinone **2a**, not only because it is both shorter and more efficient, but because it avoids experimental problems encountered with the former route due to the manipulation of quinone compounds in earlier stages of the synthesis. Moreover, this new route constitutes a novel synthetic approach to benzonaphthofurans **13**,[18] as illustrated by the preparation of benzonaphthofuran **13a** (brazan), which was originally isolated[2] from coal tar distillate.

The general interest of this novel route was immediately demonstrated by the similar transformation of methoxyindanone **7b** into benzonaphthofuran **13b** and its benzofuronaphthoquinone derivative **3b** via benzylideneindanone **9b**, benzylindanone **10b**, benzylindene **11b**, ketoaldehyde **5b** and bromophenylnaphthol **6b**. In this case, catalytic hydrogenation of benzylideneindanone **9b** was accompanied by the undesired hydrogenolysis of its C–Br bond. Indeed, an oil consisting of a mixture of the bromobenzylindanone **10c** (major component) and benzylindanone **10d** (minor component) was obtained and only a small portion the desired compound **10c** could be isolated from this. However, **10c** was efficiently obtained as follows: treatment of methoxyindanone **7b** with NaH and diethyl carbonate gave 2-ethoxycarbonyl-1-indanone **14b** in 62% yield. This compound was efficiently converted into 2-ethoxycarbonyl-1-indanone **15b** by reaction with NaH and *o*-bromobenzyl bromide.[19] Finally, a solution of **15b** and concentrated HBr was heated under reflux in acetic acid for 1.5 h. This reaction gave the desired *o*-bromobenzylindanone **10c** in 72% yield as a result of the hydrolysis of the ester functionality followed by decarboxylation of the resulting ketoacid.[20]

We next proceeded to apply this novel 2-phenylnaphthalene-based methodology for the synthesis of benzonaphthofurans **13** and benzofuronaphthoquinones **3** to the preparation of related benzonaphthopyranone **17a** and benzopyronaphthoquinone **4**.

2-Ethoxycarbonyl-1-indanone **14a** was quantitatively transformed into the corresponding 2-ethoxycarbonyl-2-benzyl-1-indanone **15a** by reaction[19] with 2-ethoxycarbonylbenzyl bromide, which was obtained[21] by reaction of *o*-ethoxycarbonyltoluene with NBS (Scheme 3). A solution of **15a** in acetic acid was reacted with HBr at 120 °C for 3.25 h in order to hydrolyse the two ester functions and to transform the resulting dicarboxylic acid **15c** into benzylindanone **10e** by decarboxylation.[20] Unexpectedly, the only compound formed was the spiro diindanone **16a**,[22] as deduced from spectroscopic and analytical data. The mass spectrum indicated a molecular formula $C_{17}H_{12}O_2$ for this compound. Moreover, the IR spectrum showed bands at 1720 and 1694 cm^{-1} due to the two carbonyl groups. The ^1H NMR spectrum showed two signals at 3.73 and 3.20 ppm, corresponding to the two methylene groups, together with signals for a total of eight aromatic protons. Characteristic signals in the ^{13}C NMR spectrum were observed at 153.8 ppm, due to the spiranic quaternary carbon, and 202.07 ppm, due to the carbonyl groups. Formation of spiro compound **16a** can be explained by assuming that indanone **15a** readily undergoes a highly regioselective hydrolysis of the ethoxycarbonyl group in the position α to the ketone. This is followed by decarboxylation and subsequent intramolecular mixed Claisen condensation of the resulting ethoxycarbonylbenzylindanone **15d** under the acidic reaction conditions.

As expected, reaction of **16a** with NaOH readily gave a retro-aldol process and led to the desired indanone ketoacid **10e**.[23] This compound was subjected to a reaction sequence similar to that used for the transformation of bromo compounds **6** into benzofuronaphthoquinones **3**. Thus, reduction of ketoacid **10e** with $NaBH_4$ gave a quantitative yield of a mixture of indanols, which were reacted with 10% HCl in dioxane to provide the desired indene **11c**. Subsequent ozonolysis of **11c** gave the key ketoaldehyde **5c**, which was reacted with NaOH directly to furnish the target compound **17a**. This process probably involves the initial formation of the expected 2-naphthol **6c** resulting



Scheme 3. 15: (a) R=H, R′=Et, X=CO_2Et; (c) R=H, R′=OH, X=CO_2H; (d) R=X=H, R′=Et; (e) R=OMe, R′=Et, X=CO_2Et; (f) R=OMe, R′=OH, X=CO_2H; (g) R=OMe, X=H, R′=Et. **10**: (e) R_1=R_2=H; (f) R_1=OMe, R_2=H; (g) R_1=H, R_2=OMe; **5**, **6**,**11**: (c) R_1=R_2=H; (d) R_1=OMe, R_2=H; (e) R_1=H, R_2=OMe. **16**, **17**: (a) R_1=R_2=H; (b) R_1=OMe, R_2=H; (c) R_1=H, R_2=OMe. Conditions. (i) HBr, AcOH, reflux, 3.25 h. (ii) 1.25 M aq NaOH, EtOH, reflux, 5 h. (iii) (a) $NaBH_4$, MeOH, 0–>5 °C, 8.25 h; (b) HCl, dioxan, reflux, 10.5 h. (iv) (a) O3, −78 °C, 3–6 min; (b) Me_2S, −78 °C (4–7 h), rt (13 h). (v) NaOH aq, rt, 1.5–2 h. (vi) CrO_3, AcOH, reflux, 10 min.

from the intramolecular aldol cyclization, followed by the spontaneous lactonization of this compound under the reaction conditions. Finally, as predicted, benzonaphthopyranone **17a** was easily oxidized to benzopyronaphthoquinone **4** when reacted with CrO_3.

The synthesis of **4** reported here is clearly more convenient than previous routes[6] via hydroxyphenylnaphthoquinones **2** and has the additional advantage that it allows the generation of the quinone moiety to be left until the final step of the synthesis. This aspect overcomes the problems associated with the manipulation of quinone compounds. Moreover, the new route constitutes the first total synthesis of 6-oxa-benzo[*a*]anthracen-5-one, as illustrated by the preparation of benzonaphthopyranone **17a**.

A predictable limitation of this route to benzonaphthopyranones **17** was confirmed in the attempt to obtain methoxybenzonaphthopyranone **17b** from 2-ethoxycarbonyl-2-benzyl-1-indanone **15e**, prepared by reaction of methoxyindanone **14b** with 2-ethoxycarbonylbenzyl bromide. As expected, treatment of **15e** with HBr, as described above, gave diindanone **16b** but reaction of this compound with NaOH gave a mixture of indanone ketoacids **10f** and **10g**. Since isolation of these compounds from the mixture was not very efficient, they could not be transformed into the corresponding benzonaphthopyranones **17b** and **17c**.

In conclusion, we describe here a divergent synthesis of benzofuronaphthoquinones **3** from phenylketopropylbenzaldehydes **5**. The route via 2-hydroxy-3-phenyl-1,4-naphthoquinones **2** constitutes a more generally applicable version of a previously described route. The alternative shorter and more efficient route includes a novel total synthesis of benzonaphthofurans **14** and the efficient oxidation of these materials to benzofuronaphthoquinones **3**. The extension of this novel synthetic methodology to benzopyronaphthoquinones **4** resulted in the first total synthesis of benzonaphthopyranone **17a**. This target compound was efficiently oxidized to unsubstituted benzopyronaphthoquinone **4**. This route does, however, seems to be limited to the preparation of benzonaphthopyranones **17** with a substitution pattern compatible with the opening of spiro compound **16** to a single indanone ketoacid **10**.

Work is now in progress to overcome this limitation and to extend the 2-phenylnaphthalene-based synthetic methodology reported here to the preparation of tetracyclic 2-phenylnaphtahlene derivatives other than benzonaphthofurans **14**, benzofuronaphthoquinones **3**, benzonaphthopyranones **17** and benzopyronaphthoquinones **4**. It is envisaged that the route will also include indolonaphthoquinones and ellipticines, which are known to show antitumour properties.

1. Experimental

1.1. General

Melting points were determined on a Kofler Thermogerate apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC FTIR spectrophotometer. Nuclear magnetic resonance spectra were recorded, unless otherwise specified, on a Bruker WM-250 apparatus, using deuterochloroform solutions containing tetramethylsilane as internal standard. Mass spectra were obtained on a Kratos MS 50 TC mass spectrometer. Thin layer chromatography (tlc) was performed using Merck GF-254 type 60 silica gel and CH_2Cl_2/MeOH mixtures as eluants; the tlc spots were

visualized with ultraviolet light or iodine vapour. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 24. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

1.1.1. 2-(2-Bromobenzylidene)indan-1-one (9a). A solution of 1-indanone (1 g, 7.5 mmol) in dry MeOH (18 mL) was added dropwise under argon to a solution of 2-benzaldehyde (0.93 mL, 7.95 mmol) and sodium methoxide (120 mg, 2.35 mmol) in dry MeOH (22 mL). The mixture was stirred at rt for 15 h and poured into water (50 mL). The resulting suspension was acidified by the addition of 20% aq HCl and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried and concentrated to dryness in vacuo. Crystallisation of the solid residue from MeOH yielded the title compound as white needless (2.2 g, 98%). Mp 134–136 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1695 (C=O), 1621 (C=C). ^1H NMR (δ, ppm): 3.94 (s, 2H, CH_2), 7.23 (m, 1H, Ar–H), 7.35–7.68 (m, 6H, 6×Ar–H), 7.91 (δ, 1H, J= 7.6 Hz, Ar–H), 7.97 (s, 1H, HC=C). ^{13}C NMR (δ, ppm): 31.7 (CH_2), 124.6 (CH), 126.2 (CH), 126.6 (C), 127.5 (CH), 127.8 (CH), 130.0 (CH), 130.5 (CH), 132.5 (CH), 133.6 (CH), 134.8 (CH), 135.4 (C), 137.1 (C), 138.0 (C), 149.8 (C), 193.8 (C=O). MS (*m/z*, %): 300 [$(M+2)^+$, 2], 298 (M^+, 1.7), 219 [$(M-79.9)^+$, 100], 189 (32). Anal. Calcd for $C_{16}H_{11}BrO$, C: 64.24; H: 3.71; Br: 26.71. Found C: 64.41; H: 3.68; Br: 27.03.

1.1.2. 2-(2-Bromobenzyl)indan-1-one (10a). 10% Pd–C (50 mg) was added to a deoxygenated solution of bromobenzylideneindanone **9a** (0.96 g, 3.21 mmol) in ethyl acetate (80 mL) and the mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 1 h 15 min. After removal of the excess of hydrogen in vacuo, the reaction mixture was filtered though Celite, which was eluted with ethyl acetate. The filtrate was concentrated to dryness in vacuo to give the title compound as white crystals (0.947 g, 98% yield). Mp 67–69 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1710 (C=O). ^1H NMR (δ, ppm): 2.86 (m, 2H, $-CH_2$), 3.11–3.18 (m, 2H, CH_2, CH), 3.53 (dd, 1H, J=14.1 Hz, J'=4.0 Hz, CH_2), 7.10 (m, 1H, Ar–H), 7.23–7.34 (m, 2H, 2×Ar–H), 7.37–7.43 (m, 2H, 2×Ar–H), 7.55–7.61 (δ, 2H, J=7.5 Hz, 2×Ar–H), 7.79 (δ, 1H, J=7.5 Hz, Ar–H). ^{13}C NMR (δ, ppm): 32.1 (CH_2), 36.9 (CH_2), 47.5 (CH), 124.1 (CH), 124.9 (C), 126.7 (CH), 127.5 (CH), 127.6 (CH), 128.2 (CH), 131.0 (CH), 133.1 (CH), 134.9 (CH), 136.6 (C), 139.2 (C), 153.5 (C), 207.4 (C=O). MS (*m/z*, %): 301 [$(M+2)^+$, 0.15], 299 (M^+, 0.09), 221 [$(M-79.9)^+$, 100], 131 (26). Anal. Calcd for $C_{16}H_{13}BrO$, C: 63.81; H: 4.35; Br: 26.53. Found C: 64.09; H: 4.23; Br: 26.87.

1.1.3. 2-(2-Bromobenzyl)-1*H*-indene (11a). Small portions of $NaBH_4$ (540 mg, 1.43 mmol) were added every 15 min during 1 h to a solution of benzylindanone **10a** (700 mg, 0.23 mmol) in MeOH (60 mL) cooled to 0–5 °C using a water/ice bath. The mixture was stirred at rt for 30 min and poured into water (100 mL). The MeOH was evaporated in vacuo and the remaining suspension was extracted with CH_2Cl_2 (3×100 mL) and the combined organic extracts were washed with water (3×100 mL), dried and concentrated to dryness in vacuo. The remaining solid was immediately mixed with 9 M H_2SO_4 (75 mL) and the stirred suspension was refluxed in a dry atmosphere for 30 min. 20% aq NaOH was added until a basic pH was attained and the suspension was extracted with CH_2Cl_2 (3× 100 mL). The combined organic extracts were dried and concentrated to dryness in vacuo. The remaining solid was submitted to flash column chromatography (eluant: ethyl acetate/hexane, 0.3:9.7) to give the title compound in 96% yield (0.638 g) as a yellow oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 3071 (C=C). ^1H NMR (δ, ppm): 3.39 (s, 2H, $-CH_2$), 4.01 (s, 2H, $-CH_2$), 6.52 (s, 1H, HC=C), 7.13–7.34 (m, 6H, 6×Ar–H), 7.42 (δ, 1H, J=7.2 Hz, Ar–H), 7.63 (d, 1H, J=8.2 Hz, Ar–H). ^{13}C NMR (δ, ppm): 37.9 (CH_2), 41.1 (CH_2), 120.4 (CH), 123.6 (CH), 124.1 (CH), 124.8 (CBr), 126.4 (CH), 127.7 (CH), 128.1 (CH), 128.5 (CH), 131.1 (CH), 139.6 (C), 143.4 (C), 145.4 (C), 147.6 (C). HRMS: $C_{16}H_{13}Br$ (M^+), calcd 284.0201; found 284.0199.

1.1.4. 2-[3-(2-Bromophenyl)-2-oxopropyl]benzaldehyde (5a). N_2 and O_2 were bubbled consecutively for 10 min each through a solution of indene **11a** (400 mg, 1.39 mmol) in CH_2Cl_2 (60 mL) at −78 °C connected to an ozonizer. O_3 was then bubbled through the solution for 2 min until a blue colour appeared due to the presence of ozonide. O_2 was then bubbled through for 10 min to destroy the excess O_3 and finally N_2 was bubbled through for 5 min. Dimethyl sulfide (1.9 mL, 26.38 mmol) was added and the mixture was stirred at −78 °C under argon for 7 h and at rt for 13 h. The solvent was removed in vacuo and the solid residue was submitted to column chromatography (eluant: ethyl acetate/hexane, 0.5:9.5) to give the target compound (324 mg) in 73% yield as white crystals. Mp 68–69 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1719, 1693 (CHO, C=O). ^1H NMR (δ, ppm): 4.11 (s, 2H, CH_2), 4.20 (s, 2H, CH_2), 7.24–7.53 (m, 7H, 7×Ar–H), 7.56 (t, 1H, J=1.8 Hz, Ar–H), 10.01 (s, 1H, CHO). ^{13}C NMR (δ, ppm): 47.1 (CH_2), 50.0 (CH_2), 125.2 (C), 127.6 (CH), 127.8 (CH), 128.8 (CH), 132.2 (CH), 132.8 (2×CH), 133.7 (CH), 134.4 (C), 134.9 (C), 135.0 (CH), 135.8 (C), 193.3 (C=O), 203.2 (C=O). MS (*m/z*, %): 318 [$(M+2)^+$, 0.37], 316 (M^+, 0.34), 237 [$(M-79.9)^+$, 2], 171 (36.4), 169 (37.6), 147 (100), 119 (88), 91 (65). Anal. Calcd for $C_{16}H_{13}BrO_2$, C: 60.59; H: 4.13; Br: 25.19. Found C: 60.32; H: 4.19; Br: 24.96.

1.1.5. 3-(2-Bromophenyl)naphthalen-2-ol (6a). A solution of ketoaldehyde **5a** (200 mg, 0.63 mmol) in 5% aq NaOH (10 mL) was magnetically stirred in a dry atmosphere at rt for 1 h. The reaction mixture was acidified by adding 10% aq HCl and the resulting suspension was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were washed with water (25 mL), dried and concentrated to dryness in vacuo to give a quantitative yield of the title compound (188 mg) as an oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 3535 (OH). ^1H NMR (δ, ppm): 7.18–7.42 (m, 6H, 6×Ar–H), 7.59 (s, 1H, Ar–H), 7.67–7.73 (m, 3H, 3×Ar–H). ^{13}C NMR (δ, ppm): 110.3 (CH), 124.0 (CH), 124.4 (C), 125.9 (C), 126.4 (CH), 126.7 (CH), 127.8 (2×CH), 128.6 (C), 130.0 (2× CH), 132.2 (CH), 133.2 (CH), 134.7 (C), 137.8 (C), 150.7 (C=O). MS (*m/z*, %): 300 [$(M+2)^+$, 66], 298 (M^+, 69), 219 (72), 218 (98), 191 880), 189 (100), 109 (42), 95 (63). HRMS: $C_{16}H_{11}BrO$ (M^+), calcd 297.9993; found 297.9994.

1.1.6. 3-(2-Bromophenyl)-1,2-naphthoquinone (12a). A solution of Fremy's salt (1.187 g, 4.42 mmol) and

potassium biphosphate (215 mg, 1.58 mmol) in water (30 mL) was added to a solution of naphthol **6a** (137 mg, 0.46 mmol) in acetone (13 mL). The suspension was stirred in a dry atmosphere at rt for 1 h and the acetone was evaporated in vacuo. The pink suspension was extracted with CH_2Cl_2 (3×25 mL) and the combined organic layers were washed with water (25 mL), dried and concentrated to dryness in vacuo. The solid residue was submitted to flash column chromatography (eluant: ethyl acetate/hexane, 1:9) and the title compound was isolated as red crystals (133 mg, 94% yield). Mp 164–166 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1675 (C=O). ^1H NMR (δ, ppm): 7.15–7.64 (m, 8H, 7× Ar–H, CH=C), 8.08 (d, 1H, J=7.6 Hz, Ar–H). ^{13}C NMR (δ, ppm): 123.4 (CBr), 127.4 (CH), 130.2 (2×CH), 130.3 (CH), 130.8 (CH), 131.1 (CH), 131.4 (C), 133.0 (CH), 134.7 (C), 135.5 (C), 135.9 (CH), 139.6 (C), 144.1 (CH), 178.8 (C=O), 178.9 (C=O). MS (*m*/*z*, %): 286 {[(M−28)+2]$^+$, 15.2}, 284 [(M−28)$^+$, 15.2}, 205 (100), 176 (43). Anal. Calcd for $C_{16}H_9BrO_2$, C: 61.37; H: 2.90; Br: 25.52. Found C: 61.72; H: 2.93; Br: 25.11.

1.1.7. 2-(2-Bromophenyl)-3-hydroxy-1,4-naphthoquinone (2a). 20% aq sulfuric acid (2 mL) was added to a suspension of quinone **12a** (31 mg, 0.09 mmol) in MeOH (2 mL) and the mixture was refluxed for 94 h. The MeOH was removed in vacuo and the resulting suspension was poured into water (25 mL) and extracted with CH_2Cl_2 (3× 25 mL). The combined organic extracts were washed with water (25 mL), dried and concentrated to dryness in vacuo. The solid residue was submitted to flash column chromatography (eluant: ethyl acetate/hexane, 1:1) and the title compound was obtained (30 mg, 93% yield) as red crystals. Mp 172–174 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 3425 (OH), 1635 (C=O). ^1H NMR (δ, ppm): 6.99–7.14 (m, 3H, 3× Ar–H), 7.46–7.55 (m, 2H, 2×Ar–H), 7.66 (t, 1H, J= 7.5 Hz, Ar–H), 7.94 (δ, 2H, J=7.6 Hz, 2×Ar–H). ^{13}C NMR (δ, ppm, $CDCl_3$/MeOD): 119.9 (C), 124.9 (C), 125.1 (2×CH), 125.7 (CH), 127.2 (CH), 129.9 (C), 130.4 (CH), 131.1 (CH), 132.2 (CH), 134.1 (CH), 134.4 (C), 136.0 (C), 167.5 (C), 181.1 (C=O), 189.1 (C=O). MS (*m*/*z*, %): 249 [(M−79.9)$^+$, 100], 165 (32). Anal. Calcd for $C_{16}H_9BrO_3$, C: 58.38; H: 2.76; Br: 24.28. Found C: 50.82; H: 2.83; Br: 24.62.

1.1.8. Benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (3a). A mixture of naphthoquinone **2a** (30 mg, 0.09 mmol), CuO (23 mg, 0.28 mmol) and K_2CO_3 (64 mg, 5.1 mmol) in dry deoxygenated pyridine (3 mL) was refluxed under argon for 4 h. The mixture was then added to 20% aq HCl solution (40 mL) and the resulting suspension was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with 10% aq NaOH (3×25 mL), dried, filtered and concentrated in vacuo. The solid residue was submitted to flash column chromatography (eluant: ethyl acetate/hexane, 1:9) to give the title compound (16 mg, 71% yield) as yellow crystals. Mp 245–247 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1674 (C=O). ^1H NMR (δ, ppm): 7.48–7.81 (m, 5H, 5×Ar–H), 8.22–8.34 (m, 3H, 3×Ar–H). ^{13}C NMR (δ, ppm): 112.9 (CH), 122.7 (C), 124.0 (CH), 124.3 (C), 126.1 (CH), 126.8 (CH), 126.9 (CH), 129.6 (CH), 132.4 (C), 133.3 (C), 133.9 (CH), 134.2 (CH), 153.5 (C), 156.5 (C), 175.5 (C=O), 181.4 (C=O). MS (*m*/*z*, %): 248 (M$^+$, 100), 220 (46), 163 (51). Anal. Calcd for $C_{16}H_8O_3$, C: 77.42; H: 3.25. Found C: 77.29; H: 3.33.

1.1.9. Benzo[*b*]naphtho[2,3-*d*]furan (13a). Reaction of a suspension of bromonaphthol **6a** (30 mg, 0.10 mmol), CuO (0.31 mg, 3.1 mmol) and potassium carbonate (70 mg, 5.1 mmol) in dry deoxygenated pyridine was subjected to the same conditions as for the preparation of benzofuronaphthoquinone **3a**. The title compound was obtained as white crystals (16 mg, 73% yield). Mp 210–212 °C (MeOH). ^1H NMR (δ, ppm): 7.35–7.58 (m, 5H, 5× Ar–H), 7.93 (s, 1H, Ar–H), 7.96–8.07 (m, 3H, 3×Ar–H), 8.42 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 106.9 (CH), 111.6 (CH), 119.1 (CH), 121.3 (CH), 122.7 (CH), 123.9 (C), 124.3 (CH), 125.4 (C), 125.9 (CH), 127.8 (CH), 128.3 (2×CH), 130.2 (C), 133.0 (C), 154.8 (CO), 157.6 (CO). MS (*m*/*z*, %): 218 (M$^+$, 100), 189 (24). Anal. Calcd for $C_{16}H_{10}O$, C: 88.05; H: 4.62. Anal. Calcd for $C_{16}H_{16}O$, C: 88.05; H: 4.62. Found C: 87.72; H: 4.67.

1.1.10. Benzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (3a). A solution of CrO_3 (75 mg, 0.76 mmol) in glacial acetic acid (6 mL) and water (1 mL) was added to a solution of benzonnaphthofuran **13a** (30 mg, 0.14 mmol) in glacial acetic acid and the mixture was refluxed during 10 min. The suspension was poured into CH_2Cl_2 (25 mL) and the organic phase was washed with water (3×25 mL), dried and concentrated in vacuo. The title compound was obtained as a yellow solid (34 mg, 100% yield).

1.1.11. 2-(2-Bromobenzylidene)-5-methoxyindan-1-one (9b). 1-Methoxyindanone **7b** (2 g, 12.33 mmol) and *o*-bromobenzaldehyde (1.526 mL, 13.07 mmol) were reacted under the same conditions as for the preparation of benzylideneindanone **9a** to give the title compound as white crystals (3.31 g, 85% yield). Mp 158–160 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1685 (C=O), 1628 (C=C). ^1H NMR (δ, ppm): 3.81 (s, 2H, CH_2), 3.86 (s, 3H, OCH_3), 6.88–6.91 (m, 2H, 2×Ar–H), 7.17 (m, 1H, Ar–H), 7.34 (t, J=7.5 Hz, 1H, Ar–H), 7.58–7.63 (m, 2H, 2×Ar–H), 7.77–7.85 (m, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm): 31.7 (CH_2), 55.6 (CH_3), 109.5 (CH), 115.3 (CH), 126.1 (CH), 126.2 (C), 127.3 (CH), 129.7 (CH), 130.1 (CH), 131.0 (CH), 131.2 (C), 133.3 (CH), 135.3 (C), 137.5 (C), 152.5 (C), 165.2 (C=O), 191.9 (C=O). MS (*m*/*z*, %): 330 [(M+2)$^+$, 42], 328 (M$^+$, 43), 249 [(M−79.9)$^+$, 100], 243 (23). Anal. Calcd for $C_{17}H_{13}BrO_2$, C: 62.03; H: 3.98; Br: 24.27. Found C: 62.31; H: 4.05; Br: 23.96.

1.1.12. 2-(2-Bromobenzyl)-5-methoxyindan-1-one (10c). Catalytic hydrogenation of bromobenzylideneindanone **9b** (1 g, 2.94 mmol), under the same conditions as for analogue **10a**, resulted in a mixture of the title compound and benzylindanone **10d**. The mixture was purified by flash column chromatography (eluant: ethyl acetate/hexane, 1:9) to give the title compound (0.099 g, 9.8% yield) as a colourless oil. IR ($\bar{\nu}$, cm^{-1}, NaCl): 1701 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 2.81 (m, 2H, CH_2), 3.09 (m, 2H, CH_2), 3.50 (m, 1H, CH), 3.85 (s, 3H, OMe), 6.81–6.91 (m, 2H, ArH), 7.08 (m, 1H, ArH), 7.21–7.29 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.70 (dd, J=8.5 Hz, J'=2.8 Hz, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 32.1 (CH_2), 36.9 (CH_2), 47.5 (CH), 55.5 (OMe), 109.6 (CH), 115.4 (CH), 124.7 (C), 125.6

(CH), 127.4 (CH), 128.0 (CH), 129.6 (C), 130.8 (CH), 132.9 (CH), 139.1 (C), 156.4 (C), 165.3 (C), 205.5 (C=O). HRMS: $C_{17}H_{15}BrO_2$ (M^+), calcd 330.0255; found 330.0258.

1.1.13. 5-Methoxy-1-oxoindan-2-carboxylic acid ethyl ester (14b). A solution of methoxyindanone **7b** (5.1 g, 32 mmol) in benzene (75 mL) was added dropwise under argon during 4.5 h to a mixture of 80% sodium hydride (1.66 g, 69 mmol), diethyl carbonate (7.5 mL, 62 mmol) and benzene (40 mL) under reflux. A further quantity of benzene (4.5 mL) was added and the mixture was heated for a further 0.5 h. Water (35 mL) and acetic acid (6 mL) were added to the reaction mixture and the organic layer was separated and the aqueous layer extracted with benzene (2× 75 mL) and diethyl ether (2×75 mL). The combined organic extracts were dried and concentrated in vacuo. The solid residue was submitted to flash column chromatography (eluant: CH_2Cl_2/hexane, 9:1) and the resulting solid was refluxed in hexane (500 mL) for 30 min and filtered immediately. The filtrate was concentrated to dryness in vacuo to give the title compound as white crystals (6.35 g, 62% yield). Mp 63–65 °C (ethyl acetate/hexane). IR ($\bar{\nu}$, cm^{-1}, KBr): 1262 (C–OMe), 1707 (CO_2Et), 1738 (C=O). ^1H NMR (δ, ppm): 1.25 (t, $J=7.2$ Hz, 3H, $-CH_3$), 3.21–3.29 (m, 1H, $-CH_2$), 3.41–3.48 (m, 1H, $-CH_2$), 3.62–3.66 (m, 1H, –CH), 3.83 (s, 3H, $-OCH_3$), 4.19 (q, $J=7.2$ Hz, 2H, $-CH_2O$), 6.84–6.87 (m, 2H, ArH), 7.61–7.64 (m, 1H, ArH). ^{13}C NMR (δ, ppm): 13.9 (CH_3), 30.0 (CH_2), 53.2 (CH), 55.4 (CH_3), 61.2 (CH_2), 109.2 (CH), 115.6 (CH), 125.8 (CH), 128.1 (C), 156.5 (C), 165.6 (C), 169.1 C=O), 197.3 (C=O). MS (*m/z*, %): 234 (M^+, 50), 188 (29), 160 (100).

1.1.14. 2-(2-Bromobenzyl)-5-methoxy-1-oxo-indan-2-carboxylic acid ethyl ester (15a). A mixture of 80% sodium hydroxide (24 mg, 1.13 mmol), indanone **14a** (237 mg, 1.10 mmol) and *N*,*N*-dimethylformamide (0.5 mL) was heated at 60 °C for 1 h. A solution of 98% 2-bromobenzyl bromide (290 mg, 1.16 mmol) in *N*,*N*-dimethylformamide (0.8 mL) was added and the mixture was heated at 60 °C for 44.5 h. A few drops of water were added and the suspension was extracted with diethyl ether (3×10 mL). The combined organic extracts were washed with saturated aq sodium chloride, dried and concentrated to dryness in vacuo. The solid residue was submitted to flash column chromatography (eluant: CH_2Cl_2/hexane, 3:1) and the title compound was isolated as a transparent oil (319 mg, 78% yield). IR ($\bar{\nu}$, cm^{-1}, KBr): 1263 (C–OMe), 1706 (CO_2Et), 1738 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 1.15 (t, $J=7.1$ Hz, 3H, $-CH_3$), 3.05 (δ, $J=17.5$ Hz, 1H, C*H*H), 3.43 (d, $J=14.7$ Hz, 1H, C*H*H), 3.58 (δ, $J=17.5$ Hz, 1H, C*H*H), 3.71 (s, 1H, C*H*H), 3.76 (s, 3H, OMe), 4.13 (q, $J=7.2$ Hz, 2H, $-OCH_2$), 6.74 (δ, $J=1.9$ Hz, 1H, ArH), 6.81 (m, 1H, ArH), 6.90–6.96 (m, 1H, ArH), 7.00–7.06 (m, 1H, ArH), 7.16 (m, 1H, ArH), m (m, 1H, ArH), 7.67 (m, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 13.8 (CH_3), 34.9 (CH_2), 37.8 (CH_2), 55.4 (CH_3), 61.6 (CH_2), 109.0 (CH), 115.7 (CH), 125.9 (CH), 126.1 (CH), 127.2 (CH), 128.1 (CH), 130.9 (CH), 132.7 (CH), 136.4 (C), 156.6 (C), 165.6 (C), 170.6 (C=O), 199.9 (C=O). HRMS: $C_{20}H_{19}BrO_4$ (M^+), calcd 402.0467; found 402.0463.

1.1.15. 2-(2-Bromobenzyl)-5-methoxyindan-1-one (10c). A suspension of indanone **15a** (128 mg, 0.317 mmol), 48% HBr (0.7 mL) and 96% AcOH (0.6 mL) was stirred at 120 °C for 1.5 h. The mixture was cooled and diluted with water (5 mL). The organic material was extracted with diethyl ether (3×10 mL) and the combined organic extracts were dried and concentrated in vacuo. The solid residue was submitted to flash column chromatography (eluant: CH_2Cl_2/hexane, 5.5:4.5) and the title compound (76 mg, 72% yield) was isolated as an oil (76 mg, 72% yield). IR (NaCl, $\bar{\nu}$, cm^{-1}): 1701 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 2.81 (m, 2H, CH_2), 3.09 (m, 2H, CH_2), 3.50 (m, 1H, CH), 3.85 (s, 3H, –OMe), 6.81–6.91 (m, 2H, ArH), 7.08 (m, 1H, ArH), 7.21–7.29 (m, 2H, ArH), 7.55 (m, 1H, ArH), 7.70 (dd, $J=8.5$ Hz, $J'=2.8$ Hz, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 32.1 (CH_2), 36.9 (CH_2), 47.5 (CH), 55.5 (CH_3), 109.6 (CH), 115.4 (CH), 124.7 (C), 125.6 (CH), 127.4 (CH), 128.0 (CH), 129.6 (C), 130.8 (CH), 132.9 (CH), 139.1 (C), 156.4 (C), 165.3 (C), 205.5 (C=O). HRMS: $C_{17}H_{15}BrO_2$ (M^+), calcd 330.0255; found 330.0251.

1.1.16. 2-(2-Bromobenzyl)-6-methoxy-1*H*-indene (11b). Following the procedure for the preparation of benzylindene **11a**, benzylindanone **10c** (780 mg, 2.35 mmol) was transformed into the title compound (3.71 mmol, 88% yield). Mp 62–64 °C (MeOH). ^1H NMR (δ, ppm): 3.29 (s, 2H, CH_2), 3.78 (s, 3H, $-OCH_3$), 3.90 (s, 2H, CH_2), 6.38 (s, 1H, HC=C), 6.76 (dd, 1H, $J=8.2$ Hz, $J'=2.4$ Hz, Ar–H), 6.96 (m, 1H, Ar–H), 7.13 (δ, 1H, $J=8.3$ Hz, Ar–H), 7.25–7.23 (m, 3H, 3×Ar–H), 7.55 (δ, 1H, $J=7.7$ Hz, Ar–H). ^{13}C NMR (δ, ppm): 37.9 (CH_2), 41.1 (CH_2), 55.5 (CH_3), 110.4 (CH), 111.7 (CH), 120.4 (CH). 124.7 (C), 126.1 (C), 127.5 (CH), 127.7 (CH), 127.9 (CH), 130.9 (CH), 132.9 (CH), 138.4 (C), 139.7 (C), 145.1 (C), 157.4 (CO). MS (*m/z*, %): 316 [$(M+2)^+$, 14.8], 316 (M^+, 15.0), 237 [$(M-79.9)^+$, 9], 145 (100). Anal. Calcd for $C_{17}H_{15}BrO$, C: 64.78; H: 4.80; Br: 25.25. Found C: 64.92; H: 4.79; Br: 24.87.

1.1.17. 2-[3-(2-Bromophenyl)-2-oxopropyl]-4-methoxybenzaldehyde (5b). Ozonolysis of benzylindene **11b** (195 mg, 0.62 mmol) under the same conditions as for analogue **11a** gave the title compound as a white solid (131 mg, 61% yield). Mp 87–88 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1723, 1684 (CHO, C=O). ^1H NMR (δ, ppm): 3.75 (s, 3H, OCH_3), 4.00 (s, 2H, CH_2), 4. 01 (s, 2H, CH_2), 6.62 (δ, 1H, $J=2.3$ Hz, Ar–H), 6.83 (dd, 1H, $J=8.5$ Hz, $J'=2.3$ Hz, Ar–H), 7.16–7.24 (m, 3H, 3×Ar–H), 7.47 (δ, 1H, $J=7.9$ Hz, Ar–H), 7.61 (δ, 1H, $J=8.5$ Hz, Ar–H), 9.76 (s, 1H, CHO). ^{13}C NMR (δ, ppm): 47.3 (CH_2), 49.9 (CH_2), 55.4 (CH_3), 112.2 (CH), 118.8 (CH), 125.0 (C), 127.5 (CH), 128.6 (C), 128.7 (CH), 132.1 (CH), 132.6 (CH), 134.8 (C), 137.8 (CH), 138.2 (C), 163.5 (C=O), 191.7 (C=O), 203.2 (C=O). MS (*m/z*, %): 348 [$(M+2)^+$, 0.52], 316 (M^+, 0.60), 267 [$(M-79.9)^+$, 2], 177 (92), 149 (100), 91 (33). Anal. Calcd for $C_{17}H_{15}BrO_3$, C: 58.81; H: 4.35; Br: 23.01. Found C: 59.12; H: 4.31; Br: 22.79.

1.1.18. 3-(2-Bromophenyl)-7-methoxynaphthalen-2-ol (6b). Reaction of ketoaldehyde **5b** with NaOH under the same conditions as for analogue **5a** provided the title compound as a colourless solid (344 mg, 95% yield). Mp 145–147 °C (EtOH/H_2O). IR ($\bar{\nu}$, cm^{-1}, NaCl): 3425 (OH). ^1H NMR (δ, ppm): 3.77 (s, 3H, $-OCH_3$), 6.87–6.92 (m, 2H,

2×Ar–H), 7.10–7.17 (m, 2H, 2×Ar–H), 7.26 (s, 1H, Ar–H), 7.27 (s, 1H, Ar–H), 7.44 (s, 1H, Ar–H), 7.51–7.60 (m, 2H, 2×Ar–H). ^{13}C NMR (δ, ppm): 55.2 (CH_3), 104.4 (CH), 109.4 (CH), 116.7 (CH), 124.0 (C), 124.5 (C), 127.6 (C), 127.7 (CH), 129.3 (CH), 127.3 (CH), 129.7 (CH), 132.2 (CH), 133.0 (CH), 136.0 (C), 138.0 (C), 151.3 (C), 158.3 (C). MS (*m*/*z*, %): 330 [$(M+2)^+$, 99.96], 316 (M^+, 100), 250 (37), 234 (60), 206 (59), 178 (46), 175 (36). Anal. Calcd for $C_{17}H_{13}BrO_2$, C: 62.03; H: 3.98; Br: 24.27. Found C: 59.69; H: 3.91; Br: 24.62.

1.1.19. 8-Methoxybenzo[*b*]naphtho[2,3-*d*]furan (13b). Reaction of naphthol **6b** (55 mg, 0.17 mmol) under the conditions used for analogue **6a** gave the title compound as a white solid (32 mg, 77% yield). Mp 208–210 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1222 (C–O–C). ^{1}H NMR (δ, ppm): 3.96 (s, 3H, $-OCH_3$), 7.14 (dd, 1H, $J=9.0$ Hz, $J'=2.4$ Hz, Ar–H), 7.24 (δ, 1H, $J=5.5$ Hz, Ar–H), 7.34 (t, 1H, $J=$ 7.3 Hz, Ar–H), 7.43–7.56 (m, 2H, 2×Ar–H), 7.79 (s, 1H, Ar–H), 7.90 (δ, 1H, $J=9.0$ Hz, Ar–H), 8.01 (δ, 1H, $J=$ 7.6 Hz, Ar–H), 8.30 (s, 1H, Ar–H). ^{13}C NMR (δ, ppm): 55.3 (CH_3), 105.4 (CH), 105.8 (CH), 111.4 (CH), 117.7 (CH), 119.1 (CH), 120.9 (CH), 122.7 (CH), 123.0 (C), 124.2 (C), 125.8 (C), 127.7 (CH), 129.8 (CH), 134.5 (C), 155.6 (C), 157.3 (C), 157.8 (C). MS (*m*/*z*, %): 248 (M^+, 93), 233 (18), 205 (100), 176 (22), 149 (29). Anal. Calcd for $C_{17}H_{12}O_2$, C: 82.24; H: 4.87. Found C: 81.89; H: 4.96.

1.1.20. 8-Methoxybenzo[*b*]naphtho[2,3-*d*]furan-6,11-dione (3b). Oxidation of benzonaphthofuran **13b** (15 mg, 0.06 mmol) under the same conditions as for analogue **13a** yielded the title compound as a yellow solid (4 mg, 24% yield). Mp 254–256 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, NaCl): 1679 (C=O). ^{1}H NMR (δ, ppm): 4.00 (s, 3H, OCH_3), 7.23 (m, 1H, Ar–H), 7.50–7.61 (m, 2H, 2×Ar–H), 7.68–7.71 (m, 2H, 2×Ar–H), 8.18 (d, 1H, $J=8.6$ Hz, Ar–H), 8.32 (d, 1H, $J=$ 7.5 Hz, Ar–H). ^{13}C NMR (δ, ppm): 56.0 (OCH_3), 111.0 (CH), 112.8 (CH), 119.9 (CH), 122.9 (C), 124.1 (CH), 124.4 (C), 126.0 (CH), 126.6 (C), 129.2 (CH), 129.6 (CH), 134.5 (C), 153.4 (C), 156.5 (C), 164.2 (C), 175.5 (C=O), 180.0 (C=O). MS (*m*/*z*, %): 278 (M^+, 13), 149 (56), 85 (37), 83 (38), 71 (50), 69 (37), 58 (100), 57 (70). Anal. Calcd for $C_{17}H_{10}O_4$, C: 73.38; H: 3.62. Found C: 73.51; H: 3.54.

1.1.21. 2-(2-Methoxycarbonylbenzyl)-1-oxoindan-2-carboxylic acid ethyl ester (15b). Treatment of indanone **14a** (4.602 g, 22.5 mmol) with *o*-methoxycarbonylbenzyl bromide under the same conditions as for analogue **14b** furnished the title compound as a white solid (650 mg, 52% yield). Mp 88–90 °C (MeOH). IR (,cm^{-1}, KBr): 1716 (3× C=O). ^{1}H NMR (δ, ppm, $CDCl_3$): 1.18 (t, $J=7$ Hz, 3H, CH_3), 3.05 (d, $J=17.5$ Hz, 1H, C*H*H), 3.58–3.70 (m, 2H, CH_2), 3.82 (s, 3H, OMe), 4.05 (d, $J=14$ Hz, 1H, C*H*H), 4.16 (q, $J=7$ Hz, 2H, CH_2O), 7.16–7.34 (m, 5H, ArH), 7.48–7.53 (m, 1H, ArH), 7.72–7.81 (m, 2H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 13.9 (CH_3), 35.6 (CH_2), 35.8 (CH_2), 52.0 (Me), 61.8 (C), 124.5 (CH), 126.1 (CH), 126.7 (CH), 127.4 (CH), 130.5 (CH), 131.1 (C), 131.4 (CH), 131.7 (CH), 135.1 (CH), 138.1 (C), 153.7 (C), 168.1 (C=O), 170.9 (C=O), 202.6 (C=O). MS (*m*/*z*, %, CI): 353 ($M^+ +1$, 48), 321 (100), 307 (58), 275 (69), 205 (68). Anal. Calcd for $C_{21}H_{20}O_5$, C: 71.58; H: 5.72. Found C: 71.96; H: 5.59.

1.1.22. 2,2′-Spirobiindanone (16a). A mixture of indanone **15b** (2.67 g, 7.58 mmol), 96% AcOH (5.5 mL) and 48% HBr (5 mL) was refluxed for 3.25 h. The cooled reaction mixture was diluted with water (40 mL) and the resulting suspension was extracted with diethyl ether (3×30 mL). The combined organic extracts were dried and concentrated in vacuo. Crystallisation of the solid residue from MeOH yielded the title compound as white crystals (1.731 g, 92% yield). Mp 171–173 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1694 (C=O), 1720 (C=O). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.20 (d, $J=17$ Hz, 2H, $-CH_2$), 3.73 (d, $J=17$ Hz, 2H, $-CH_2$), 7.39–7.45 (m, 2H, ArH), 7.55–7.78 (m, 6H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 38.0 (CH_2), 65.3 (C), 124.9 (CH), 126.3 (CH), 127.8 (CH), 135.2 (CH), 135.4 (C), 153.8 (C), 202.7 (C=O). MS (*m*/*z*, %): 248 (M^+, 100), 220 (47), 191 (33). Anal. Calcd for $C_{17}H_{12}O_2$, C: 82.24; H: 4.87. Found C: 81.93; H: 4.79.

1.1.23. 2-(1-Oxoindan-2-ylmethyl)benzoic acid (10e). A stirred suspension of diindanone **16a** (1.731 mg, 6.97 mmol) and 1 M NaOH (1.25 mL) in EtOH (40 mL) was refluxed during 5 h. The ethanol was removed in vacuo and the remaining suspension was acidified by addition of 0.625 M HCl. The mixture was extracted with $CHCl_3$ (3× 75 mL) and the combined organic extracts were dried and concentrated in vacuo. Crystallisation of the solid residue from benzene provided the title compound as a white solid (1.632 mg, 88% yield). Mp 141–143 °C (benzene). IR ($\bar{\nu}$, cm^{-1}, KBr): 1688 (C=O), 1706 (C=O), 2906 (C–OH). ^{1}H NMR (δ, ppm, $CDCl_3$): 2.89 (d, $J=13.6$ Hz, 1H, C*H*H), 3.10–3.24 (m, 3H, C*H*H and CH_2), 3.77–3.87 (m, 1H, CH), 7.30–7.58 (m, 6H, Ar–H), 7.77 (d, 1H, Ar–H), 8.07–8.10 (m, 1H, ArH), 10.70 (br s, 1H, –OH). ^{13}C NMR (δ, ppm, $CDCl_3$): 32.3 (CH_2), 34.9 (CH_2), 48.6 (CH), 123.9 (CH), 126.4 (CH), 126.5 (CH), 127.3 (CH), 128.7 (C), 131.6 (CH), 131.8 (CH), 132.8 (CH), 134.7 (CH), 136.4 (C), 142.5 (C), 153.5 (C), 172.6 (C=O), 208.1 (C=O). MS (*m*/*z*, %): 266 (M^+, 46), 248 (100), 220 (49), 131 (63). Anal. Calcd for $C_{17}H_{14}O_3$, C: 76.68; H: 5.30. Found C: 77.03; H: 5.19.

1.1.24. 2-(1*H*-Inden-2-ylmethyl)benzoic acid (11c). Reaction of indanone **10e** (1.601 g, 6.01 mmol) under the same conditions as for analogue **10a** provided the title compound as a white solid (1.281 g, 85% yield). Mp 143–145 °C (ethyl acetate/hexane). IR ($\bar{\nu}$, cm^{-1}, KBr): 1687 (C=O), 2881 (C–OH). ^{1}H NMR (δ, ppm, $CDCl_3$): 3.34 (s, 2H, CH_2), 4.28 (s, 2H, CH_2), 6.37 (s, 1H, CH), 7.07–7.54 (m, 7H, ArH), 8.07–8.10 (m, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.8 (CH_2), 41.2 (CH_2), 120.2 (CH), 123.4 (CH), 123.8 (CH), 126.2 (CH), 126.5 (CH), 127.7 (CH), 128.3 (C), 131.7 (CH), 131.8 (CH), 133.0 (CH), 142.6 (C), 143.3 (C), 145.3 (C), 149.4 (C), 172.7 (C=O). MS (*m*/*z*, %): 250 (M^+, 60), 232 (100), 202 (63), 115 (66). Anal. Calcd for $C_{17}H_{14}O_2$, C: 81.58; H: 5.64. Found C: 81.72; H: 5.57.

1.1.25. 2-[3-(2-Formylphenyl)-2-oxopropyl]benzoic acid (5c). Indene **10e** (100 mg, 0.40 mmol) was subjected to the ozonolysis conditions used for the transformation of analogue **10a** and the title compound was obtained as a white solid (50 mg, 44% yield). Mp 143–145 °C (ethyl acetate/hexane). IR ($\bar{\nu}$, cm^{-1}, KBr): ^{1}H NMR (δ, ppm, DMSO): 3.40 (s, 2H, CH_2), 3.47 (s, 2H, $-CH_2$), 6.27–6.78 (m, 7H, ArH), 6.94–7.05 (m, 1H, ArH), 9.13 (s, 1H, –CHO), 12.06 (br s, 1H, $-CO_2H$). ^{13}C NMR (δ, ppm, $CDCl_3$): 37.9

(CH_2), 38.5 (CH_2), 127.5 (CH), 127.8 (CH), 128.1 (CH), 128.7 (CH), 128.8 (CH), 129.2 (C), 129.4 (CH), 134.2 (CH), 134.8 (CH), 136.6 (C), 136.9 (C), 137.7 (C), 165.0 (C=O), 194.0 (C=O), 205.0 (C=O). HRMS: $C_{17}H_{14}O_4$, (M^{+}), calcd 282.0892; found 282.0888.

1.1.26. 6-Oxabenzo[*a*]anthracen-5-one (17a). Ketoaldehyde **5c** (88 mg, 0.31 mmol) was reacted with NaOH in the same way as analogue **5a** to give the title compound as a white solid (43 mg, 56% yield). Mp 190–192 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1725 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 7.42–7.89 (m, 7H, ArH), 8.20 (d, $J=8$ Hz, 1H, ArH), 8.33–8.42 (m, 2H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 113.5 (CH), 118.0 (C), 121.4 (C), 121.9 (CH), 122.4 (CH), 125.7 (CH), 127.2 (CH), 127.5 (CH), 128.2 (CH), 128.9 (CH), 130.1 (C), 130.6 (CH), 133.9 (C), 134.5 (C), 134.7 (CH), 148.7 (C), 160.9 (C=O). MS (*m*/*z*, %): 246 (M^{+}, 100), 218 (32), 189 (48). Anal. Calcd for $C_{17}H_{10}O_2$, C: 82.91; H: 4.09. Found C: 83.24; H: 3.97.

1.1.27. 6-Oxabenzo[*a*]anthracene-5,7,12-trione (4). Oxidation of dibenzochromanone **17a** (35 mg, 0.13 mmol) under the same conditions as for benzonaphthofuran **13a** gave the title compound as a yellow solid (16 mg, 41% yield). Mp 251–253 °C (MeOH/acetone/CH_2Cl_2). IR ($\bar{\nu}$, cm^{-1}, KBr): 1755 (C=O), 1679 (C=O). ^1H NMR (δ, ppm, TFA): 7.78–8.05 (m, 4H, ArH), 8.23 (t, $J=7.5$ Hz, 2H, ArH), 8.47 (d, $J=8$ Hz, 1H, ArH), 9.27 (d, $J=8.5$ Hz, 1H, ArH). ^{13}C NMR (δ, ppm, TFA): 118.0 (C), 121.3 (C), 126.7 (CH), 126.9 (CH), 128.3 (CH), 128.3 (C), 129.1 (C), 129.9 (CH), 131.1 (C), 131.8 (CH), 134.4 (CH), 135.8 (CH), 136.7 (CH), 149.5 (C), 161.7 (C=O), 178.8 (C=O), 184.1 (C=O). MS (*m*/*z*, %): 276 (M^{+}, 13), 248 (100), 220 (20), 163 (43). Anal. Calcd for $C_{17}H_8O_4$, C: 73.91; H: 2.82. Found C: 74.36; H: 2.77.

1.1.28. 5-Methoxy-2-(2-methoxycarbonylbenzyl)-1-oxoindan-2-carboxylic acid ethyl ester (15e). Reaction of 2-ethoxycarbonylindanone **14b** (1.159 g, 3.16 mmol) with *o*-methoxycarbonylbenzyl bromide under the same conditions as for analogue **14a** furnished the title compound as an oil (1.323 g, 73% yield). IR ($\bar{\nu}$, cm^{-1}, KBr): 1735 (C=O), 1717 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 1.19 (t, $J=7.0$ Hz, 3H, $-CH_3$), 3.56 (d, $J=17.5$ Hz, 1H, –C*H*H), 3.65 (d, $J=14.0$ Hz, 1H, –C*H*H), –), 3.81 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.87 (s, 1H, –C*H*H), 4.03 (d, $J=14.0$ Hz, 1H, –C*H*H), 4.16 (q, $J=7.0$ Hz, 2H, $-CH_2O$), 6.73 (d, $J=2.0$ Hz, 1H, ArH), 6.84 (m, 1H, ArH), 7.16–7.27 (m, 3H, ArH), 7.66 (d, $J=8.5$ Hz, 1H, ArH), 7.79 (m, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 35.4 (CH_2), 35.7 (CH_2), 52.0 (CH_3), 55.5 (CH_3), 61.7 (CH_2), 61.9 (C), 109.0 (CH), 115.5 (CH), 126.0 (CH), 126.4 (CH), 128.1 (C), 130.3 (CH), 130.9 (CH), 131.2 (CH), 131.5 (C), 138.1 (C), 156.7 (C), 165.4 (C), 167.9 (C), 170.9 (C), 200.3 (C=O). HRMS: $C_{22}H_{22}O_6$ ($M^{+}+1$), calcd 383.1416; found 383.1419.

1.1.29. 5-Methoxy-2,2′-spirobiindanone (16b). A mixture of benzylindanone **15d** (1.393 g, 3.80 mmol) in 96% AcOH (5.5 mL) and 48% HBr (2.9 mL) was subjected to the same reaction conditions as for analogue **15b**. The title compound was obtained as a white solid (531 mg, 53% yield). Mp 176–78 °C (MeOH). IR ($\bar{\nu}$, cm^{-1}, KBr): 1709 (C=O), 1690 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 3.10–3.20 (m, 2H, CH_2), 3.63–3.75 (m, 2H, CH_2), 3.91 (s, 3H, OMe), 6.93–6.98 (m, 2H, ArH), 7.40 (t, $J=7.5$ Hz, 1H, ArH), 7.54–7.77 (m, 4H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 38.0 (CH_2), 38.1 (CH_2), 55.7 (CH_3), 65.4 (C), 109.4 (CH), 115.9 (CH), 124.7 (CH), 126.2 (CH), 126.4 (CH), 127.6 (CH), 128.4 (C), 135.1 (CH), 135.4 (C), 153.7 (C), 156.7 (C), 165.6 (C), 200.4 (C=O), 202.9 (C=O). MS (*m*/*z*, %): 278 (M^{+}, 100), 250 (52), 178 (28). Anal. Calcd for $C_{18}H_{14}O_3$, C: 77.68; H: 5.07. Found C: 77.84; H: 5.02.

1.1.30. 2-(5-Methoxy-1-oxoindan-2-ylmethyl)benzoic acid and 4-methoxy-2-(1-oxoindan-2-ylmethyl)benzoic acid (10f–10g). Reaction of spiroindanone **16b** (451 mg, 1.72 mmol) under the same conditions as for analogue **16a** provided a solid reaction mixture. Purification by flash column chromatography (eluant: CH_2Cl_2/MeOH, 98.5/1.5) led to the isolation of small fractions of ketoacid **10f** (71 mg, 30% yield) and ketoacid **10g** (29 mg, 12% yield) as white solids.

1.1.31. Ketoacid a. Mp 150–152 °C (benzene/CH_2Cl_2). IR ($\bar{\nu}$, cm^{-1}, KBr): 3434 (OH), 1709 (C=O), 1679 (C=O). ^1H NMR (δ, ppm, $CDCl_3$): 2.90 (d, $J=13.5$ Hz, 1H, C*H*H), 3.16–3.23 (m, 3H, C*H*H and CH_2), 3.77–3.85 (m, 4H, CH and OMe), 6.80–6.87 (m, 2H, ArH), 7.32–7.41 (m, 2H, ArH), 7.52–7.57 (m, 1H, ArH), 7.77 (d, $J=7.5$ Hz, 1H, ArH), 8.11 (d, $J=9.0$ Hz, 1H, ArH) ^{13}C NMR (δ, ppm, $CDCl_3$): 32.3 (CH_2), 35.1 (CH_2), 48.6 (CH), 55.4 (CH_3), 111.7 (CH), 117.1 (CH), 120.6 (C), 123.9 (CH), 126.5 (CH), 127, (CH), 134.5 (CH), 134.7 (CH), 136.6 (C), 139.3 (C), 145.7 (C), 153.6 (C), 163.1 (C=O), 207.9 (C=O). MS (*m*/*z*, %): 296 (M^{+}, 25), 278 (100), 250 (46). Anal. Calcd for $C_{18}H_{16}O$, C: 72.96; H: 5.44. Found C: 73.15; H: 5.37.

1.1.32. Ketoacid b. Mp 143–145 °C (benzene/CH_2Cl_2). IR ($\bar{\nu}$, cm^{-1}, KBr): 1257 (C–OMe), 1703 (C=O ketone and C=O acid); 3430 (C–OH). ^1H NMR (δ, ppm, $CDCl_3$): 2.84 (d, $J=14.5$ Hz, 1H, –C*H*H), 3.06–3.17 (m, 3H, C*H*H and CH_2), 3.77–3.84 (m, 4H, CH and OMe), 6.83–6.90 (m, 2H, ArH), 7.29–7.38 (m, 2H, ArH), 7.46–7.52 (m, 1H, ArH), 7.71 (d, $J=8.5$ Hz, 1H, ArH), 8.05–8.08 (m, 1H, ArH). ^{13}C NMR (δ, ppm, $CDCl_3$): 32.3 (CH_2), 35.0 (CH_2), 48.8 (CH), 55.6 (CH_3), 109.6 (CH), 115.4 (CH), 125.7 (CH), 126.5 (CH), 129.7 (C), 131.6 (CH), 131.8 (CH), 132.8 (CH), 140.5 (C), 142.5 (C), 148.0 (C), 156.5 (C), 165.4 (C=O), 206.3 (C=O). MS (*m*/*z*, %): 296 (M^{+}, 74), 278 (57), 250 (29), 161 (100). Anal. Calcd for $C_{18}H_{16}O$, C: 72.96; H: 5.44. Found C: 72.69; H: 5.48.

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Catalytic electronic activation as a tool for the addition of stabilised nucleophiles to allylic alcohols

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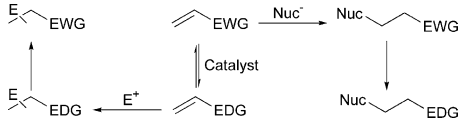
Abstract—This paper describes the activation of 2-cyclohexen-1-ol (**1**) and 2-cyclopenten-1-ol (**11**) through the use of aluminium-catalysed transfer hydrogenation. The electronically activated substrates are demonstrated to undergo facile conjugate addition and, when the alcohol functional group is subsequently restored in a one-pot procedure, this leads to an indirect addition of nucleophiles to allylic alcohols. This novel methodology has been termed catalytic electronic activation.The aluminium *tert*-butoxide catalysed conversion of 2-cyclohexen-1-ol (**1**) into 2-(3-hydroxycyclohexyl)-2-methylmalononitrile (**18**) and 2-cyclopenten-1-ol (**11**) into 2-(3-hydroxycyclopentyl)-2-methylmalononitrile (**16**) in 90 and 60% yield, respectively has been demonstrated through an efficient domino Oppenauer/Michael addition/Meerwein–Ponndorf–Verley process.

1. Introduction

The reactivity of an alkene is highly dependent upon the nature of any nearby substituents. For example, whilst alkenes conjugated to electron-withdrawing groups can be susceptible to nucleophilic addition reactions, alkenes attached to electron-donating groups are more susceptible to electrophilic addition. Conversion of electron-donating groups and electron-withdrawing groups would achieve reversible catalytic electronic activation of the alkene, and enable a cross-over in the reactivity of alkene substrates (Scheme 1). Thus, alkenes attached to electron-withdrawing groups (EWG) could undergo indirect electrophilic addition, and alkenes attached to electron donating groups (EDG) could undergo indirect nucleophilic addition.



Scheme 1. Reversible crossover of alkene reactivity.

By designing a reaction whereby an alcohol is reversibly oxidised to a carbonyl compound, we have reported preliminary results which show that it is possible to effect indirect nucleophilic addition to allylic alcohols.[1] A related concept has been applied by this group to indirect Wittig reactions on alcohols[2,3] and other processes.[4–7]

Transfer hydrogenation reactions have been used widely in the reduction of carbonyl compounds, as well as the reverse process.[8–12] One of the hallmarks of these reactions is their reversibility, which has been exploited in the racemisation of secondary alcohols.[13] Whilst there are many reagents and catalysts capable of effecting a reversible oxidation/reduction sequence, we reasoned that the use of aluminium catalysts would be less likely to promote isomerisation of allylic alcohol substrates than many transition metal catalysts.[14,15]

2. Results and discussion

2.1. Use of malonate nucleophiles

Aluminium alkoxides have been used extensively to carry out reversible hydride transfer to a carbonyl acceptor.[16–18] The most commonly used reagent, aluminium isopropoxide, is available commercially and promotes both the Meerwein–Ponndorf–Verley (MPV) reduction and Oppenauer oxidation effectively under suitable reaction conditions, generally employing an excess of either oxidant (acetone, 2-butanone) or reductant (propan-2-ol).

It was envisaged that the catalytic electronic activation process would only require a catalytic amount of ketone added at the start of the reaction. Equilibrium would then be

Keywords: Aluminium; Catalytic electronic activation; Homogeneous catalysis; Hydrogenation; Michael addition.
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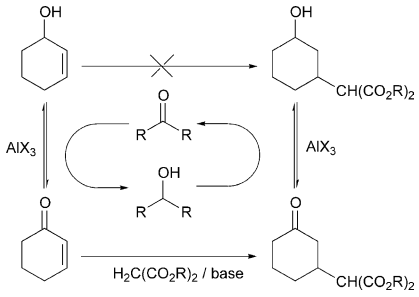
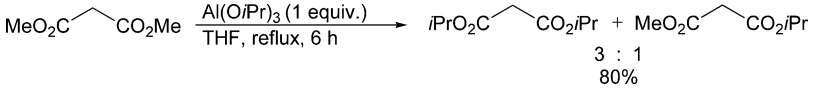


Scheme 2. Principal of catalytic domino Oppenauer/Michael addition/MPV reduction.

maintained between the alcohol and ketone components during the course of the reaction (Scheme 2).

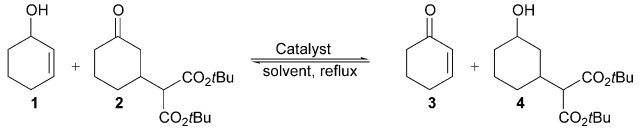
Preliminary studies indicated that both dimethyl malonate derived nucleophiles and the corresponding Michael addition adducts were susceptible to aluminium isopropoxide mediated *trans*-esterification (Scheme 3).[19,20] The labile methoxy ester groups are replaced readily by the isopropoxide ligands on the aluminium catalyst.



Scheme 3. Aluminium isopropoxide catalysed trans-esterification of dimethyl malonate.

In an attempt to block *trans*-esterification and base-catalysed hydrolysis reactions, the more robust *tert*-butyl ester was chosen; for these substrates *trans*-esterification proceeds almost exclusively through alkyl-oxygen cleavage.[21]

In order to ascertain the equilibrium position for the desired transfer hydrogen reaction, arguably the most important factor in catalytic electronic activation, a 1:1 mixture of 2-cyclohexen-1-ol (**1**) and ketone **2** was heated to reflux in solvent into which aluminium *tert*-butoxide was added dropwise (Scheme 4, Table 1).



Scheme 4. Aluminium catalysed Oppenauer/MPV crossover reaction.

Table 1. Results of malonate derived Oppenauer/MPV crossover reaction

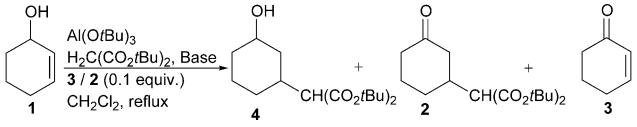
Entry	Catalyst (mol%)	Solvent[a]	*t* (h)	Conv. (%)[b]	Recovery (%)[c]
1	$Al(OtBu)_3$ (100)	THF	6	>95	96
2	$Al(OtBu)_3$ (100)	CH_2Cl_2	24[d]	>95	99
3	$Al(OtBu)_3$ (10)	CH_2Cl_2	24	>95	100
4	Na(O*i*Pr) (100)	CH_2Cl_2	24	<5	76

[a] The reactions were carried out on a 1 mmol scale in solvent (10 mL) at reflux.
[b] Analysed by ^{1}H NMR.
[c] Crude recovery upon work-up.
[d] Reaction reached completion in 6 h.

After 6 h, ^{1}H NMR analysis of the crude product indicated a >95% conversion into 2-cyclohexen-1-one (**3**) and alcohol **4** in both tetrahydrofuran and dichloromethane (Table 1, entries 1 and 2), thus proving conclusively that the equilibrium position for the transfer hydrogenation reaction lies firmly to the right, that is, towards the thermodynamically more favourable conjugated ketone. This is beneficial for ensuring a constant supply of enone ready for conjugate addition. Surprisingly, aluminium *tert*-butoxide also exhibited excellent activity at substoichiometric levels (Table 1, entry 3); a property not normally associated with MPV-type systems.[16] However, a repeat experiment conducted at room temperature gave no conversion into the desired products after 6 h, while the use of a sodium isopropoxide catalyst[22] (Table 1, entry 5) provided equally disappointing results.

The data collected thus far suggested that the following reaction scheme could be envisaged (Scheme 5).

A series of experiments was designed in order to test this hypothesis: the general procedure involved the addition of 2-cyclohexen-1-ol (**1**) and a catalytic amount of 2-cyclohexen-1-one (**3**) to a stirred solution of di-*tert*-butyl malonate (**5**) and base in dichloromethane. This solution was subsequently heated at reflux into which aluminium *tert*-butoxide was added slowly over 30 min (Table 2).



Scheme 5. Malonate derived domino Oppenauer/Michael addition/MPV process.

Table 2. Results of malonate derived domino Oppenauer/Michael addition/MPV process

Entry	Base[a] (mol%)	Malonate (mol%)	$Al(OtBu)_3$ (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	NaH (20)	200	100	1	12:14:1
2	NaH (20)	200	100	6	19:12:5
3	NaH (10)	200[c]	100	24	0:0:10
4	KO*t*Bu (10)	100[d]	100	24	0:0:10
5	NaH (30)	200	10	24	0:29:0
6	NaH (50)	500	100	24	0:43:0
7	NaH (20)	200	100	72	10:2:6

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (5–8 mL) at reflux.
[b] Analysed by ^{1}H NMR.
[c] Added portionwise over 7 h.
[d] Heated at 100 °C in an ACE pressure tube.

The initial results were rather disappointing: under a variety of experimental conditions, only low conversions (10–19%; Table 2, entries 1, 2 and 7) into alcohol **4** were obtained, even after 72 h. Of some concern was the presence of ketone **2** in

the reaction mixture (Table 2, entries 5 and 6). This suggested that the efficient aluminium catalysed transfer hydrogenation between ketone **2** and allylic alcohol **1** (Scheme 4) was inhibited by the presence of di-*tert*-butylmalonate (**5**).

Surprisingly, a repeat experiment using 10 mol% of ketone intermediate **2** as oxidant (Scheme 5) provided appreciably enhanced, yet still moderate, conversions into alcohol **4** (Table 3). We are not sure why the choice of ketone has such a pronounced effect on conversion, however a possible solution is postulated (vide infra).

Table 3. Results of domino Oppenauer/Michael addition/MPV process using catalytic ketone **2**

Entry	Solvent[a] (mL)	Malonate (mol%)	$Al(OtBu)_3$ (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	THF (10)	100	100	96	43:20:5
2	THF (10)	100[c]	10	24	29:67:0[d]
3	CH_2Cl_2 (10)	200	100	72	38:0:0
4	CH_2Cl_2 (5)	200	100	10	0:23:0
5	CH_2Cl_2 (5)	200	100	10	10:0:9
6	CH_2Cl_2 (25)[e]	120	100	24	24:0:1

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (5–25 mL) at reflux.
[b] Analysed by ^1H NMR.
[c] 0.1 equiv KO*t*Bu.
[d] Main product consistent with malonic acid dicyclohex-2-enyl ester.
[e] 5 mmol in CH_2Cl_2 at reflux.

Both Wilds[17] and Okano[23] have reported that β-diketones deactivate aluminium and lanthanide(III) catalysts by strong chelate formation. Furthermore, Okano and co-workers were able to isolate the acetylacetonate complex $gd(acac)_3$ from the reaction mixture which displayed no catalytic activity. It is therefore probable that the low conversions to date are attributed to an analogous complex formation (Fig. 1, A).

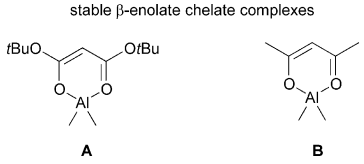


Figure 1. Comparison of proposed aluminium complex and aluminium acetylacetonate.

This idea is reinforced by the fact that aluminium acetylacetonate (Fig. 1, B) was demonstrated to be an ineffective promoter in the Oppenauer/MPV crossover reaction (Scheme 4, Table 4).

Snider[24] and more recently Node[25,26] demonstrated that dimethylaluminium chloride was able to catalyse both an Oppenauer/ene annelation and a domino Michael addition/MPV reduction, respectively. In each case, the reaction proceeded at room temperature to give the desired products in excellent yield.

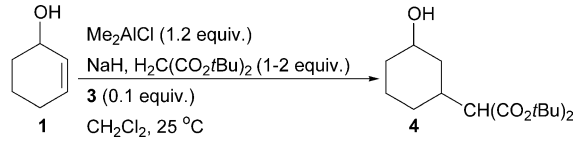
Table 4. Results of dimethylaluminium chloride catalysed Oppenauer/MPV crossover reaction

Entry	Catalyst[a] (mol%)	Temperature (°C)	Conv. (%)[b]
1	$Al(acac)_3$ (100)	44	<5
2	Me_2AlCl (10)	25	>95
3	Me_2AlCl (120)	25	>90

[a] The reactions were carried out on a 1 mmol scale in solvent (5 mL).
[b] Analysed by ^1H NMR.

In view of this evidence dimethylaluminium chloride appeared to be an excellent candidate for the domino Oppenauer/Michael addition/MPV process. Thus, the transfer hydrogenation capabilities of dimethylaluminium chloride were investigated for the crossover Oppenauer/MPV process (Scheme 4, Table 4).

These promising results prompted further investigation towards the domino Oppenauer/Michael addition/MPV process. The general procedure involved adding dimethylaluminium chloride to a nitrogen-purged dichloromethane solution of 2-cyclohexen-1-ol (**1**). After 20 min, a catalytic amount of 2-cyclohexen-1-one (**3**), di-*tert*-butyl malonate (**5**) and sodium hydride were added and the reaction maintained at room temperature (Scheme 6, Table 5).



Scheme 6. Dimethylaluminium chloride catalysed Domino Oppenauer/Michael addition/MPV reaction.

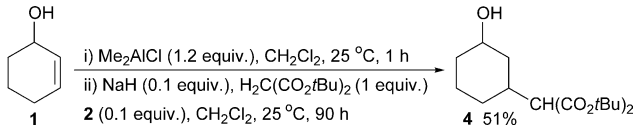
Table 5. Dimethylaluminium chloride catalysed Domino Oppenauer/Michael addition/MPV reaction

Entry	NaH (mol%)	Malonate[a] (mol%)	*t* (h)	Conv. **4**:**2**:**3** (%)[b]
1	10	100[c]	6	9:1:15
2	20	100[c]	6	22:12:11
3	10	100[d]	24	25:1:5
4	20	100[c]	72	11:1:20
5	20	200[c]	72	23:12:10

[a] The reactions were carried out on a 1 mmol scale in CH_2Cl_2 (7–10 mL) at room temperature.
[b] Analysed by ^1H NMR.
[c] 2-Cyclohexen-1-one (0.2 equiv) and 4 Å MS were added.
[d] 2-Cyclohexen-1-ol and catalyst stirred for 1 h.

Unfortunately, the conversions into alcohol **4** were still low (9–25%), even after prolonged reaction times (Table 5, entries 4 and 5). However, the presence of unreacted 2-cyclohexen-1-one (**2**) (Table 5, entries 2 and 5), again suggests that the malonate salt may be forming an acac-type complex (Fig. 1, A) with the aluminium catalyst, inhibiting both the Michael addition and Meerwein–Ponndorf–Verley–Oppenauer (MPVO) chemistry.

Yager and co-workers[27] have demonstrated that the rates of MPVO reactions were affected directly by the degree of pre-association of the aluminium complex and the alcohol substrate. Thus, a final experiment was performed in order to discover whether prior reaction of cyclohexenol with the aluminium promoter could lead to an improved yield. Thus, reaction of 2-cyclohexen-1-ol (**1**) with dimethylaluminium chloride for 1 h presumably forms an aluminium cyclohexenyl alkoxide intermediate, and this was found to provide an increase in the rate of reaction (Scheme 7).

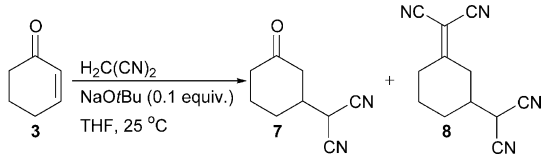


Scheme 7. In situ generated aluminium alkoxide domino Oppenauer/Michael addition/MPV reaction.

After 90 h an increased conversion into alcohol **4** (51%) was realised. The formation of the desired product, at room temperature, albeit at moderate conversion, was considered a notable improvement.

2.2. Use of malononitriles as nucleophiles

In order to realise high conversions in the allylic alcohol catalytic electronic activation procedure it was proposed that an alternative non-chelating nucleophile should be investigated. Malononitrile (**6**) is a useful building block in synthetic chemistry[28] and it is therefore an appealing substrate for the domino Oppenauer/Michael addition/MPV process. However competitive Knoevenagel condensation/dehydration was found to occur either preferentially or subsequent to the desired conjugate addition (Scheme 8, Table 6).[29,30]



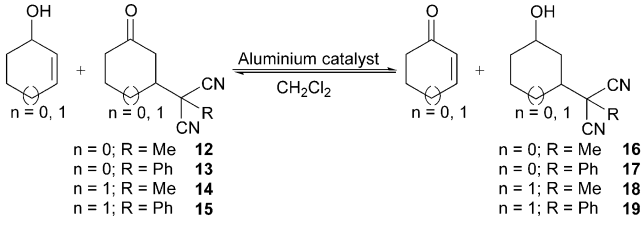
Scheme 8. Addition of malononitrile to 2-cyclohexen-1-one.

Table 6. Results of the addition of malononitrile to 2-cyclohexen-1-one

Entry	Malononitrile[a] (mol%)	*t* (h)	Conv. **7**:**8** (%)[b]
1	100	1	>90:0
2	200	4	43:57
3	100	8	29:71

[a] Reactions were performed on a 1 mmol scale in solvent (10–20 mL).
[b] Analysed by ^{1}H NMR.

It was proposed that a simple solution to prevent the aldol/dehydration reaction was to place a substituent at the acidic ($pK_a = 11.2$)[31] α-position of malononitrile (**6**). Thus, methylmalononitrile (**9**) and benzylmalononitrile (**10**) were synthesised according to a recent procedure reported by Díez-Barra and co-workers.[32] This procedure was adopted as other simple base-catalysed routes are known to lead to di-substituted products.



Scheme 9. Aluminium catalysed Oppenauer/MPV crossover reaction of malononitrile derived substrates.

The next objective was to establish the equilibrium position for the transfer hydrogenation reaction. Thus, dimethylaluminium chloride and aluminium *tert*-butoxide were investigated for their ability to effect transfer hydrogenation between 2-cyclohexen-1-ol (**1**), 2-cyclopenten-1-ol (**11**) and the corresponding ketone intermediates (Scheme 9, Table 7).

Table 7. Results of aluminium catalysed Oppenauer/MPV crossover reaction of malononitrile derived substrates

Entry	Substrate	Catalyst[a] (mol%)	Temperature (°C)	*t* (h)	Conv. (%)[b]
1	**14**	Me_2AlCl (10)	25	15	>95
2	**15**	$Al(OtBu)_3$ (10)	44	6	>95
3	**12**	$Al(OtBu)_3$ (10)	44	24	41
4	**13**	$Al(OtBu)_3$ (100)	44	24	68

[a] Reactions were performed on a 1 mmol scale in solvent (5 mL).
[b] Analysed by ^{1}H NMR.

Whilst the equilibrium position for the transfer hydrogenation reaction between cyclohexyl derivatives lies firmly to the right (Table 7, entries 1 and 2), the effect is not quite as pronounced for the cyclopentyl adducts (Table 7, entries 3 and 4). This suggests that the thermodynamic driving force to produce the conjugated ketone is less well defined. Feringa[33] and Pfaltz[34] have also observed an analogous significant difference in reactivity between 2-cyclohexen-1-one (**3**) and 2-cyclopenten-1-one (**20**) towards asymmetric conjugate addition.

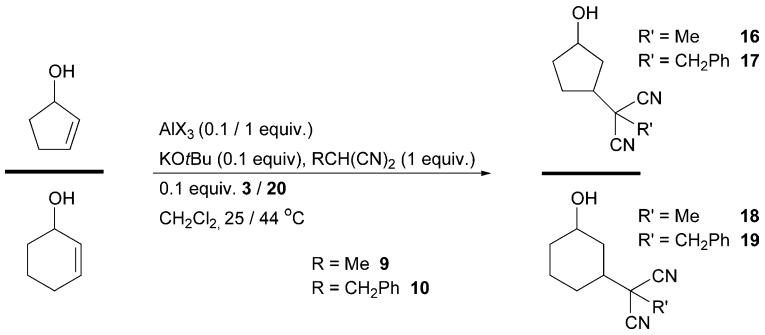
Based on the conditions needed for conjugate addition and for transfer hydrogenation an indirect nucleophilic addition of methylmalononitrile (**9**) and benzylmalononitrile (**10**) to 2-cyclohexen-1-ol (**1**) and 2-cyclopenten-1-ol (**11**) was attempted (Scheme 10, Table 8). These experiments employed the aluminium reagent in stoichiometric amounts.

These data demonstrated for the first time an efficient domino Oppenauer/Michael addition/MPV process (Table 8, entries 5 and 6); it is worth noting that the maximum expected yield is 90%. However, significantly poorer yields were obtained when using the dimethylaluminium chloride catalyst (Table 8, entries 1 and 2) and in the cyclopentyl system (Table 8, entries 7–9).

Nevertheless, it was hoped that a fully catalytic reaction could be employed. Thus, both aluminium *tert*-butoxide and dimethylaluminium chloride were investigated for their ability to effect a catalytic electronic activation process (Scheme 10, Table 9).

Poor results were obtained initially when using substoichiometric amounts of catalyst (Table 9, entries 1–3). To address these problems the reactions were studied at elevated temperatures using ACE pressure tubes (Table 9, entries 4–9). Thus we were able to realise the catalytic reaction within 8 h when the higher temperatures were employed; even when using 10 mol% of cyclohexanone as an alternative catalytic oxidant (Table 9, entry 5). Under the same conditions a 57% yield of alcohol **18** could be obtained using 5 mol% cyclohexanone.

The initial results for the attempted domino Oppenauer/



Scheme 10. Aluminium catalysed domino Oppenauer/Michael addition/MPV process using malononitrile derived substrates.

Table 8. Results of malononitrile derived domino Oppenauer/Michael addition/MPV process

Entry	Product	Catalyst[a]	Temperature (°C)	*t* (h)	Yield (%)[b]
1	**18**	Me_2AlCl	25	24	43
2	**18**	Me_2AlCl[c]	25	24	46
3	**18**	$Al(OiPr)_3$	44	24	78
4	**18**	$Al(OtBu)_3$	44	8	69
5	**18**	$Al(OtBu)_3$[d]	44	48	90
6	**19**	$Al(OtBu)_3$	44	24	81
7	**16**	$Al(OtBu)_3$	44	6	10
8	**16**	$Al(OtBu)_3$	44	24	31[e]
9	**17**	$Al(OtBu)_3$	44	24	19

[a] Reactions were performed on a 1 mmol scale in CH_2Cl_2 (5–10 mL).
[b] Yield of isolated product after flash-column chromatography.
[c] Tetrabutylammonium bromide (0.04 equiv) added to increase dissolution of malononitrile salt.
[d] Reaction carried out on a 5 mmol scale.
[e] NaO*t*Bu (0.1 equiv) used as base.

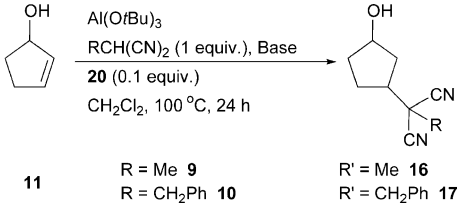
Table 9. Results of malononitrile derived catalytic domino Oppenauer/Michael addition/MPV process

Entry	Product	Catalyst[a] (mol%)	Temperature (°C)	*t* (h)	Yield (%)[b]
1	**18**	Me_2AlCl (10)	25	24	<5
2	**18**	Me_2AlCl (30)	25	24	37
3	**18**	$Al(OtBu)_3$ (10)[c]	44	24	<5
4	**18**	$Al(OtBu)_3$ (10)[c]	100	8	90
5	**18**	$Al(OtBu)_3$ (10)[c,d]	100	8	70
6	**19**	$Al(OtBu)_3$ (10)[c]	100	8	64
7	**16**	$Al(OtBu)_3$ (100)[c]	100	24	60
8	**16**	$Al(OtBu)_3$ (100)[c]	150	24	61
9	**17**	$Al(OtBu)_3$ (100)[c]	100	24	21

[a] Reactions were performed on a 1 mmol scale in CH_2Cl_2 (3–10 mL).
[b] Yield of isolated product after flash column chromatography.
[c] Reactions were performed on a 1 mmol scale in an ACE pressure tube.
[d] Cyclohexanone (0.1 equiv) used as oxidant.

Michael addition/MPV process between 2-cyclopenten-1-ol (**11**) and malononitrile derivatives were disappointing (Table 9, 7–9), although an increase in temperature does provide an appreciable enhancement in yield (Table 9, entries 7 and 8 cf. Table 8, entries 7–9). Nevertheless, these yields are moderate in comparison with the cyclohexyl system (vide supra) and require a stoichiometric amount of catalyst. Unidentified by-products were formed when 2-cyclopenten-1-ol (**11**) was employed as a substrate. This may be attributable to self-condensation of the enone, malononitrile or to Ritter or Pinner reactions on the nitrile. Spectroscopic analysis on the intractable mixtures was inconclusive.

In order to address these problems, two further approaches were explored: organic and fluoride bases (Scheme 11, Table 10).



Scheme 11. 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process.

Table 10. Results of 2-Cyclopenten-1-ol domino Oppenauer/Michael addition/MPV process

Entry	Product	$Al(OtBu)_3$ (mol%)[a]	Base (mol%)	Temperature (°C)	*t* (h)	Conv. (%)[b]
1	**16**	100	CsF (10)	100	20	71
2	**16**	10	CsF (100)	100	24	<5
3	**16**	100[c]	DBU[d] (10)	44	24	<5
4	**16**	100	MTBD[e] (10)	100	24	48[f]
5	**17**	100	—	100	24	44
6	**17**	100	—	100	72	60[f]

[a] Reactions were performed on a 1 mmol scale in an ACE pressure tube.
[b] Analysed by ^1H NMR.
[c] Reaction was performed on a 1 mmol scale in solvent at reflux.
[d] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[e] 7-Methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene.
[f] Yield of isolated product after flash column chromatography.

Catalytic caesium fluoride (Table 10, entry 1) was demonstrated to be an excellent base in the domino Oppenauer/Michael addition/MPV process. Michael addition reactions using caesium fluoride do have literature precedent: Yamaguchi and co-workers[35] have reported previously the stereoselective addition of di-*tert*-butyl malonate (**5**) to 2-cyclohexen-1-one (**3**) catalysed by 20 mol% caesium fluoride. In addition, fluoride bases provided a very 'clean' reaction profile appearing to suppress the minor side-reactions which were previously observed. This trend was also reflected in the result obtained using the strong organic base, MTBD ($pK_a \sim 23$).[36] Whereas the weaker organic base DBU (pK_a 11–12), did not display any activity in the allylic alcohol catalytic electronic activation process (Table 10, entry 3), MTBD was

able to catalyse the reaction in moderate yield (Table 10, entry 4).

Whilst the yield of alcohol **17** was low at reflux and elevated temperatures (Tables 8 and 9, entries 9), a moderate yield was finally obtained through using a system in which the potassium *tert*-butoxide base was omitted (Table 10, entries 5 and 6). It therefore appeared that under the prolonged high temperatures, the aluminium catalyst was able to form the desired malononitrile nucleophile,[37] whilst not possessing sufficient basicity to facilitate the formation of base-catalysed by-products.

An issue not discussed thus far is product diastereoselectivity. For the cyclohexyl-derived substrates an approximate 60:40 ratio of product diastereomers was delivered, whereas the cyclopentyl-derived products displayed a moderate bias towards the *cis* configuration (Fig. 2). The ratio of diastereoisomers was established by analysis of the ^{1}H NMR spectra. Absolute stereochemistry was confirmed through X-ray crystallographic analysis of the individual diastereomers.

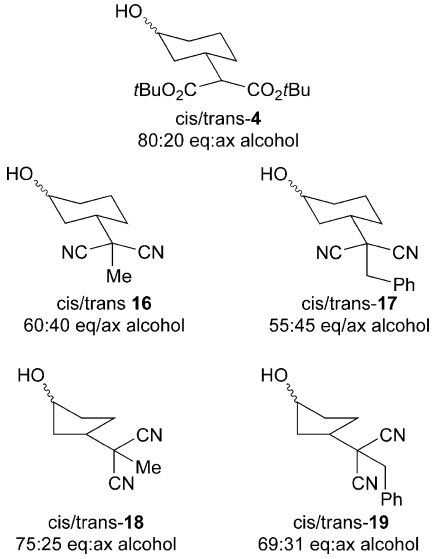


Figure 2. Axial/equatorial product ratios.

The thermodynamic product distribution was explored through the equilibration of pure axial alcohol (*trans*-**16**) in 1:1 acetone/propan-2-ol at reflux (Scheme 12).

Thus, the axial alcohol (*trans*-**16**) was converted into a thermodynamic product ratio (62:38 equatorial/axial) efficiently under aluminium *tert*-butoxide catalysis within 12 h. This is essentially the same ratio that is observed in the overall domino process.

The application of the current procedure towards acyclic substrates is, at present, unfulfilled. The required reaction was found to be fatally inhibited by both poor crossover transfer hydrogenation, and undesired cyclisation processes.[38]

3. Conclusion

In summary, it has been demonstrated that whilst nucleophiles will not normally add to allylic alcohols, this reaction becomes possible by a procedure involving catalytic electronic activation of the substrate.

The concept of temporarily oxidising alcohols to carbonyl compounds as an approach to catalytic electronic activation processes is under further investigation.

4. Experimental

4.1. General procedures

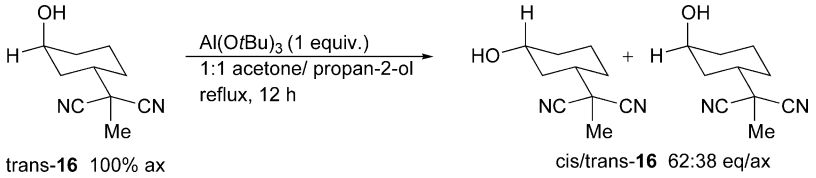
All reactions were performed under an atmosphere of dry nitrogen using oven-dried (150 °C) glassware. Dichloromethane was distilled from CaH_2 before use. THF was distilled from the anion of benzophenone ketyl radical. Unless preparative details are provided all chemicals were available commercially and were purchased from Acros, Fluka, Lancaster or Sigma-Aldrich. Methylmalononitrile (**9**) and benzylmalononitrile (**10**) were prepared by the method of Díez-Barra.[32] 2-Cyclopenten-1-ol (**11**) was prepared by the method of Larock.[39]

Melting points were recorded on a Büchii 535 Series instrument and are uncorrected.

IR spectra were recorded as thin films, solutions ($CDCl_3$) or KBr discs using a Perkin–Elmer 1600 Series FT-IR spectrophotometer in the range 4000–600 cm^{-1}, with internal background scan. Absorption maxima are recorded in wavenumbers (cm^{-1}).

Proton (δ ^{1}H) NMR spectra were run in $CDCl_3$ using either a Bruker AM-300 (300 MHz), Jeol (270 MHz), or Jeol (400 MHz) instrument. Chemical shifts are reported relative to Me_4Si (δ 0.00 ppm) as internal standard. Coupling constants (*J*) are given Hz and multiplicities denoted as singlet (s), doublet (d), triplet (t), multiplet (m), or broad (br). Carbon-13 (δ ^{13}C) NMR spectra were run in $CDCl_3$ and were recorded using a Bruker WH-400 (100 MHz) or a Bruker AM-300 (75 MHz).

Mass spectra, including high-resolution spectra, were



Scheme 12. Equilibration of axial alcohol.

recorded on a Micromass Autospec Spectrometer using electron impact (EI+) ionisation, chemical impact (CI+, *iso*-butane) ionisation, electrospray (ES+) ionisation and/or Fast Atom Bombardment (FAB+) ionisation.

Elemental analyses were performed using a Carlo Erba 1106 Elemental Analyser or an Exeter Analytical Inc. CE-440 Elemental Analyser.

4.1.1. Aluminium isopropoxide catalysed trans-esterification of dimethyl malonate. Dimethyl malonate (0.132 g, 1.0 mmol) and aluminium isopropoxide (0.204 g, 1.0 mmol) were heated to 62 °C in THF (8 mL). After 6 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo to give a mixture of *iso*-propylmethylmalonate and di-*iso*-propylmalonate (1:3) as yellow oil (80% conversion determined by ^{1}H NMR). An authentic sample of *iso*-propylmethylmalonate was prepared by the method of Wakasugi.[40]

4.1.2. Preparation of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2). 2-Cyclohexen-1-one (**3**) (1.00 g, 10 mmol) in THF (2 mL) was added dropwise to a suspension of sodium hydride (0.025 g, 1.0 mmol) and di-*tert*-butyl malonate (**5**) (2.25 g, 10 mmol) in THF (10 mL). After 6 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (100 mL) and washed with water (2×50 mL). The aqueous phase was separated and extracted with diethyl ether (3×100 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave **2** as a white crystalline solid (3.05 g, 94%) (Fig. 3).

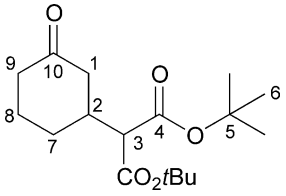


Figure 3.

Compound **2**. Mp 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=1.42 (br s, 9H, H_6), 1.42–1.75 (m, 2H), 1.94–2.03 (m, 1H), 2.04–2.12 (m, 1H), 2.20–2.32 (m, 2H), 2.36–2.50 (m, 3H), 3.09 (d, J=8 Hz, 1H, H_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=24.7, 28.0 (C_6), 28.0 (C_6), 37.9, 41.2, 45.2, 58.8 (C_3), 81.8 (C_5), 81.8 (C_5), 167.0 (C_4), 209.7 (C_{10}); IR ($CHCl_3$): ν (cm^{-1})=1740 (C=O), 1724 (C=O); MS (FAB+): *m/z* 313 [$M^{\cdot+}$]; HRMS (FAB+): $C_{17}H_{28}O_5$ requires 313.2015, found 313.2028; $C_{17}H_{28}O_5$ requires C 65.36%, H 9.03%, found C 65.60%, H 9.05%.

4.1.3. Preparation of *cis*/*trans*-2-(3-hydroxy-cyclohexyl)-malonic acid di-*tert*-butyl ester (4). 2-(3-Oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**4**) (0.312 g, 1.0 mmol) in anhydrous methanol (5 mL) was cooled to 0 °C whilst sodium borohydride (0.038 g, 1.0 mmol) was added gradually over 0.1 h. After 1 h, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash-column chromatography (SiO_2, 4:1 petroleum ether/ethyl acetate) gave *cis*/*trans*-**5** as colourless oil (0.311 g, 99%, 80:20 *cis*/*trans*) (Fig. 4).

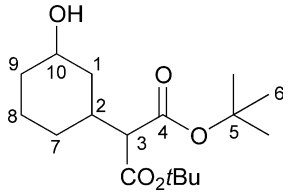


Figure 4.

Compound cis/*trans*-**4**. ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ=0.90–1.22 (m, 2H), 1.24–1.40 (m, 1H), 1.43 (br s, 18H), 1.50–1.64 (m, 3H), 1.66–1.77 (m, 1H), 1.78–1.83 (m, 1H), 1.93–2.11 (m, 1H), 2.98 (d, J=9 Hz, 1H, H_3), 2.98 (d, J=9 Hz, 1H, H_3), 3.59 (m, 1H, H_{10ax}), 4.09 (br s, 1H, H_{10eq}); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=23.6, 27.9 (C_6), 27.9 (C_6), 35.2, 35.9, 39.7, 59.5 (C_3), 70.0 (C_{10}), 81.3 (C_5), 81.3 (C_5), 167.5 (C_4), 167.6 (C_4); IR ($CHCl_3$): ν (cm^{-1})=3436 (O–H); 1750 (C=O); MS (FAB+): *m/z* 315 [$M^{\cdot+}$]; $C_{17}H_{30}O_5$ requires C 64.92%, H 9.62%, found C 64.40%, H 9.62%.

4.1.4. General procedure for the aluminium *tert*-butoxide catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2) (Scheme 4, Table 1). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise over a period of 30 min to a stirred solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.312 g, 1.0 mmol) in dichloromethane (8 mL) at 44 °C under nitrogen. After 24 h, the reaction was cooled, diluted with diethyl ether (50 mL), and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to give **3/4** as a yellow oil (0.387 g, 94% recovery, >95% conversion determined by ^{1}H NMR).

4.1.5. General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (2) (Scheme 4, Table 4). Dimethylaluminium chloride (0.1 mL, 1.0 M solution in hexane, 0.1 mmol) was added to a nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) in dichloromethane (3 mL). The reaction was stirred at room temperature for 0.25 h followed by the addition of 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.312 g, 1.0 mmol) in dichloromethane (2 mL). After 24 h, the reaction was quenched with

saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **3/4** as a yellow oil (0.369 g, 90% recovery, >95% conversion determined by ^1H NMR).

4.1.6. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 5, Table 2). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol) in dichloromethane (1 mL) were added to a suspension of di-*tert*-butyl malonate (**5**) (0.624 g, 2.0 mmol) and NaH (0.005 g, 0.2 mmol) in dichloromethane (5 mL) at room temperature. The solution was heated to 44 °C and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (2 mL) was added dropwise. After 6 h, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated in vacuo to give **4/2/3** as a yellow oil (0.673 g, 92% recovery, 19:12:5% conversion determined by ^1H NMR).

4.1.7. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 6, Table 5). Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol), 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol), di-*tert*-butyl malonate (**5**) (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL). After 24 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **4/2/3** as a yellow oil (0.309 g, 93% recovery, 25:1:5% conversion determined by ^1H NMR).

4.1.8. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 7). Dimethylaluminium chloride (1.2 mL, 1.0 M solution in hexane, 1.2 mmol) was added to nitrogen-purged (0.25 h) stirred solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) in dichloromethane (2 mL). After 1 h at room temperature, 2-(3-oxo-cyclohexyl)-malonic acid di-*tert*-butyl ester (**2**) (0.031 g, 0.1 mmol), di-*tert*-butyl malonate (**5**) (0.216 g, 1.0 mmol) and sodium hydride (0.002 g, 0.1 mmol) in dichloromethane (3 mL) were added. After 90 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give (**4**) as a yellow oil (0.304 g, 91% recovery, 51% conversion determined by ^1H NMR).

4.1.9. Preparation of 2-(3-dicyanomethyl-cyclohexylidene)-malononitrile (8). 2-Cyclohexen-1-one (**3**) (0.192 g, 2.0 mmol) in THF (10 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.019 g, 0.2 mmol) and malononitrile (**6**) (0.264 g, 4.0 mmol) in THF (10 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with dichloromethane (50 mL) and washed with water (100 mL). The aqueous phase was separated and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **8** as a yellow gum (0.306 g, 67%) (Fig. 5).

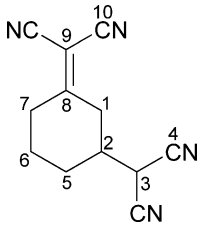


Figure 5.

Compound **8**. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.60–1.76 (m, 2H), 2.18–2.46 (m, 5H), 3.12–3.26 (m, 2H), 3.85 (d, J=5 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=25.4, 28.2, 28.8, 30.7, 40.0, 75.3 (C_3), 85.7 (C_9), 111.5 (C_4), 111.5 (C_{10}), 111.6 (C_4), 111.8 (C_{10}), 179.3 (C_8); IR ($CHCl_3$): ν (cm^{-1})=2339 (C≡N), 2232 (C≡N), 1598 (C=C); MS (EI+, 70 eV): m/z (%) 210 (23) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{12}H_{10}N_4$ requires 210.0906, found 210.0910.

4.1.10. Preparation of 2-(3-oxo-cyclohexyl)-malononitrile (7). 2-(3-Oxo-cyclohexyl)-malonic acid dimethyl ester[41] (1.00 g, 4.38 mmol) was stirred for 18 h in 35% aqueous NH_4OH (5 mL) at room temperature. The aqueous phase was concentrated in vacuo to give 2-(3-oxo-cyclohexyl)-malonamide as an off-white solid (0.966 g, 97% recovery). Phosphoryl chloride (0.91 mL, 9.75 mmol) was added to a stirred suspension of 2-(3-oxo-cyclohexyl)-malonamide in anhydrous acetonitrile (25 mL). After 5 h at 82 °C, the solution was filtered and concentrated in vacuo. The oily residue was dissolved in chloroform (100 mL) and extracted with a saturated solution of Na_2CO_3 (2×50 mL). The combined aqueous phases were neutralised with 10% v/v aqueous HCl and NaCl added until a saturated solution was obtained. The aqueous phase was extracted with chloroform (4×50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave 2-(3-oxo-

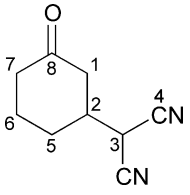


Figure 6.

cyclohexyl)-malononitrile (**7**) as a colourless oil (0.593 g, 75%) (Fig. 6).

Compound **7**. ^{1}H NMR (400 MHz, $CHCl_3$, 25 °C): δ=1.67–1.82 (m, 2H), 2.18–2.27 (m, 2H), 2.29–2.54 (m, 4H), 2.53–2.60 (m, 1H, H_2), 3.75 (d, J=5 Hz, 1H, H_3); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=24.0, 28.4, 39.7, 40.7, 44.6, 75.3 (C_3), 111.5 (C_4), 111.6 (C_4), 206.9 (C_8); IR (thin film): ν (cm^{-1})=2251 (C≡N), 1700 (C=O); MS (EI+, 70 eV): *m/z* (%) 162 (7) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_9H_{10}N_2O$ requires 162.0793, found 162.0790.

4.1.11. Preparation of 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile (14). 2-Cyclohexen-1-one (**3**) (0.144 g, 1.50 mmol) in THF (3 mL) was added dropwise to a suspension of sodium *tert*-butoxide (0.014 g, 0.15 mmol) and methylmalononitrile (**9**) (0.120 g, 1.50 mmol) in THF (7 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave **14** as a white solid (0.202 g, 83%) (Fig. 7).

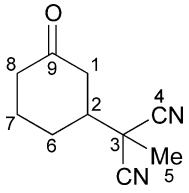


Figure 7.

Compound **14**. Mp 59–61 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.63–1.80 (m, 2H), 1.81 (s, 3H), 2.16–2.41 (m, 5H), 2.46–2.54 (m, 1H), 2.67–2.74 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=22.5 (C_5), 23.7, 27.2, 40.5, 42.7, 45.3 (C_3), 114.5 (C_4), 115.0 (C_4), 206.2 (C_9); IR ($CHCl_3$): ν (cm^{-1})=2360 (C≡N), 1700 (C=O); MS (EI+, 70 eV): *m/z* (%) 176 (32) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{10}H_{12}N_2O$ requires 176.0950, found 176.0952; $C_{10}H_{12}N_2O$ requires C 68.16%, H 6.86%, N 15.90%, found C 68.10%, H 6.88% N 15.80%.

4.1.12. Preparation of *cis/trans*-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile *cis/trans*-(18). 2-Methyl-2-(3-oxo-cyclohexyl)-malononitrile (**14**) (0.016 g, 0.71 mmol) in anhydrous methanol (15 mL) was cooled to 0 °C whilst sodium borohydride (0.027 g, 0.71 mmol) was added portionwise over 0.1 h. After 1 h, the reaction was quenched with distilled water (50 mL) and extracted with dichloromethane (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 100% diethyl ether) gave *cis/trans*-**18** as a white solid (0.037 g, 32%, 94:6 *cis/trans*) (Fig. 8).

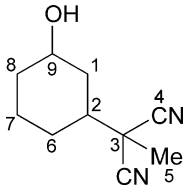


Figure 8.

Compound cis/trans-**18**. Mp 75–76 °C; ^{1}H NMR (300 MHz, $CHCl_3$, 25 °C): δ=1.20 (app dq, J=4, 16 Hz, 2H), 1.41 (app ddt, J=2, 4, 16 Hz, 2H), 1.55–1.80 (m, 3H), 1.71 (s, 3H, H_5), 1.89–2.10 (m, 2H), 2.22 (app ddt, J=3, 3, 12 Hz, 1H), 3.50–3.65 (m, 1H, H_{9ax}), 4.23 (br s, 1H, H_{9eq}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, single diastereomer): δ=22.7 (C_5), 23.2, 27.5, 35.0, 37.0, 37.4, 43.9 (C_3), 69.9 (C_9), 70.0 (C_9), 115.9 (C_4), 116.0 (C_4); IR ($CHCl_3$): ν (cm^{-1})= 3383 (O–H), 2249 (C≡N); MS (CI+): *m/z* (%) 179 (88) [MH^+]; HRMS (CI+): $C_{10}H_{15}N_2O$ requires 179.1184, found 179.1177.

4.1.13. General procedure for the dimethylaluminium chloride catalysed crossover transfer hydrogenation reaction between 2-cyclohexen-1-ol (1) and 2-methyl-2-(3-oxo-cyclohexyl)-malononitrile (14) (Scheme 9, Table 7). Carried out following the procedure described above. After 15 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo to give **3/16** as a yellow solid (0.294 g, 100% recovery, >95% conversion determined by ^{1}H NMR).

4.1.14. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 8). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile (**9**) (0.080 g, 1.0 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (5 mL). The solution was heated to 44 °C under nitrogen and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) in dichloromethane (3 mL) was added dropwise. After 24 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3 x 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**18** as a white crystalline solid (0.153 g, 85%).

4.1.15. General procedure for the dimethylaluminium chloride catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 8). Dimethylaluminium chloride (1.0 mL, 1.0 M solution in hexane, 1.0 mmol) was added to nitrogen-purged solution of 2-cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol), 2-cyclohexen-1-one (**3**) (0.010 g, 0.1 mmol), methylmalononitrile (**9**) (0.080 g, 1.0 mmol) TBAB (0.012 g, 0.04 mmol) and potassium *tert*-butoxide (0.012 g, 0.1 mmol) in dichloromethane (3 mL). After 24 h, the reaction was quenched with saturated aqueous NH_4Cl (1 mL), diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The

combined organic extracts were washed with brine (50 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** as a white crystalline solid (0.076 g, 45%).

4.1.16. General procedure for the catalytic aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 10, Table 9). 2-Cyclohexen-1-ol (**1**) (0.098 g, 1.0 mmol) and 2-cyclohexen-1-one (**3**) (0.009 g, 0.1 mmol) were added to a suspension of methylmalononitrile (**9**) (0.080 g, 1.0 mmol), potassium *tert*-butoxide (0.012 g, 0.1 mmol) and aluminium *tert*-butoxide (0.025 g, 1.0 mmol) in dichloromethane (3 mL). The solution was heated to 100 °C in an ACE pressure tube. After 8 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** as a white crystalline solid (0.160 g, 90%).

4.1.17. Preparation of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile (15). 2-Cyclohexen-1-one (**3**) (0.096 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and benzylmalononitrile (**10**) (0.156 g, 1.0 mmol) in THF (3 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **15** as a cubic white solid (0.217 g, 86%) (Fig. 9).

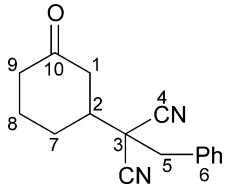


Figure 9.

Compound **15**. Mp 132–134 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.68 (dddd, J=2, 12, 12, 12 Hz, 1H), 1.83 (app dtq, J=1, 4, 12 Hz, 1H), 2.22–2.54 (m, 5H), 2.77–2.84 (m, 1H), 3.16 (d, J=14 Hz, 1H, H_5), 3.15 (d, J=14 Hz, 1H, H_5), 7.36–7.43 (m, 5H, H_6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=23.8, 27.5, 40.6, 43.2, 43.8, 44.7, 44.7, 113.6 (C_4), 114.0 (C_4), 128.9, 128.9, 129.0, 130.0, 130.0, 131.4, 206.2 (C_{10}); IR (thin film): ν (cm^{-1})=2241 (C≡N), 1716 (C=O); MS (EI+, 70 eV): *m*/*z* (%) 252 (37) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_{16}H_{16}N_2O$ requires 252.1263, found 252.1251; $C_{16}H_{16}N_2O$ requires C 76.16%, H 6.39%, N 11.10%, found C 76.0%, H 6.41% N 11.10%.

4.1.18. Preparation of *trans*-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile (19). A solution of 2-benzyl-2-(3-oxo-cyclohexyl)-malononitrile (**15**) (0.590 g, 2.34 mmol) in THF (2 mL) was added dropwise to a nitrogen-purged 1.0 M solution of L-Selectride (2.81 mL, 2.81 mmol) in THF (3 mL) at −78 °C. After 3 h, aqueous 3 M NaOH (0.17 mL, 0.5 mmol) was added dropwise followed by slow addition of 30% H_2O_2 (0.55 mL, 12.0 mmol). After a further 0.5 h stirring at room temperature the mixture was diluted with water (50 mL), extracted with ethyl acetate (5×30 mL). The combined organic phases were washed with brine (100 mL), dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *trans*-2-benzyl-2-(3-hydroxy-cyclohexyl)-malononitrile (**19**) as a white crystalline solid (0.244 g, 41%) (Fig. 10).

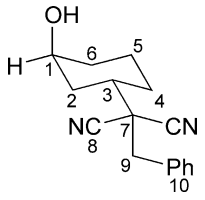


Figure 10.

Compound trans-**19**. Mp 106–108 °C; ^{1}H NMR (500 MHz, C_6D_6, 25 °C): δ=0.35 (br s, 1H, O*H*), 0.81 (app. ddt, J=2, 4, 13.5 Hz, 1H, H_{6ax}), 0.96 (app. dq, J=4, 13 Hz, 1H, H_{4ax}), 1.12 (app. dt, J=2, 13 Hz, 1H, H_{2ax}), 1.17–1.21 (m, 1H, H_{5eq}), 1.25 (br d, J=14 Hz, 1H, H_{6eq}), 1.37 (app. tq, J=4, 13 Hz, 1H, H_{5ax}), 1.64 (br d, J=12.5 Hz, 1H, H_{4eq}), 1.70 (br d, J=13 Hz, 1H, H_{2eq}), 1.99 (app. tt, J=3, 12 Hz, 1H, H_{3ax}), 2.41 (d, J=14 Hz, 1H, H_7), 2.51 (d, J=14 Hz, 1H, H_7), 3.53 (br s, 1H, H_{1eq}), 7.02–7.25 (m, 5H, H_{10}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=19.6, 28.7, 32.4, 35.3, 38.7, 40.9, 45.6, 66.0 (C_1), 66.1 (C_1), 115.0 (C_8), 129.1, 129.3, 130.6, 132.8; IR (C_6D_6): ν (cm^{-1})=3592 (O–H), 2282 (C≡N); MS (EI+, 70 eV): *m*/*z* (%) 254 [$M^{\cdot+}$], 91 (100) [$PhCH_2^+$]; $C_{16}H_{18}N_2O$ requires C 75.56%, H 7.13%, N 11.01%, found C 74.8%, H 7.34% N 11.30%.

4.1.19. Preparation of 2-methyl-2-(3-oxo-cyclopentyl)-malononitrile (12). 2-Cyclopenten-1-one (**20**) (0.082 g, 1.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.011 g, 0.1 mmol) and methylmalononitrile (**9**) (0.080 g, 1.0 mmol) in THF (3 mL). After 4 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50

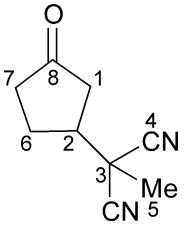


Figure 11.

petroleum ether/diethyl ether) gave **12** as a white solid after recrystallisation from acetonitrile (0.139 g, 86%) (Fig. 11).

Compound **12**. Mp 37–40 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=1.86 (br s, 3H, H_5), 1.90–2.02 (m, 1H), 2.22–2.39 (m, 2H), 2.41–2.50 (m, 1H), 2.52–2.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=23.5 (C_5), 25.8, 35.8 (C_3), 38.2, 40.6, 44.5 (C_2), 114.6 (C_4), 114.7 (C_4), 212.1 (C_8); IR (thin film): ν (cm^{-1})=2245 (C≡N), 1747 (C=O); MS (EI+, 70 eV): *m/z* (%) 162 (21) [$M^{\cdot+}$]; HRMS (EI+, 70 eV): $C_9H_{10}N_2O$ requires 162.0793, found 162.0795; $C_9H_{10}N_2O$ requires C 66.65%, H 6.21%, N 17.27%, found C 66.40%, H 6.22% N 17.26%.

4.1.20. Preparation of *cis/trans*-2-(3-hydroxy-cyclopentyl)-2-methyl-malononitrile (16). 2-Methyl-2-(3-oxo-cyclopentyl)-malononitrile (**12**) (0.415 g, 2.6 mmol) and aluminium *tert*-butoxide (0.640 g, 2.6 mmol) were heated to 82 °C in anhydrous propan-2-ol (10 mL). After 18 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**12** as pale yellow oil (0.401 g, 94%, 75:25 *cis/trans*) (Fig. 12).

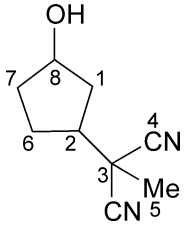


Figure 12.

Compound cis/trans-**12**. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.50–1.70 (m, 1H), 1.72 (br s, 3H, H_5), 1.90–2.20 (m, 3H), 2.25–2.38 (m, 2H), 2.59–2.71 (m, 1H), 4.30–4.34 (m, 1H, H_{8eq}), 4.42–4.45 (m, 1H, H_{8ax}); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=23.8 (C_5), 24.3 (C_5), 26.9, 26.9, 31.3, 31.3, 34.9, 36.1, 36.3, 39.1, 45.8, 46.3, 72.6 (C_3), 73.1(C_3), 115.0 (C_4), 115.1 (C_4), 115.2 (C_4), 116.1 (C_4); IR (thin film): ν (cm^{-1})=3610 (O–H), 2250 (C≡N); MS (CI+): *m/z* (%) 165 (100) [MH^+]; HRMS (CI+): $C_9H_{13}N_2O$ requires 165.1028, found 165.1026.

4.1.21. Preparation of 2-benzyl-2-(3-oxo-cyclopentyl)-malononitrile (13). 2-Cyclopenten-1-one (**20**) (0.164 g, 2.0 mmol) in THF (2 mL) was added dropwise to a suspension of potassium *tert*-butoxide (0.022 g, 0.1 mmol) and benzylmalononitrile (**10**) (0.312 g, 2.0 mmol) in THF (3 mL). After 6 h at room temperature, the reaction was quenched with acetic acid, diluted with diethyl ether (50 mL) and washed with water (2×25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave **13** as a cubic white solid (0.280 g, 61%) (Fig. 13).

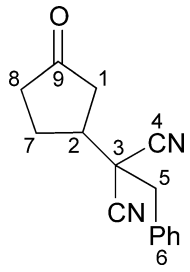


Figure 13.

Compound **13**. Mp 122–123 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=2.00–2.14 (m, 1H), 2.25–2.41 (m, 3H), 2.42–2.78 (m, 3H), 3.23 (d, J=14 Hz, 1H, H_5), 3.24 (d, J=14 Hz, 1H, H_5), 7.38–7.61 (m, 5H, H_6); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ=25.8, 37.8, 40.5, 41.6, 42.4, 43.6, 113.8 (C_4), 113.8 (C_4), 128.8, 129.0, 129.8, 131.5, 212.5 (C_9); IR (thin film): ν (cm^{-1})=2245 (C≡N), 1747 (C=O); MS (CI+): *m/z* (%) 239 (67) [MH^+]; HRMS (CI+): $C_{15}H_{15}N_2O$ requires 239.1184, found 239.1193; $C_{15}H_{14}N_2O$ requires C 75.61%, H 5.92%, N 11.76%, found C 74.80%, H 5.96% N 11.60%.

4.1.22. Preparation of *cis/trans*-2-benzyl-2-(3-hydroxy-cyclopentyl)-malononitrile (17). 2-Benzyl-2-(3-oxo-cyclopentyl)-malononitrile (**13**) (0.265 g, 1.11 mmol) and aluminium *tert*-butoxide (0.274 g, 1.11 mmol) were heated to 82 °C in anhydrous propan-2-ol (10 mL). After 13 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis/trans*-**17** as a white crystalline solid (0.214 g, 80%) (Fig. 14).

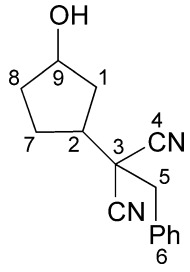


Figure 14.

Compound trans-**17**. Mp 84–86 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ=1.61–1.82 (m, 3H), 1.90–2.10 (m, 2H), 2.13–2.23 (m, 1H), 2.66–2.77 (m, 1H), 3.09 (d, J=14 Hz, 1H, H_5), 3.10 (d, J=14 Hz, 1H, H_5), 4.44 (br s, 1H, H_9), 7.24–7.60 (br s, 5H, H_6).

Compound cis-**17**. 4.26–4.35 (m, 1H, H_9); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, *cis/trans*-**17**): δ=27.2, 34.8, 35.2, 38.9, 39.3, 42.5, 42.8, 44.4, 44.6, 44.7, 72.5 (C_9), 72.9 (C_9), 115.3 (C_4), 115.3 (C_4), 129.2, 129.4, 130.5, 132.6, 132.7; IR (thin film): ν (cm^{-1})=3396 (O–H), 2245 (C≡N); MS (ES+): *m/z* 263 [MNa^+]; HRMS (CI+): $C_{15}H_{17}N_2O$

requires 241.1333, found 241.1335; $C_{15}H_{16}N_2O$ requires C 74.97%, H 6.71%, N 11.66%, found C 74.70%, H 6.79% N 11.60%.

4.1.23. General procedure for the aluminium *tert*-butoxide catalysed domino Oppenauer/Michael addition/MPV process (Scheme 11, Table 10). 2-Cyclopenten-1-ol (**11**) (0.084 g, 1.0 mmol) and 2-cyclopenten-1-one (**20**) (0.008 g, 0.1 mmol) were added to a suspension of benzylmalononitrile (**10**) (0.156 g, 1.0 mmol) in dichloromethane (3 mL). Aluminium *tert*-butoxide (0.246 g, 1.0 mmol) was added and the solution heated to 100 °C in an ACE pressure tube. After 72 h, the reaction was cooled, diluted with ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with ether (3×50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**17** as a white crystalline solid (0.144 g, 60%).

4.1.24. Meerwein–Ponndorf–Verley equilibration of *trans*-2-(3-hydroxy-cyclohexyl)-2-methyl-malononitrile *trans*-18. *trans*-2-(3-Hydroxy-cyclohexyl)-2-methyl-malononitrile *trans*-**18** (0.134 g, 0.75 mmol) and aluminium *tert*-butoxide (0.246 g, 1.0 mmol) were heated to 82 °C in a 1:1 mixture of anhydrous propan-2-ol/acetone (10 mL). After 12 h under nitrogen, the reaction was cooled, diluted with diethyl ether (50 mL) and washed with 10% v/v aqueous HCl (25 mL). The aqueous phase was separated and extracted with diethyl ether (3×50 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (SiO_2, 50:50 petroleum ether/diethyl ether) gave *cis*/*trans*-**18** (62:38 *cis*/*trans*, determined by ^1H NMR) as a white crystalline solid (0.145 g, 100% recovery).

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Corrigendum

Corrigendum to "Synthesis of novel, boron-containing cavitands derived from calix[4]resorcinarenes and their molecular recognition of biologically important polyols in langmuir films" [Tetrahedron 60 (2004) 10747]

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Available online 16 December 2004

Cavitand rim boronic esters and acids of the type reported in this paper have been prepared previously using the same synthetic route.[1,2] The sugar binding properties of mono-, A,C-di-, A,B-di-, tri- and tetraboronic acids have also been reported previously.[2] This work should have been cited and discussed in our paper. We thank Dr. Sherburn for bringing these papers to our attention.

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