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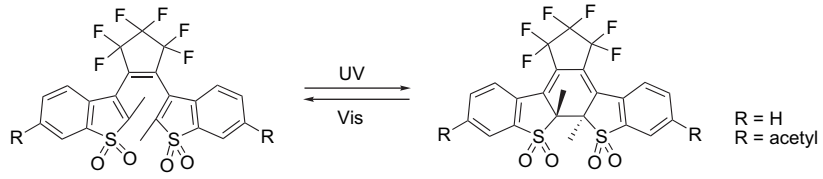
Tetrahedron

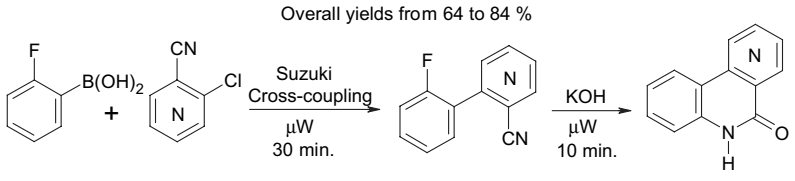
Tetrahedron Vol. 62, No. 25, 2006

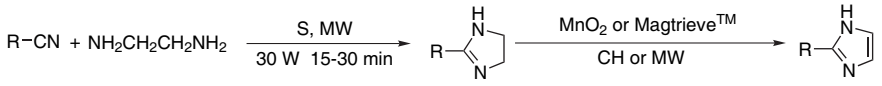
Contents

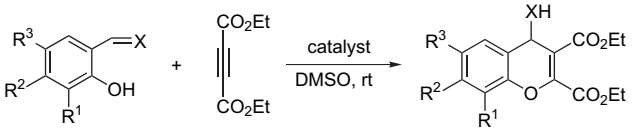
REPORT

ARTICLES



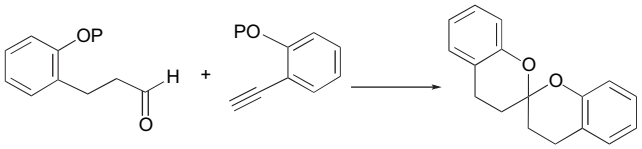


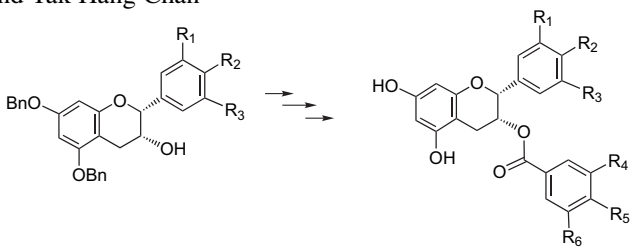




X = NTs: catalyst = DABCO yield: 83 - 98%.
X = O: catalyst = $PPhMe_2$ yield: 83 - >99%.

Reactions of diethyl acetylenedicarboxylate with salicyl *N*-tosylimines or salicylaldehydes proceeded smoothly in the presence of DABCO or dimethylphenylphosphine under mild conditions to give the corresponding chromenes in excellent yields.





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7: R_3=H, R_1=R_2=R_4=OH, R_5=R_6=OMe; **8**: R_1=R_2=R_3=R_4=R_5=OH, R_6=OMe;
9: R_1=R_2=R_3=R_4=R_6=OH, R_5=OMe; **10**:R_1=R_2=R_3=R_4=OH, R_5=R_6=OMe;
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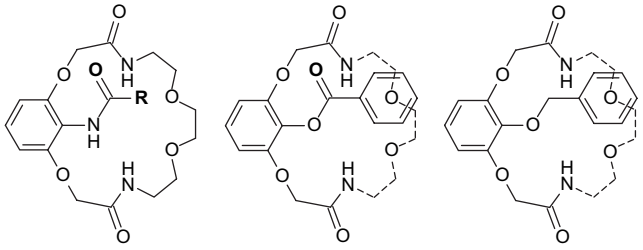
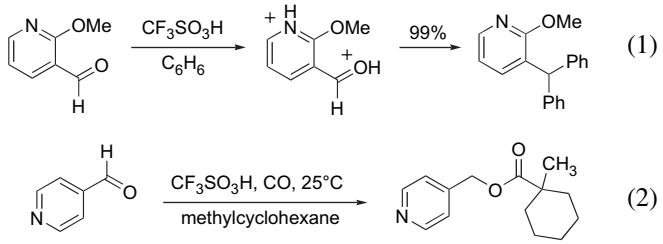
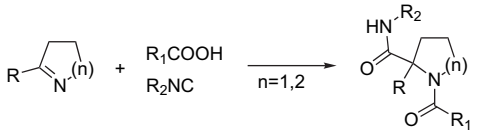
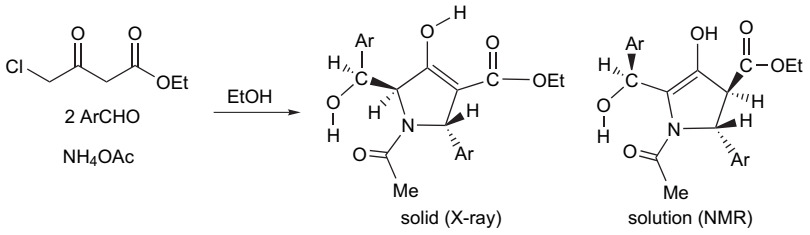
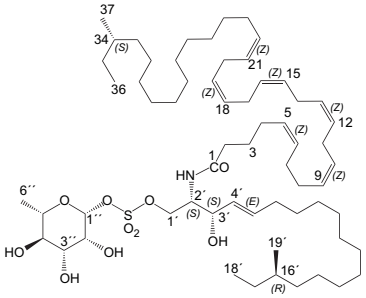
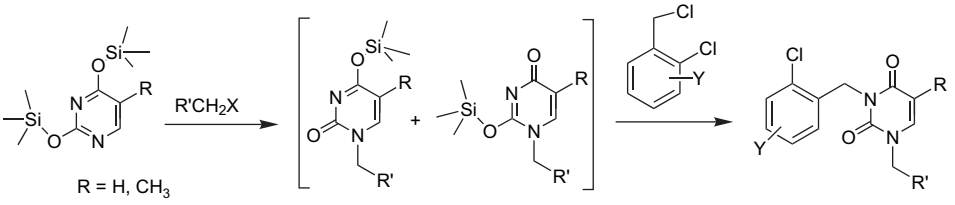




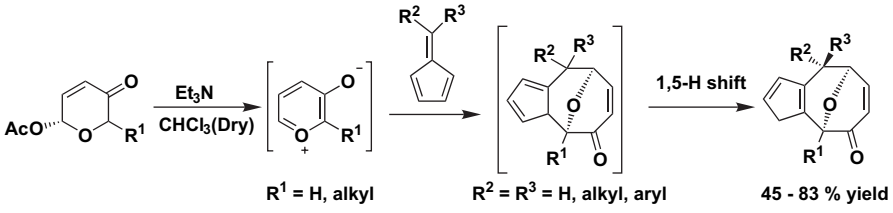


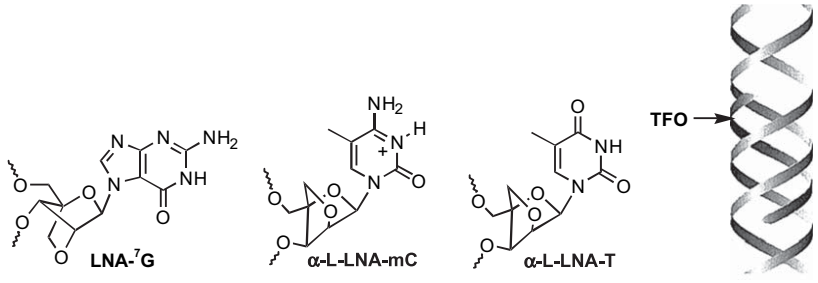


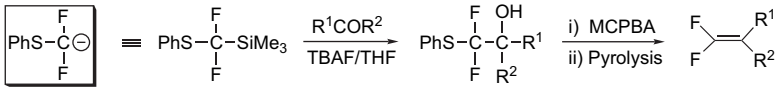


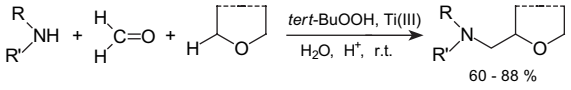


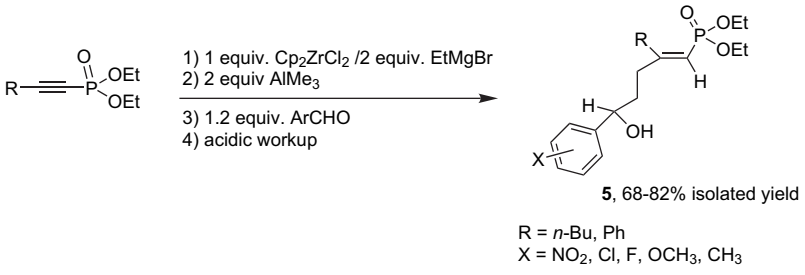
2,4-Bis(trimethylsilyloxy)pyrimidines on reaction with alkyl-/allyl-/benzyl halides, followed by the subsequent addition of *o*-chlorobenzyl chlorides, provide a one-pot synthesis of 1,3-unsymmetrical alkylated pyrimidine-2,4-diones.





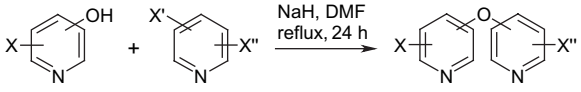






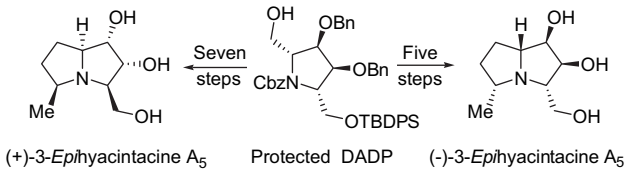
5, 68-82% isolated yield

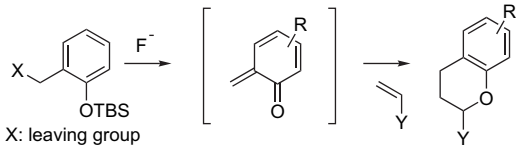
R = *n*-Bu, Ph
X = NO_2, Cl, F, OCH_3, CH_3

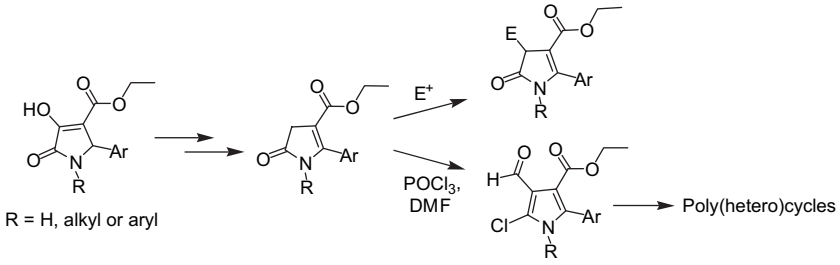


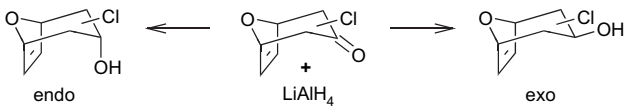
X = H, Cl; X' = Br, I; X'' = Br, I

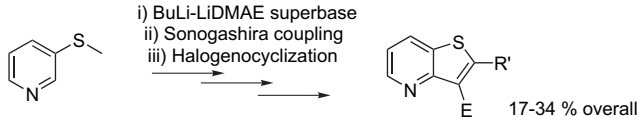
The synthesis of novel halo-oxybispyridines is described, synthetic aspects are described in detail, and examples are set forth within.

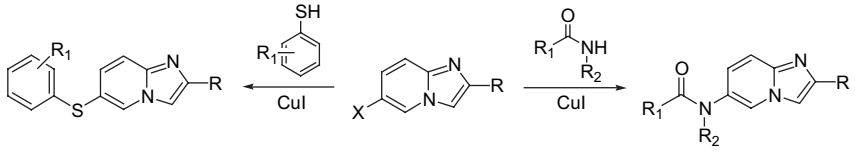


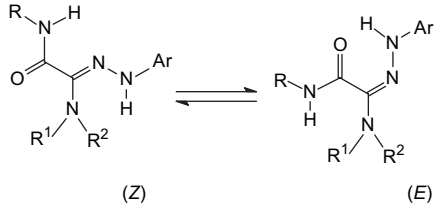


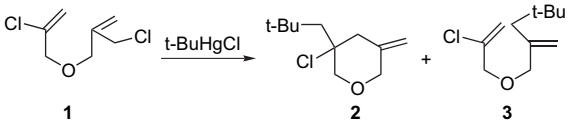




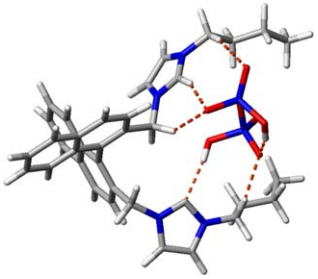


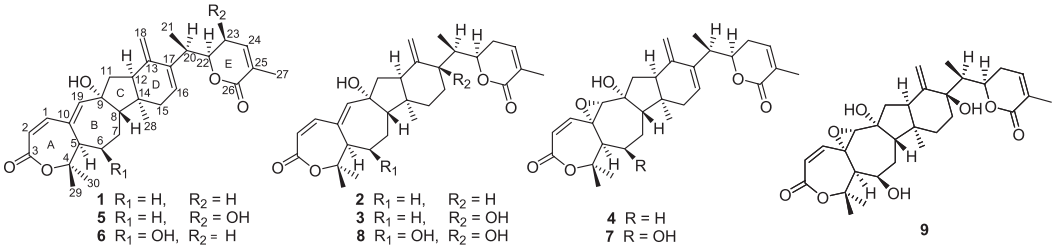


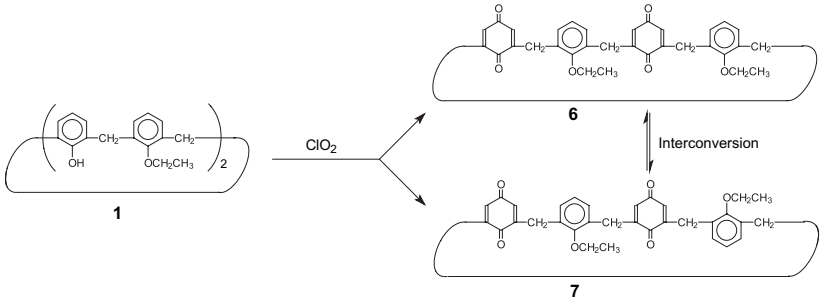


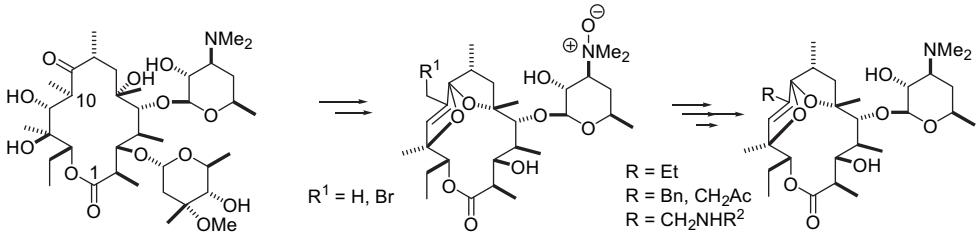


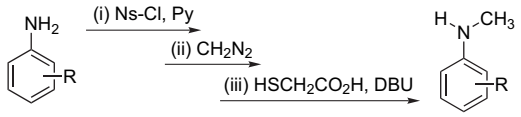
The relative rates of the competitive free radical addition to two different double bonds in (2-chloroallyl)-(2-choromethylallyl) ether have been determined. There are two competitive free radical addition reactions, one is free radical S_H2' reaction and the other is free radical addition reaction. The mechanism of the S_H2' reaction is discussed.

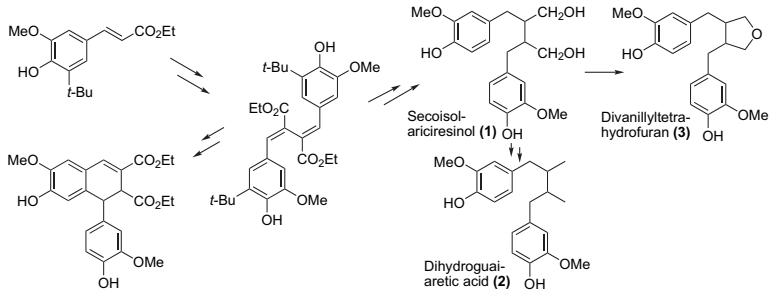


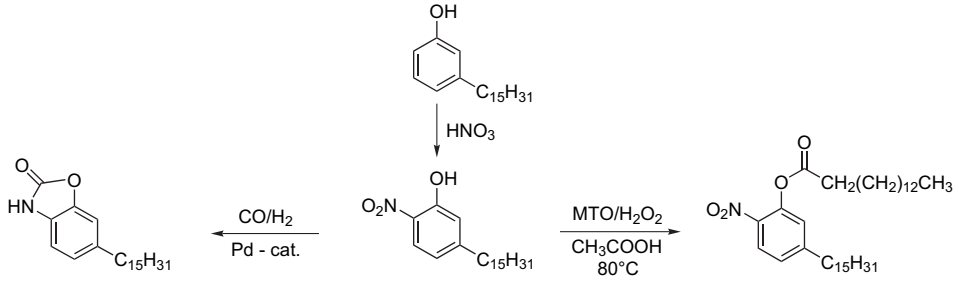


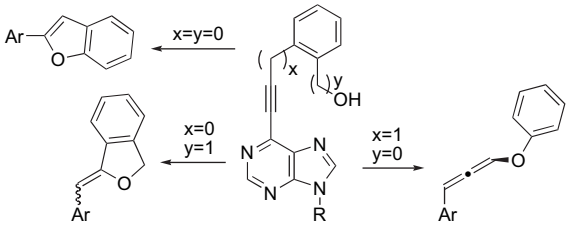












OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Biocatalysis as a profound tool in the preparation of highly enantiopure β-amino acids

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Contents

Keywords: β-Amino acid; Kinetic resolution; Biocatalysis; Enzymatic preparation; Lipase; Protease; Esterase; β-Lactamase; Transferase; Isomerase; Nitrile hydratase; Acylase I; Penicillin G amidase; Peptide deformylase; Hydantoinase.
Abbreviations: Ac, acetyl; Asp, aspartic acid; Bn, benzyl; Bz, benzoyl; Bu, butyl; CAL-A, lipase A from *Candida antarctica*; CAL-B, lipase B from *Candida antarctica*; CRL, lipase from *Candida rugosa*; de, diastereomeric excess; DIPE, diisopropyl ether; *E*, enantiomer ratio; ee, enantiomeric excess; ee_s, enantiomeric excess of the substrate; ee_p, enantiomeric excess of the product; Et, ethyl; Gln, glutamine; His, histidine; Ile, isoleucine; LG, leaving group; MOPS, 4-morpholinepropanesulfonic acid; PDF, peptide deformylase; Ph, phenyl; PG, protective group; PGA, penicillin G amidase; PLE, pig liver esterase; PPL, porcine pancreatic lipase; Pr, propyl; Ser, serine; TBME, *tert*-butyl methyl ether; Thr, threonine; TMS, trimethylsilyl; Trp, tryptophan; Ts, *p*-toluenesulfonyl; Z, benzyloxycarbonyl.
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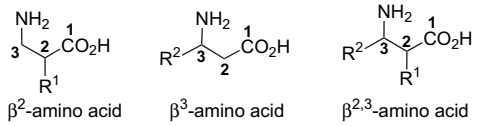
doi:10.1016/j.tet.2006.03.109

1. Introduction

β-Amino acids have unique pharmacological properties and their utility as building blocks of β-peptides, pharmaceutically important compounds and natural products is of growing interest.[1–6] This arises, for instance, from the ability of β-peptides to fold to secondary structures in predictable ways. Furthermore, the enzymes in the body do not act on β-peptide bonds. Several review articles on the asymmetric synthesis of β-amino acids are available.[7–14] This review covers the enzymatic methodology developed up to the present day for the preparation of various highly enantiopure β^2-, β^3- and $\beta^{2,3}$-amino acids (Scheme 1). Most of the reported methods exploit hydrolytic enzymes in kinetic resolutions of racemic mixtures.

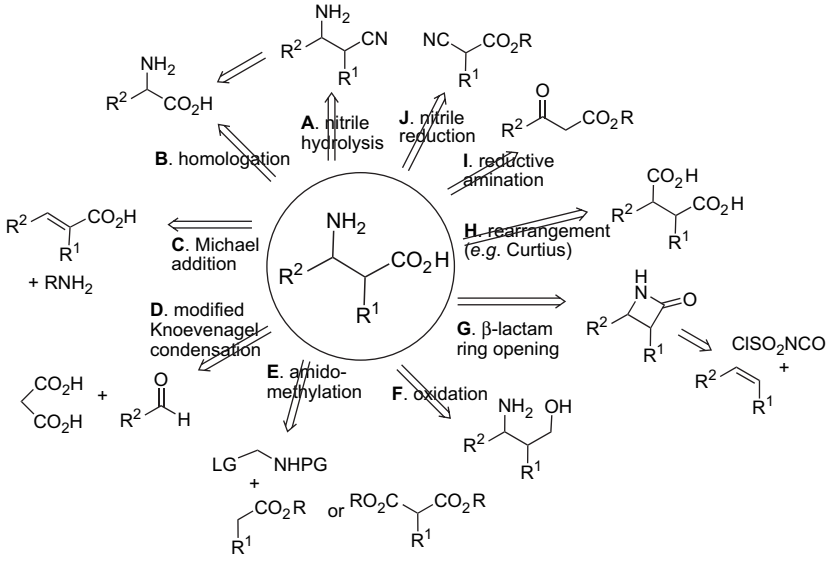


Scheme 1. General structures of β-amino acids.

A plethora of methods have been used for the preparation of racemic β-amino acids. Some useful alternatives are outlined retrosynthetically in Scheme 2. Thus, β-amino acids have been prepared by hydrolysis of β-amino nitriles (A),[15–21] homologation of α-amino acids (B),[22] Michael-type additions to double bonds (C),[15,23–25] Knoevenagel-type condensations of an aldehyde and malonic acid in the presence of ammonium acetate (D),[26–28] amidomethylation of aryl acetic or malonic esters (E),[29–32] oxidation of amino alcohols (F), ring opening of β-lactams (G),[33] transformation of a carboxylic functionality of a dicarboxylic acid into an amine (like the Curtius or Hofmann rearrangements),[34] reductive amination via an enamine (I)[35] and reduction of α-cyano carboxylic esters (J).[36,37] In particular, the Michael-type addition (C) and β-lactam ring opening (G) after formation of the ring from an alkene and chlorosulfonyl isocyanate have been widely employed in the preparation of racemic β^3- and $\beta^{2,3}$-amino acids. Homologation of α-amino acids (B) is usually performed by the Arndt–Eistert homologation, which requires the use of diazomethane. For this reason, it is not suitable for large-scale use. α-Amino acids can also serve as synthons for β-amino nitriles, which can be hydrolysed into β-amino acids (A). Method F, the preparation of β-amino acids by oxidation of 1,3-amino alcohols, is seldom applied due to the limited availability of appropriate 1,3-amino alcohols. In fact, 1,3-amino alcohols are often prepared by reducing β-amino acids.[38–40] In addition to 1,3-amino alcohols, 1,2-amino alcohols serve as synthons for β-amino nitriles in method A. Amino alcohols and dicarboxylic acids (H) form a field of their own, and their preparation in an enantiopure form is excluded from this review.

The main chemo-enzymatic paths for obtaining highly enantiopure β-amino acids are based on the kinetic resolution of racemic β-amino acids or some of their derivatives and intermediates. In this review, the efficiency of the kinetic resolution is described by the enantioselectivity ratio, *E*.[41] Besides kinetic resolutions, biocatalytic studies towards enantiopure β-amino acids encompass homologation of α-amino acids (B) by aminomutases, the Michael addition (method C) and the reductive amination of ketones by β-aminotransferase (I). Reaction steps in methods D, E, F, H and J have not been biocatalytically performed, to the best of our knowledge.

This review is divided into kinetic resolutions and other biotransformations. Each utilized enzyme is discussed separately in a specific section. The resolutions of β^2-amino acids have not yet been studied to the same extent as their β^3- and $\beta^{2,3}$-counterparts. This is possibly due to the more laborious synthesis of β^2-amino acids, which is often based on the use of acrylic, cyanoacetic or malonic ester derivatives,[14] whereas the synthesis of the β^3- and $\beta^{2,3}$-counterparts is relatively straightforward by many methods in Scheme 2.



Scheme 2. Retrosynthetic analysis for the synthesis of β-amino acids.

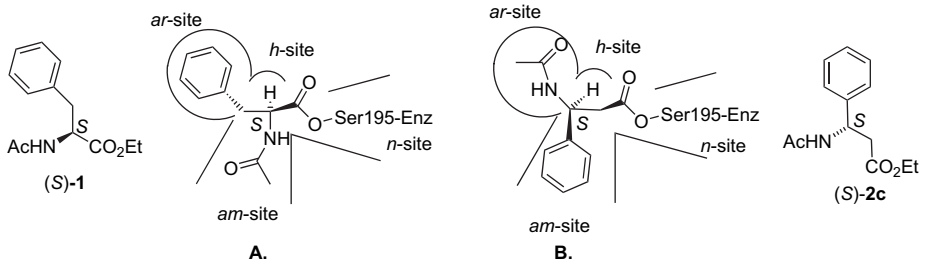
2. Kinetic resolutions

2.1. Enzymes acting on C–N bonds

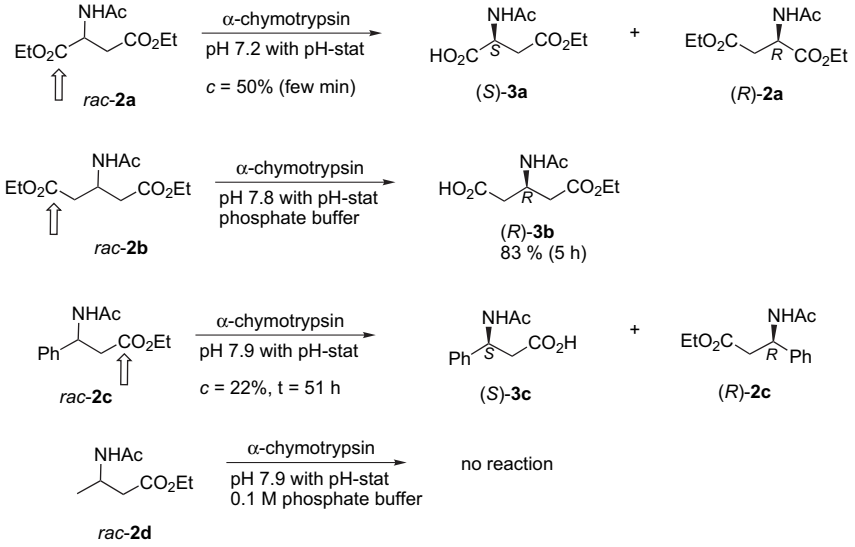
2.1.1. α-Chymotrypsin. A proteolytic enzyme, α-chymotrypsin [EC 3.4.21.1], was applied to one of the earliest resolutions of β^3-amino acids in the 1960s.[42–45] The structure and characteristics of the enzyme are well known, and a good deal of molecular modelling has been carried out for explaining the substrate–chymotrypsin interactions.[46–51] α-Chymotrypsin is a serine protease catalysing the hydrolysis of peptide bonds of protein foods in the gut via an acyl-enzyme intermediate in the same way as lipases (see Scheme 18). The enzyme acts specifically on non-terminal amide bonds adjacent to aromatic α-L-tryptophan, -tyrosine or -phenylalanine. It has a pH optimum of 7.8, digesting itself at neutral pH. Thus, the enzyme can best be used for hydrolysing ester groups at pH 5, where it is more stable.

α-Chymotrypsin exhibits a high enantioselectivity, especially towards *N*-acetyl-α-amino esters, giving highly enantiopure (*S*)-acids as the reaction products. This was first rationalised by Cohen's active site model, which is still useful for rough predictions.[48] According to this model, at the asymmetric centre the four substituents of *N*-acetyl-(*S*)-phenylalanine derivative [(*S*)-**1**], as an example, bind into four different pockets (Scheme 3, A). The ester group with the Ser195-hydroxyl of the catalytic triad locates at the *n*-site. The closed hydrophobic pocket (*ar*-site) accommodates the aromatic residue of the substrate. The site is large enough to accommodate e.g., an indole ring. The third pocket (*am*-site) contains Ser214, which is able to hydrogen bond to the carbonyl oxygen of the substrate. Both the *n*- and the *am*-sites are open to the solvent and are able to accommodate long or large groups. The small *h*-site accepts H, Cl or HO, but not, for instance, CH_3.

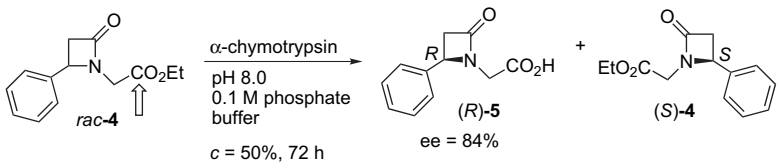
The reported kinetic resolutions of β-amino acid derivatives with α-chymotrypsin have been collected in Scheme 4. The reported high enantioselectivities are based on the measured $[\alpha]_D$ values of the substrate and the product. Cohen's model for α-amino acids also holds for diethyl *N*-acetyl aspartate **2a** (both α- and β-amino acids) and diethyl 3-acetamidoglutarate **2b**.[42,44] Thus, the more hindered α-ester group of diethyl *N*-acetyl aspartate **2a** is hydrolysed in a few minutes with high (*S*)-enantioselectivity into (*S*)-**3a**. The hydrolysis of *meso*-diethyl β-acetamidoglutarate **2b** was shown to proceed to 83% conversion in 5 h, yielding the highly enantiopure (*R*)-monoacid **3b**. On the other hand, the α-chymotrypsin-catalysed highly enantioselective ester hydrolysis of ethyl 3-acetamido-3-phenylpropanoate **2c** contradicts the model, as the resolution yields the corresponding (*R*)-**2c** and the hydrolysed (*S*)-**3c** (Scheme 3, B).[43,45] Even though many subtle behavioural forms of α-chymotrypsin have been solved by molecular modelling, an exhaustive explanation for this phenomenon has not been presented.



Scheme 3. Cohen's active site model of α-chymotrypsin.[48]



Scheme 4. Kinetic resolution of β^3-amino acid derivatives by α-chymotrypsin.[42–45]



Scheme 5. Kinetic resolution of *rac*-**4** by α-chymotrypsin.[52]

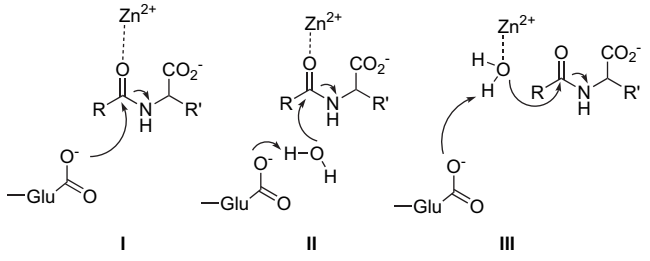
Despite the high enantioselectivity, the hydrolysis of **2c** is slow (c=22%, t=51 h). Moreover, **2c** was reported to have a low solubility in water (pH 7.8), limiting the preparative utility of the reaction. Ethyl 3-acetamidobutanoate **2d** is not hydrolysed.

As an alternative method, Achilles et al. applied α-chymotrypsin for the resolution of a β-lactam derivative **4** (Scheme 5).[52] The reaction yields the (*R*)-product (*R*)-**5** with 84% ee at an estimated 50% conversion. Thus, α-chymotrypsin produces the enantiomer, which corresponds to the less reactive enantiomer for the hydrolysis of the hydrolysed ester **2c**.

The above results indicate that α-chymotrypsin may have some potential for the enantioselective hydrolysis of β^3-amino esters with aromatic or polar substituents. The reactions are considerably slower when compared to the hydrolysis of the corresponding α-amino esters.

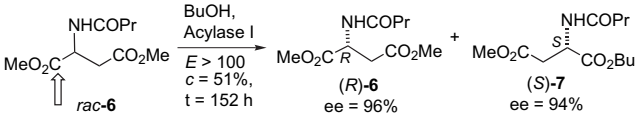
2.1.2. Acylase I. Acylases are cytosolic enzymes, the concentrations of which are high, especially in the kidney.[53,54] Various acylase I enzymes [EC 3.5.1.14] have been isolated and purified from different sources. Acylases from porcine kidney and different *Aspergillus* species are commercially available. Acylase I has been applied to industrial-scale resolutions for the production of enantiopure α-L-amino acids using the fungal *Aspergillus* enzyme, which has a higher stability, compared to the renal enzyme.[55] Other reported acylase I enzymes have been isolated, e.g., from human or rat kidney, bovine liver, *Thermococcus litoralis*, *Pyrococcus horikoshii* and *Bacillus stearothermophilus*.[56–61] In addition, acylases hydrolysing D-amino acids have been isolated from a variety of microorganisms and used in the industrial production of D-amino acids.[62–67]

Even though a considerable amount of structural information on different acylase I enzymes has been unravelled,[56–61,68–70] only the partial crystal structure of the Thr347Gly mutant of human acylase I has been reported in the Protein Data Bank (PDB).[71,72] A preliminary X-ray diffraction analysis of acylase I from *T. litoralis* has also been carried out.[73] The mechanism is generally assumed to be similar to that of carboxypeptidase A, a Zn(II)-exopeptidase (Scheme 6).[74,75]



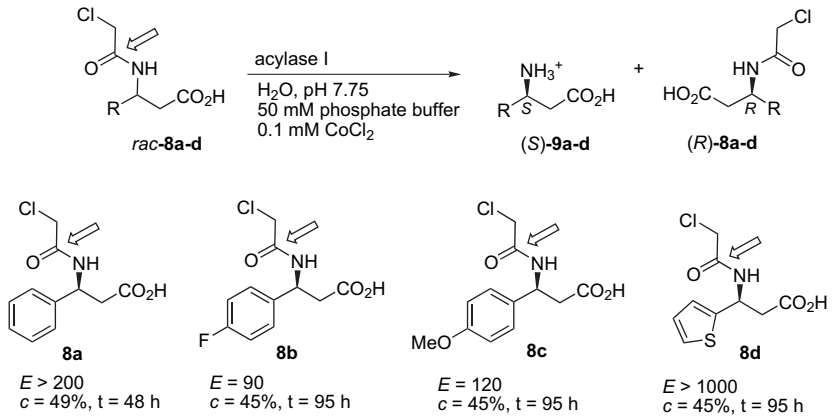
Scheme 6. Proposed mechanisms of carboxypeptidase A as generally used models for acylase I.[74,75]

Acylase I, typically, catalyses the hydrolysis of *N*-acyl groups of *N*-acyl-α-L-amino acids other than *N*-acyl-L-aspartic acid.[76] Moreover, the hydrolysis and alcoholysis of *N*-acyl-α-L-amino esters with exquisite chemo- and regioselectivity towards the ester bond have been reported.[77–79] In such cases, even dimethyl *N*-butanoyl aspartate *rac*-**6** is a substrate (Scheme 7).[77] It is crucial that only the α-ester group of the aspartate reacts, giving (*S*)-**7** and, under the alcoholysis conditions, no *N*-acyl transfer is observed. Based on these experimental findings, it can be proposed that an amino acid substrate of acylase I needs structural elements, which make the C–N bond sufficiently weak (Scheme 6). A carboxylate group at the α-position to the cleavable amide bond, together with the coordination of the carbonyl oxygen to Zn^{2+}, is sufficient for hydrolysis, but not for alcoholysis. It is therefore not surprising that the acylase I-catalysed hydrolyses of *N*-chloroacetyl-3-aminobutanoic and *N*-acetyl-3-amino-2-methylpropanoic acid have failed.[76] Acylase I from porcine kidney was, however, recently reported to hydrolyse *N*-chloroacetyl-3-aryl-β-amino acids *rac*-**8a–d** with high enantioselectivity, giving (*S*)-**9a–d** (Scheme 8).[80] Evidently, the electron-withdrawing chlorine at the *N*-acetyl group and the aromatic ring at the adjacent carbon to the cleavable bond make the hydrolysis possible. The predictability of other β-amino acid substrates for acylase I or the synthetic utility of the enzyme cannot, however, be determined on the basis of the present knowledge.



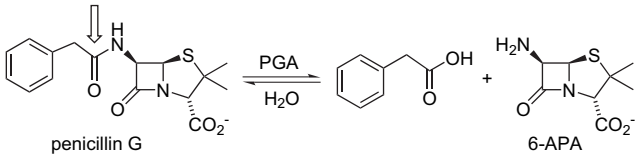
Scheme 7. Kinetic resolution of *rac*-**6** by acylase I from *Aspergillus melleus*.[77]

2.1.3. Penicillin G amidase from *Escherichia coli*. Among the penicillin amidases [EC 3.5.1.11], penicillin G amidase (PGA, also called penicillin acylase, main source *E. coli*) was discovered in the 1950s.[81–86] PGA catalyses the hydrolysis of the phenylacetyl group of **10** (penicillin G), giving 6-aminopenicillanic acid **11** (6-APA, Scheme 9). The enzyme has been immobilised on several supports in order to optimise its performance.[87] Penicillin amidases have been applied to the industrial production of β-lactam antibiotics.[88,89] The physiological role of PGA is obscure, even though it has been suggested to play a role as a scavenger enzyme with an ability to detach the phenylacetyl group for use as a carbon source.[90] The key catalytic amino acid



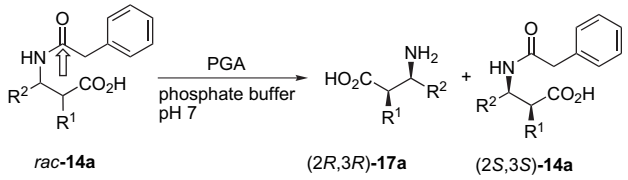
Scheme 8. Kinetic resolution of *rac*-**8** by acylase I from porcine kidney.[80] *E* values have been calculated according to the reported ee_p and *c* values. More reactive enantiomers have been presented.

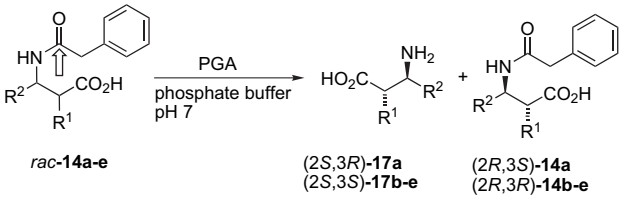
residue is SerB1, which has been proposed to act as an attacking nucleophile for **10**, leading to the formation of an anionic tetrahedral intermediate.[91,92] Asn241 of the B-subunit stabilises the intermediate. The main mechanistic difference to the serine hydrolases (see Scheme 18) is the lack of general acid–base catalysis by adjacent histidine in the formation of the intermediate. In addition, pH affects the catalytic properties of PGA. Hydrolysis takes place over the pH range 7–8.5, whereas the equilibrium favours acylation at pH 5–6.[81,82] To some extent, PGA accepts groups other than phenylacetyl, e.g., 4-pyridylacetyl and phenoxyacetyl, in the substrate, whereas a wide variety of structurally different leaving groups (the amine part of amides) are tolerated, which makes the enzyme highly useful.[93]



Scheme 9. Natural reaction of penicillin G amidase.

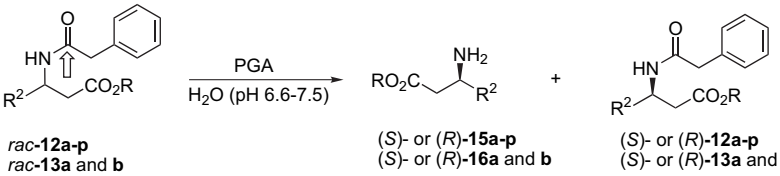
PGA has proved to be one of the most powerful tools for the preparation of highly enantiopure β^3- and $\beta^{2,3}$-amino acids **12a**–**p**, **13a**,**b** and **14a**–**e** (Schemes 10 and 11).[94–101] Over 95% ee values of the unreacted substrate enantiomer and the produced product enantiomers **15a**–**p**, **16a**,**b** and **17a**–**e** are typically obtained at 50% conversion within a few hours. The catalyst is readily available and functions at catalytic amounts in aqueous buffers. Substrate concentrations of up to 0.22 M have been used with *rac*-**12i**–**n**.[96]





(a) R^1 = Me, R^2 = CF_3
(b) R^1 = Et, R^2 = Me
(c) R^1 = $CH_2CH{=}CH_2$, R^2 = Me
(d) R^1 = CH_2Ph, R^2 = Me
(e) R^1 = Me, R^2 = Me

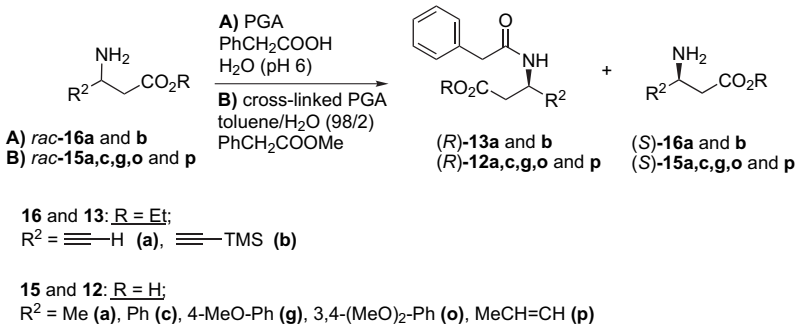
Scheme 11. Kinetic resolution of N-phenylacetylated $\beta^{2,3}$-amino acids by PGA.[100,101] The starting material consists of one enantiomeric pair.



12 and **15**: R = H;
R^2 = Me **(a)**, Et **(b)**, Ph **(c)**, 2-F-Ph **(d)**, 4-F-Ph **(e)**, 4-Cl-Ph **(f)**, 4-MeO-Ph **(g)**, 3,4,5-$(MeO)_3$-Ph **(h)**, CF_3 **(i)**, C_2F_5 **(j)**, C_3F_7 **(k)**, CHF_2 **(l)**, $H(CF_2)_2$ **(m)**, $H(CF_2)_4$ **(n)**, 3,4-$(MeO)_2$Ph **(o)**, MeCH=CH **(p)**

13 and **16**: R = Et;
R^2 = ≡—H **(a)**, ≡—TMS **(b)**

Scheme 10. Kinetic resolution of N-phenylacetylated β^3-amino acids by PGA.[94–99]



Scheme 12. Kinetic resolution of *rac*-**15** and *rac*-**16** by PGA.[98,102]

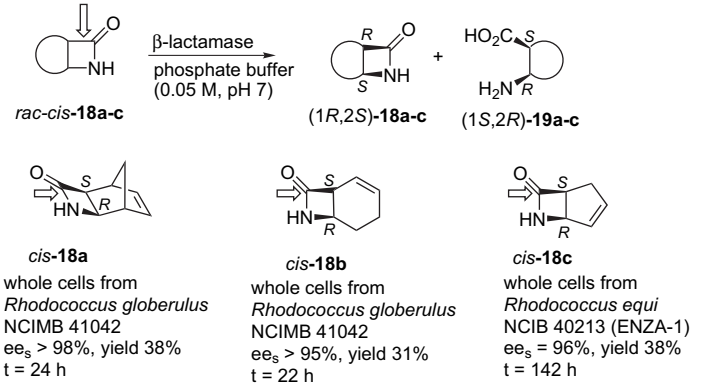
Kinetic resolutions based on enzymatic N-acylation of β^3-amino acid derivatives are scarce, compared to the hydrolysis reactions (Scheme 12).[98,102] For substrates *rac*-**16a** and **b**, the equilibrium for amide hydrolysis is diminished, because the resolution product crystallises from the solution (Scheme 12, method A).[98] Under the acylation conditions for *rac*-**15a**,**c**,**g**,**o** and **p**, the activity of cross-linked PGA strongly increases by adding 2% of water in toluene as a solvent. The *E* values are, typically, over 100 for compounds with aromatic substituents (**15c**, **g** and **o**), whereas, with *rac*-**15a** and **p**, the *E* values are only around 10 (Scheme 12, method B).

PGA has been shown to work excellently for the kinetic resolution of β^3- and $\beta^{2,3}$-amino acids when the phenylacetyl group is transferred to or from the amino group. On the other hand, the PGA-catalysed hydrolysis of N-phenylacetylated α-methyl-β-alanine takes place with low enantioselectivity, suggesting that β^2-amino acid derivatives are less suitable substrates for the enzyme.[94]

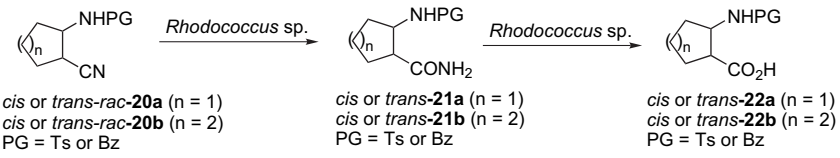
2.1.4. β-Lactamases. β-Lactamases [EC 3.5.2.6] are bacterial enzymes, naturally cleaving the β-lactam ring, and are therefore responsible for challenging β-lactam antibiotics. β-Lactamases have been divided into classes A, B, C and D, those in classes A, C and D are serine hydrolases, whereas the active site of class B β-lactamases utilises a metal ion, which is usually zinc.[103–105]

Even though β-lactamases impact negatively on therapies with β-lactam antibiotics, they have been successfully used in organic synthesis. Promising whole-cell systems from *Rhodococcus* sp. have been reported for *rac-cis*-**18a–c** (Scheme 13).[106,107] Although the enantiomeric excess of the product (1*S*,2*R*)-**19a–c** was not determined, the relatively high substrate recoveries with high ee values point to highly enantioselective reactions. In gram-scale resolutions of *cis*-**18a** and *cis*-**18b**, substrate concentrations of 0.38 and 0.30 M were used, respectively. Enzyme screenings revealed that, among a number of other commercially available β-lactamases, the enzymes from *Bacillus cereus*, *Enterobacter cloacae*, *E. coli* and *Staphylococcus aureus* do not catalyse the ring opening of *cis*-**18c**.[106]

2.1.5. Nitrilases and nitrile hydratases. In recent years, nitrile-hydrolysing enzymes have been introduced as an attractive alternative in the search for mild reaction conditions for nitrile hydrolysis. Nitrilases (EC 3.5.5.1) transform nitriles directly into acids, whereas nitrile hydratases (EC 4.2.1.84) transform them into amides. The ability of various strains of *Rhodococcus* sp. to hydrolyse β-amino nitriles into the β-amino amides and acids has been investigated (Scheme 14).[108–110] Because there is also amidase activity in the whole-cell system, sequential kinetic resolution results. The authors found five- and six-membered alicyclic racemic nitriles (*cis*- and *trans*-**20a** and **b**) to be suitable substrates for *Rhodococci* (Table 1). Racemic substrates *cis*-**20a** and **b** (PG=Ts) yield exclusively the amide *cis*-**21a** and **b** (entries 10–12 and 16–18). The enantioselectivities of the reactions, however, remain low. With the trans-compounds, both products amide **21a** and **b** and acid **22a** and **b** are formed and, typically, only one of these displays a relatively



Scheme 13. Kinetic resolution of *rac*-**18a–c** by β-lactamases.[106,107] More reactive enantiomers have been presented.



Scheme 14. Nitrile hydrolysis by whole cells from *Rhodococcus* sp.[110]

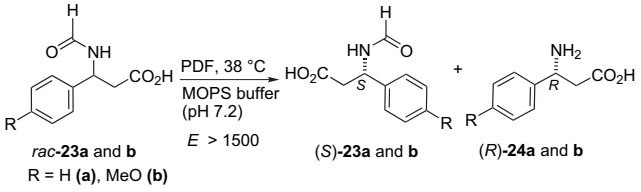
Table 1. Isolated yields and ee values for nitrile hydrolysis by whole cells from *Rhodococcus* sp. (after a reaction time of 24 h)[110]

Entry	Substrate	Nitrile % (ee %)	Amide % (ee %)	Acid % (ee %)	Microorganism
1	*trans*-**20a** (PG=Bz)	0	40 (94)	55 (75)	*R. equi* A4
2		0	30 (>99)	63 (48)	*R. erythropolis* NCIMB 11540
3		0	7 (>99)	87 (15)	*R.* sp. R 312
4	*trans*-**20b** (PG=Bz)	38 (99)	22 (56)	36 (>95)	*R. equi* A4
5		59 (44)	16 (67)	15 (>95)	*R. erythropolis* NCIMB 11540
6		61 (82)	14 (38)	7 (>95)	*R.* sp. R 312
7	*trans*-**20a** (PG=Ts)	40 (47)	14 (>99)	44 (2)	*R. equi* A4
8		0	13 (>99)	86 (5)	*R. erythropolis* NCIMB 11540
9		46 (30)	10 (>99)	34 (14)	*R.* sp. R 312
10	*cis*-**20a** (PG=Ts)	71 (5)	14 (51)	0	*R. equi* A4
11		50 (16)	49 (15)	0	*R. erythropolis* NCIMB 11540
12		11 (51)	75(7)	0	*R.* sp. R 312
13	*trans*-**20b** (PG=Ts)	26 (78)	54 (65)	13 (>99)	*R. equi* A4
14		24 (98)	56 (59)	15 (97)	*R. erythropolis* NCIMB 11540
15		33 (47)	42 (77)	16 (87)	*R.* sp. R 312
16	*cis*-**20b** (PG=Ts)	47 (8)	48 (6)	0	*R. equi* A4
17		50 (10)	41 (8)	0	*R. erythropolis* NCIMB 11540
18		44 (10)	43 (4)	0	*R.* sp. R 312

high enantiopurity. Thus, the sequential resolution of the trans-five-membered **20a** (PG=Ts or Bz) yields the amides **21a** (PG=Ts or Bz) with high enantiopurity (entries 1–3 and 7–9), whereas the trans-six-membered **20b** (PG=Ts or Bz) yields the acids **22b** (PG=Ts or Bz) with high enantiopurity (entries 4–6 and 13–15). The tosyl protective group is favoured over its benzoyl counterpart, e.g., for benzoylated *cis*-**20a** and **b** are not accepted as substrates for the enzymes. The absolute configurations of the resolved products were not determined.

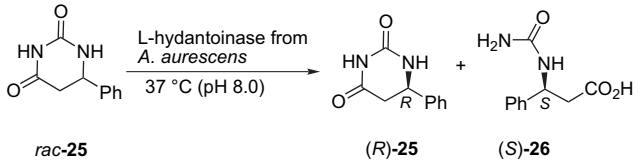
Nitrile-hydrolysing enzymes provide a mild method to hydrolyse nitriles into amides or carboxylic acids. The real value of nitrile-hydrolysing enzymes for the kinetic resolution of β-amino acids and amides has, however, not yet been discovered.

2.1.6. Peptide deformylases. Peptide deformylases (PDF [EC 3.5.1.31]) catalyse the hydrolysis of the *N*-terminal formyl group from nascent polypeptides. The recent work with PDF from *E. coli* describes good activity and high enantioselectivity with certain N-formylated α-amino acids, α-amino acid amides and α-amino nitriles.[111] In the same study, the hydrolysis of *N*-formyl-3-amino-3-arylpropanoic acid **23a** and **b** (10 mM) was observed to take place with excellent enantioselectivity (E>1500), giving highly enantiopure (*R*)-**24a** and **b** as reaction products (Scheme 15). The exact reaction time was not reported, but it was stated to be approximately the same as that for the α-amino acid derivatives (ca. 1 h). Studies of PDF with other β-amino acids need to be carried out before it is possible to say more about the synthetic potency of the method.



Scheme 15. Kinetic resolution of *rac*-**23** by PDF.[111]

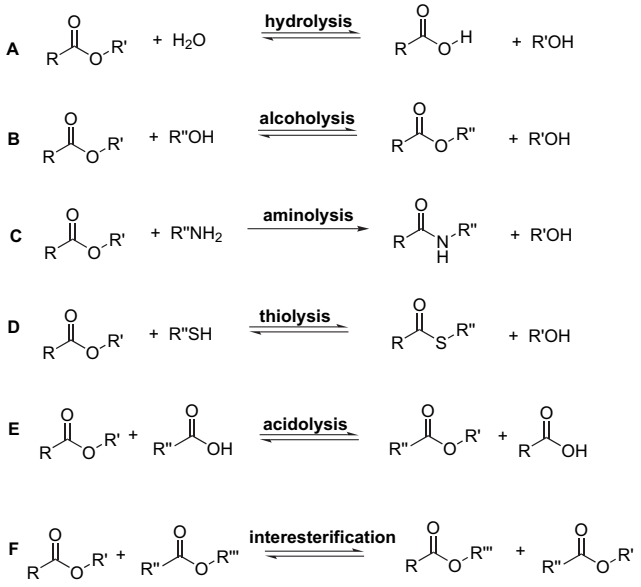
2.1.7. Hydantoinases. Hydantoinases [EC 3.5.2.x] hydrolyse cyclic amides. The process is well known in the industrial production of enantiopure α-amino acids.[112] In the Biotrans 2005 meeting (Delft, The Netherlands), a new L-hydantoinase from *Arthrobacter aurescens* was reported to catalyse the hydrolysis of 6-substituted aromatic dihydrouracils *rac*-**25** as β-amino acid-derived substrates into *N*-carbamoyl derivative (*S*)-**26** with good enantioselectivity (Scheme 16).[113,114] The use of this novel enzyme could therefore open up a new kinetic resolution route to enantiopure β-amino acids. On the other hand, commercially available hydantoinases from *E. coli* and *V. angularis* catalyse the same reactions with low enantioselectivity.



Scheme 16. Kinetic resolution of *rac*-**25** by L-hydantoinase from *Arthrobacter aurescens*.[113,114]

2.2. Enzymes acting on C–O-bonds

2.2.1. Lipases: reaction types and mechanism. Lipases are serine hydrolases [EC 3.1.1.3], the natural reaction of which is the hydrolysis of triglycerides. Lipases accept a wide range of compounds as their substrates. Besides ester hydrolysis (A), in organic solvents lipases catalyse alcoholysis (B), aminolysis (C), thiolysis (D), acidolysis (E) and interesterification (F) when water is not present (Scheme 17). In a broad sense, the reactions can be considered as acylations of a nucleophile (Nu^2H) and as deacylations of an acyl donor ($RCONu^1$) for the reaction $RCONu^1+Nu^2H=RCONu^2+Nu^1H$ (Scheme 18). It is worth mentioning that the terms inter- and transesterification are often used as synonyms.[115] We felt that it is necessary to reserve the term interesterification to describe reactions (F) where two esters change their alkyl parts. Examples of interesterifications are scarce.[116–120]



Scheme 17. Types of lipase-catalysed reactions.

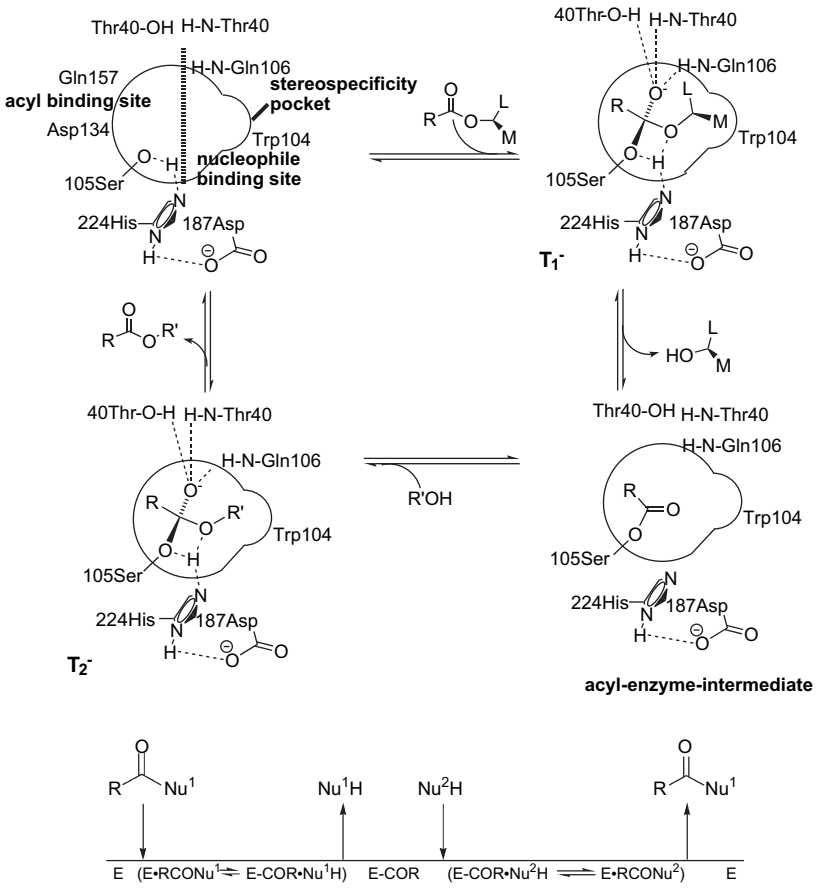
The ping-pong bi–bi mechanism for the lipase-catalysed reaction of an ester enantiomer (RCO_2CHLM, an acyl donor $RCONu^1$) with R′OH (a nucleophile Nu^2H) and CAL-B is presented in Scheme 18 as a model reaction (L and M denote large- and medium-sized groups, respectively). The mechanism is known as a serine hydrolase mechanism. At the beginning, the ester substrate enters the active site where the serine residue (Ser105) is activated by a hydrogen bond to histidine (His224). Nucleophilic attack of the serine hydroxyl at the carbonyl carbon of the substrate leads to the formation of the anionic tetrahedral intermediate (T_1^-), which is stabilised by three hydrogen bonds at the oxyanion hole, one of which is formed with Gln106 and two with Thr40. The intermediate breaks down with the formation of an acyl-enzyme intermediate liberating the LMOH (Nu^1H). The attack of R′OH (an added nucleophile Nu^2H) leads to the formation of a second anionic tetrahedral intermediate (T_2^-), which finally leads to the second product (RCO_2R' or $RCONu^2$). The enzyme (E) is released and the cycle recurs.

2.2.2. Lipase B from *Candida antarctica*.

2.2.2.1. Characteristics. Two entirely different lipases, CAL-A and CAL-B, have been isolated from *C. antarctica* yeast.[121,122] CAL-B is, perhaps, the most common enzyme used by synthetic chemists. CAL-B could better be classified as an esterase, or as an intermediate form of a lipase and an esterase. This is because of the lack of typical interfacial activation characteristics for lipases.[123] Moreover, CAL-B hydrolyses long-chain triglycerides slowly.[124] The most common form of CAL-B in organic synthesis is Novozym 435 from Novo Nordisk. The enzyme was also available earlier with the trade name Chirazyme L2 (carrier-fixed C2, lyophilised) from Roche. In these preparations, CAL-B is immobilised on a polyacrylic resin. CAL-B is stable in aqueous solutions over the pH range 3.5–9.5 and the denaturation temperature of the free enzyme varies between 50 and 60 °C, depending on the pH and buffer. CAL-B accepts a wide range of substrates and solvents from polar to apolar, which makes it a highly useful catalyst for synthetic work.[125] A lot of effort has been focused on tailoring and extending the catalytic properties of CAL-B.[126]

The three-dimensional structure of CAL-B has been elucidated.[127,128] The funnel-shaped active site is located in the core of the enzyme. CAL-B-catalysed reactions are assisted by a catalytic triad Ser105-His224-Asp187, where Ser105 is situated at the bottom of the active site in rather polar surroundings (Scheme 18). In addition to His224 being projected into the active site, Gln157 is hydrogen bonded to Asp134 and Thr40. Otherwise, the active site is coated with hydrophobic amino acids, Trp104 being the only aromatic residue. The acyl and nucleophile-binding sites run almost parallel from the bottom to the surface and are barely separated by the hydrophobic side chains of Ile189 and Ile285. The nucleophile-binding site contains the stereospecificity pocket where substituents smaller than propyl can fit.[129] The pocket is delineated by the side chain of Trp104. The structure of the acyl binding site has not been thoroughly investigated, but it is known to be more spacious than the nucleophile site. Accordingly, chiral recognition by CAL-B is different for reactions at the amino and carboxylate functionalities of the amino acid-based substrates of Scheme 1. Generally, higher enantioselectivities are expected for chiral recognition at the nucleophile-binding site.[128] The results reviewed below, however, indicate excellent chiral recognitions of the acyl part with proper substrate structures. The most prominent feature of CAL-B catalysis is the low chemoselectivity observed when alicyclic β-amino esters react with an achiral ester.[119,120] For this reason, we want to distinguish the terms interesterification and transesterification.

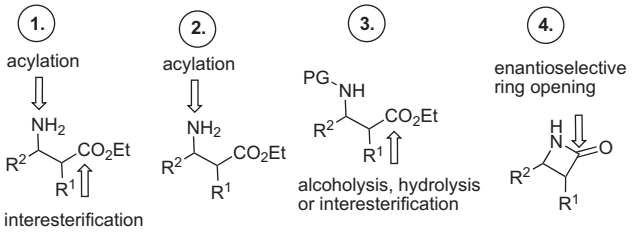
The mechanism of interesterification seems to be more complex than is assumed on the basis of the ping-pong bi–bi mechanism (Scheme 18). This is most clearly seen when 2,2,2-trifluoroethyl butanoate $PrCO_2R$ ($R=CF_3CH_2$) acts as an acyl donor for the reaction with **27a**, leading to the formation of an interesterification product **28a** (Scheme 19). As expected, alcoholysis of **27a** with a weak nucleophile, 2,2,2-trifluoroethanol, in DIPE does not take place.[119] This may indicate that 2,2,2-trifluoroethanol is not able to enter the active site, but rather needs to be liberated from its ester by the enzyme and to stay in the polar surroundings of the



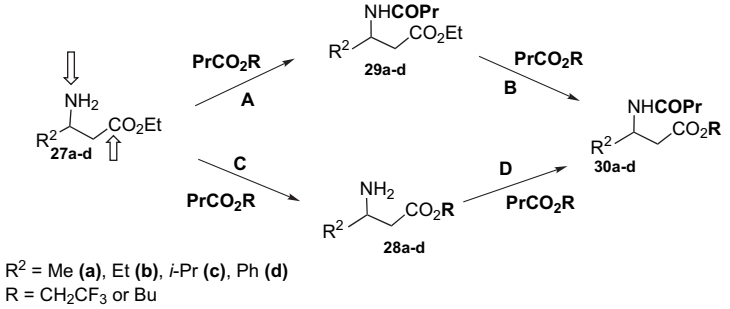
Scheme 18. Top view for the ping-pong bi–bi mechanism of CAL-B.

active site close to the catalytic triad. Possible hydrogen bonds from the active site amino acid residues to fluorine atoms can increase the nucleophilic character of 2,2,2-trifluoroethanol. Moreover, hydrogen bonds from His224 can further activate the hydroxyl group of the alcohol, as previously predicted by computer modelling.[130] When the released alcohol remains in the active site, the effect on the enantioselectivity is evident. Thus, acylation of a chiral alcohol with 2,2,2-trifluoroethyl and other alkyl butanoates has been observed to proceed with differing enantioselectivities, although the acyl-enzyme intermediate is the same butanoate ester in each case.[131,132] This effect has also been observed with PPL and CAL-A.[77,133,134]

The most successful approaches to the enantiomers of β-amino acid derivatives by CAL-B are shown in Scheme 20 in general forms. The first method exploits the low enzymatic chemoselectivity, and the second method is based on highly chemoselective N-acylation. In the third method, the reaction is directed to the ester group of an *N*-protected β-amino ester and, in the fourth method, a β-lactam ring is enzymatically cleaved.

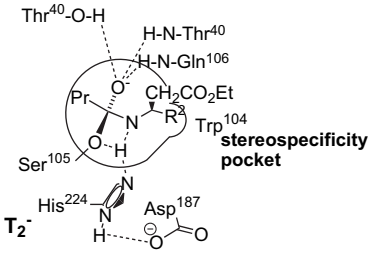


Scheme 20. Strategies for the kinetic resolution of β-amino acid derivatives by CAL-B.



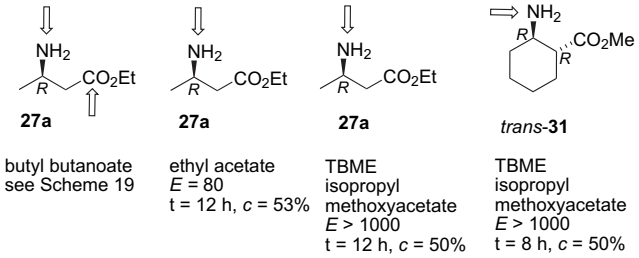
Scheme 19. Chemoselective reaction possibilities of **27a–d** with $PrCO_2R$ by CAL-B.[119,120]

2.2.2.2. N-acylation and/or interesterification. The reaction of an acyclic β-amino ester with an achiral acyl donor leads to competitive N-acylation (route A) and interesterification reactions (route B) in the presence of CAL-B (Scheme 19).[119,120] As a consequence, when one of the bifunctional substrates **27a–d** is subjected to the CAL-B-catalysed reaction with butanoate esters ($PrCO_2R$, R=Bu or CF_3CH_2), the reaction gives **30a–d** as the most advanced products through routes A+B and C+D. The chemoselectivity depends on the nature of $PrCO_2R$ and R^2. With **27a** in neat butyl butanoate, the route C+D prevails and, at 80% total conversion, the initially racemic mixture is transformed into a mixture of enantiopure products (*S*)-**27a** (20%), (*S*)-**28a** (R=Bu, the amount 24%) and (*R*)-**30a** (R=Bu, the amount 54%) with all ees over 95%. The amount of (*R*)-**29a** stays always minimal. Accordingly, the enantiomers were effectively obtained by a sequential resolution path on a preparative scale in 2 h. For the reaction of **27a** with 2,2,2-trifluoroethyl butanoate in DIPE, the route A+B clearly prevails over C+D. Steps C+D, however, proceed smoothly with low enantioselectivity, finally ruining the attempt for successful kinetic resolution. The increased size of R^2 favours interesterification (C+D), due to the stereospecificity pocket of CAL-B becoming too crowded with increasing size of R^2, preventing the substrate binding as a nucleophile (Scheme 21). Accordingly, when R^2=^{i}Pr in the case of **27c**, interesterification with low enantioselectivity (*E*=15 for butyl butanoate and *E*=4 for trifluoroethyl butanoate in DIPE) through route C is the only reaction observed. With phenyl-substituted **27d**, the reaction proceeds sluggishly with low enantioselectivity, leading to a product distribution (**29d**:**28d**:**30d**) of 20:100:7 after 55 h.



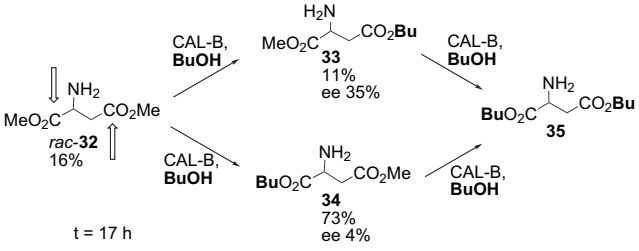
Scheme 21. Top view for T_2^- for N-acylation of β-amino ethyl esters **27**.

Interesterification is, of course, seen only when two esters with different alkyl parts react. The resolution of **27a** in ethyl acetate was successfully performed with *E*=80 (Scheme 22).[135] On the other hand, interesterification was suppressed by using isopropyl methoxyacetate as an acyl donor for the kinetic resolution of **27a** (1.7 M) in TBME.[136] The total isolated yield of 86% for the unreacted (*S*)-**27a** and the formed product were reported after a reaction time of 12 h and distillation. The same method results in excellent enantioselectivities also for the kinetic resolution of methyl *trans*-2-aminocyclohexanecarboxylate **31** (1.6 M, *t*=8 h) as an alicyclic β-amino acid, suggesting further versatility of the method. N-Acylations of ethyl *cis*- and *trans*-2-aminocyclohexane-1-carboxylates as $\beta^{2,3}$-amino acid derivatives with trifluoroethyl acetate in diethyl ether were, however, reported to proceed with low enantioselectivity.[137]



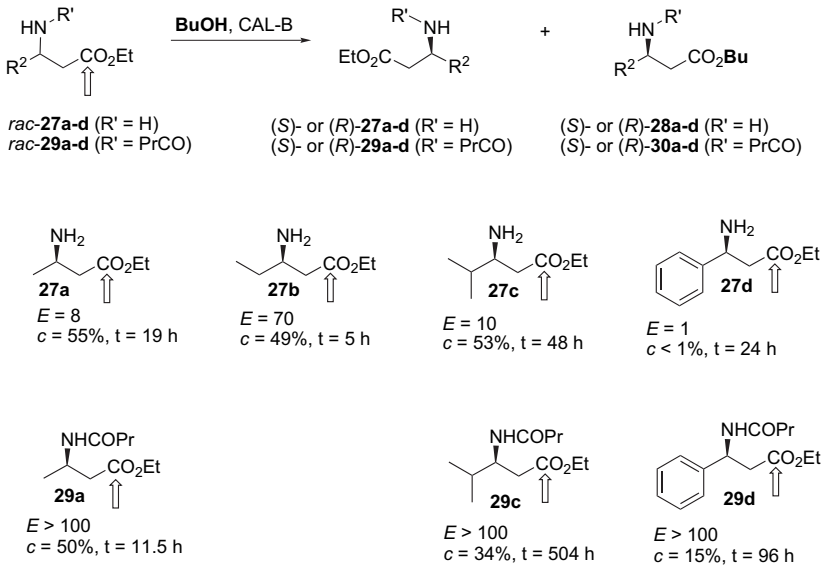
Scheme 22. Kinetic resolution of *rac*-**27a** and *rac*-**31** by CAL-B. More reactive enantiomers have been presented.[119,135,136]

2.2.2.3. Alcoholysis. Two ester groups of acidic amino esters entail the possibility for enzymatic regioselective recognition through alcoholysis and interesterification. This is shown for the butanolysis of racemic dimethyl aspartate **32** and dimethyl *N*-butanoyl aspartate **6** in Scheme 23.[77,120] The reaction of *rac*-**32** yields a 1:7 mixture of β- and α-butyl methyl esters **33** and **34** at 84% conversion in 17 h with negligible enantioselectivity. At this stage, the dibutyl ester **35** is not yet formed. After *N*-protection (formation of *rac*-**6**), the reaction in neat butanol (*E*=55) and in neat butyl butanoate (*E*=30) turns regiospecific, i.e., CAL-B recognises the amino ester as a β-amino ester, leading to the enantioselective formation of (*S*)-**36**. Butanolysis has been successfully used for the kinetic resolution of *rac*-**6** at 52% conversion, yielding (*R*)-**6** (ee=96%) and (*S*)-**36** (ee=88%), and for the enantiomeric purification of (*S*)-**6** (ee=65%) to an enantiopure stage (ee>99%). Competitive inhibition of CAL-B by alcohols and/or solvent effects may explain the slow reaction in butanol (ca. 55% conversion in 124 h), compared to interesterification (ca. 55% conversion in 6 h) in butyl butanoate.[123,138]



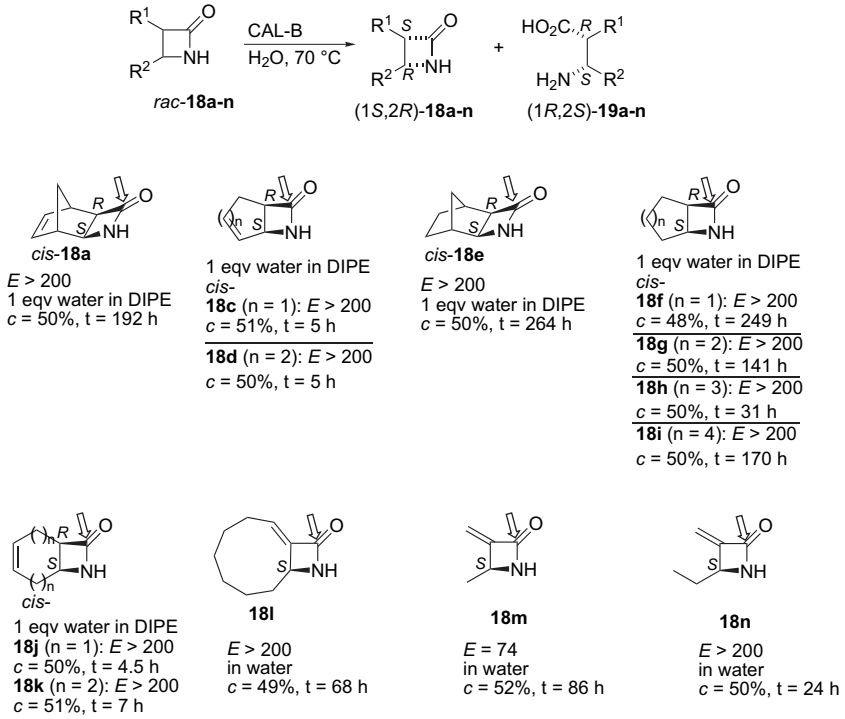
Scheme 23. Regioselective alcoholysis of *rac*-**32** and kinetic resolution of *rac*-**6** by CAL-B.[77,120]

Acyclic β-amino esters *rac*-**27a–d** and *rac*-**29a–d** have been subjected to alcoholysis in neat butanol in the presence of CAL-B (Scheme 24).[120] As with the aspartate above, *rac*-**29** with *N*-protection gives high enantioselectivities (*E*>100). Due to long reaction times, the method is of practical value only for the kinetic resolution of *rac*-**29a**, where (*S*)-**29a** (ee 99%) and (*R*)-**30a** (ee 99%) were separated after 11.5 h.



Scheme 24. Kinetic resolution of *rac*-**27a–d** and *rac*-**29a–d** in neat butanol.[120] More reactive enantiomers are presented.

2.2.2.4. Hydrolysis of β-lactams. CAL-B-catalysed ring opening of β-lactams shows a high potential for the preparation of enantiopure β^3- and $\beta^{2,3}$-amino acids (Scheme 25).[130,139–142] Even though lipases are generally unable to act on stable amide bonds, CAL-B has been found to catalyse the hydrolysis and alcoholysis of β-lactam rings, due to diminished resonance stabilisation at the amide bond in a strained four-membered ring. This method allows high enantioselectivities and easy purification of the products (1*S*,2*R*)-**18a–n** and (1*R*,2*S*)-**19a–n**. Water activity under low water conditions is of importance for enzymatic reactivity. Accordingly, high water contents clearly decrease both enantioselectivity and conversion as shown by an increase in *E* from 44 (conversion 13%) to 117 (conversion 48%) when 10 equiv of water are replaced by 1 equiv for the ring opening of *cis*-**18h**.[140] The reactions tend to proceed sluggishly, especially with saturated *cis*-**18e**,**f**,**g** and **i**, even at elevated temperature, taking 141–264 h before 50% conversion is reached.[140,142] This may be partly due to the consumption of water by the reaction under low water contents. With unsaturated *cis*-**18c**,**d**,**j** and **k**, 50% conversion is reached in a few hours (4.5–7 h) at 70 °C. The resolutions of *rac*-**18l–n** have been carried out as 0.03 M solutions in water at 70 °C, and 50% conversion is reached in 86, 86 and 24 h, respectively. The method can also be readily applied to β^3-lactams.[130] The highest substrate concentrations



Scheme 25. Hydrolysis of β-lactams. More reactive enantiomers have been presented.[130,139–142]

used in the gram-scale resolutions have been 0.2 M with *cis*-**18a**,**c**,**j** and **k**. It has been crucial for high enantioselectivity that the reactions are performed at elevated temperatures, usually at 60–70 °C. It is also worth noting that the enantiopreference is different than in the β-lactamase-catalysed reactions (Scheme 13).

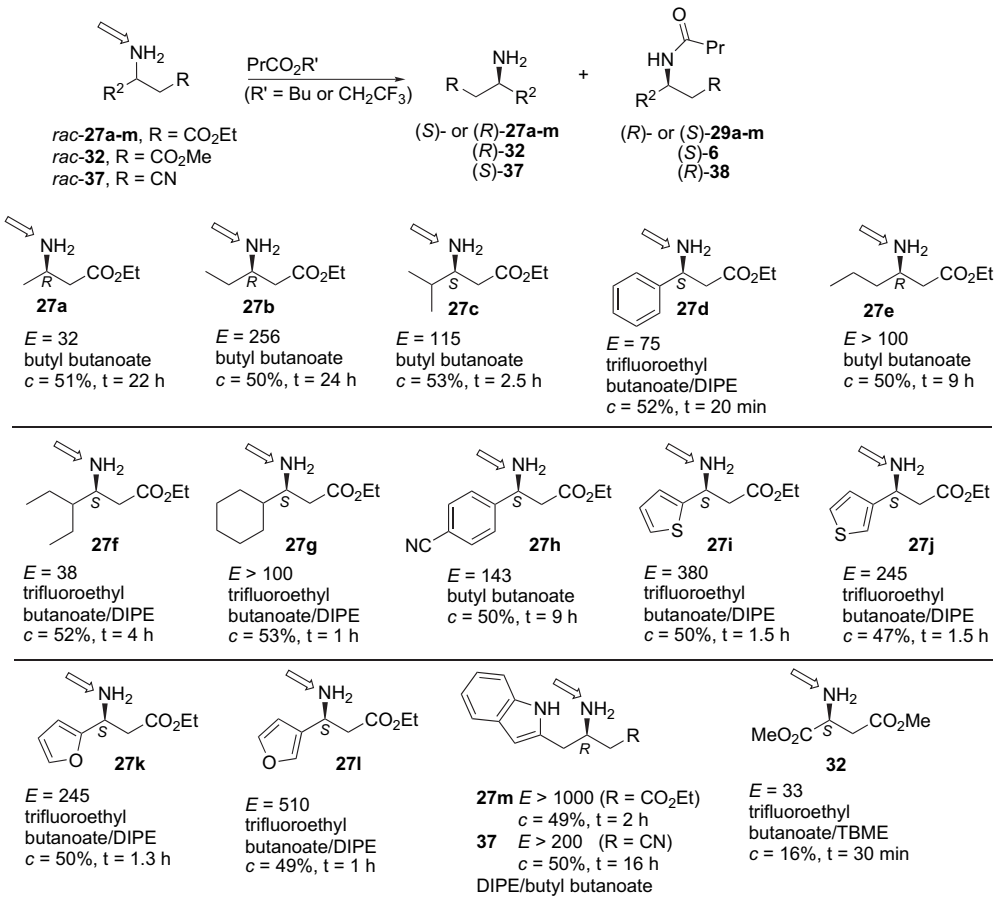
2.2.2.5. Summary. The above results show that, although CAL-B is generally of high practical value for kinetic resolution of racemates, its use is relatively limited for the kinetic resolution of β-amino esters. This is mainly due to the low chemoselectivity of the enzyme, which allows both functional groups of an amino ester to react with achiral acyl donors, except when an isopropyl ester is used. On the other hand, CAL-B-catalysed hydrolysis of β-lactams is a highly valuable method for the preparation of many alicyclic β-amino acid enantiomers by kinetic resolution.

2.2.3. Lipase A from *C. antarctica*. The crystal structure of CAL-A has not been elucidated, but its primary structure is available.[143] The enzyme consists of 431 amino acids, and it has a unique structure deviating from other known protein structures. The ability of CAL-A to catalyse the acylation of bulky substrates is noteworthy. Even tertiary alcohols have been esterified with good enantioselectivity.[144,145] Henke et al. have used molecular modelling for explaining the recognition of bulky substrates.[146] This was shown to be based on a GGGX-motif at the active site coating, whereas other lipases consist of a GX-motif.

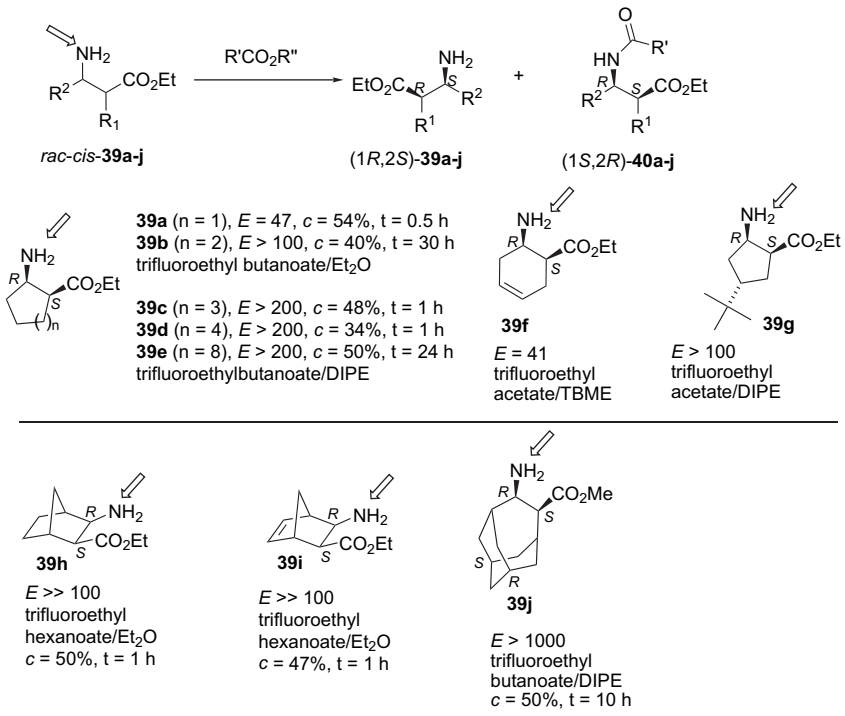
Several promising properties are making CAL-A increasingly interesting today. Even though *C. antarctica* is not a thermophilic organism, lipase A is one of the most thermostable enzymes known to date. Its denaturation temperature is 93 °C at pH 7 and 96 °C at pH 4.5.[147] Because of its thermostability, it is used in the pulp and textile industries to hydrolyse high-melting fatty acid glycerides and resin esters.[148] Earlier trade names of CAL-A encompass lyophilised SP 526 and Novozym 868 (both from Novo Nordisk). The latter product was an aqueous solution and seems to be mentioned only once in the literature.[149] Later, CAL-A has been produced with the trade name Chirazyme L5 (from Roche) and Novozym 735 (from Novo Nordisk). Novozym 735 is an aqueous solution containing 50% glycerol. Chirazyme L5 distributed by Roche corresponds to Novozym 735, except that L5 is lyophilised.

The crucial action for enabling the synthetic use of CAL-A in organic solvents is immobilisation. The common method is based on adsorption of CAL-A (10–20%) on Celite in the presence of sucrose (12%).[150] Polypropylene powder, Accurel EP-100, has also proved to be an excellent carrier.[144]

We belong to pioneers working with CAL-A as a highly enantioselective catalyst. In this laboratory, CAL-A has been especially useful for the highly enantioselective N-acylation of several β^3- and $\beta^{2,3}$-amino esters (Schemes 26 and 27).[77,137,151–157] Kinetic resolution of all compounds

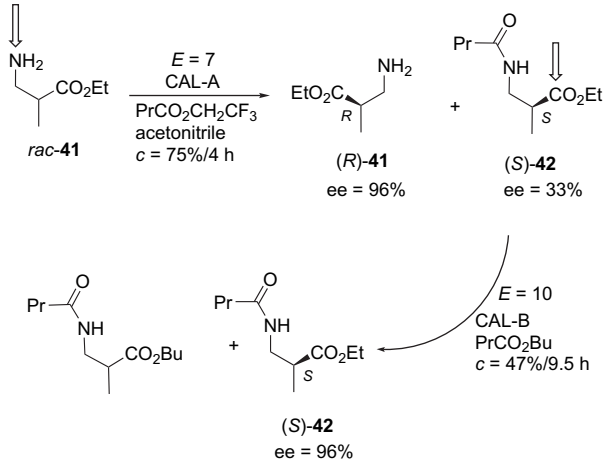


Scheme 26. N-Acylation of β^3-amino esters by CAL-A. More reactive enantiomers have been presented.[77,151,153,156,157]



Scheme 27. N-Acylation of racemic $\beta^{2,3}$-amino esters *cis*-**39a–j** by CAL-A. More reactive enantiomers have been presented.[137,154,155]

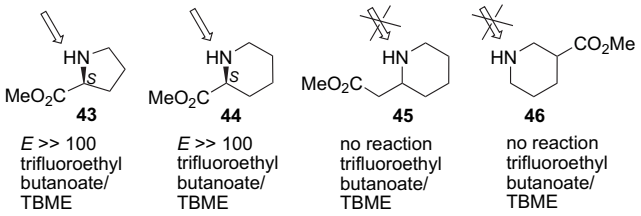
27a–m, **32**, **37** and **39a–j** has been performed on a preparative scale, and the enantiomers of the starting material and the product **29a–m**, **6**, **38** and **40a–j** have been separated and characterised. The reactions have been typically performed at room temperature (22–24 °C), the N-acylation of **39e** (47 °C) being an exception. Unlike CAL-B, CAL-A does not catalyse interesterification. The enantioselectivities are generally high, except for the N-acylation of **41** (E=7) as a β^2-amino acid (Scheme 28).[156] This is not surprising, because the amino group is not attached directly to the asymmetric centre, and the enzyme prefers sterically hindered substrates. CAL-A has also performed successfully in the kinetic resolution of a β-amino nitrile **37** (R=CN). Even though the enantioselectivity of the reaction is slightly lower (E>200) than the corresponding β-amino ester **27m** (E>1000), the reaction is roughly 8-fold faster under the same conditions. Thus, 50% conversion into (*R*)-**38** and (*R*)-**29m** is reached in 2 and 16 h, respectively. Another possibly useful method for CAL-A might be the enantioselective opening of a β-lactam ring. Thus, the slow hydrolysis of *cis*-**18h** takes place (E=47) in the presence of CAL-A.[140] This reaction cannot, however, compete with that in the presence of CAL-B (Scheme 25).



Scheme 28. Kinetic resolution of *rac*-**41** by CAL-A and CAL-B.[152]

To our knowledge, only two enzymatic kinetic resolutions of β^2-amino acids have been reported. Penicillin G amidase-catalysed resolution of *N*-phenylacetyl-α-methyl-β-alanine has already been mentioned to take place with low enantioselectivity.[94] CAL-A-catalysed N-acylation of *rac*-**41** with 2,2,2-trifluoroethyl butanoate also proceeds at negligible enantioselectivity (Scheme 28).[152] Surprisingly, the best enantioselectivity (E=7) was observed with acetonitrile as a solvent. The chemoselectivity of CAL-A for N-acylation and the possibility of CAL-B for interesterification were, however, exploited in two successive kinetic resolutions. Moreover, the opposite enantioselectivities of the lipases in these reactions were utilised. In this method, CAL-A produces the *R*-enantiomer at 75% conversion as an unreacted isomer, whereas CAL-B-catalysed interesterification in butyl butanoate purifies the enantiomerically enriched (*S*)-**42**, now as an unreacted counterpart.

Among the α-amino esters, acylation of a secondary ring nitrogen of *N*-heterocyclic methyl esters of proline **43** and pipecolic acid **44** proceeds with high enantioselectivity (E>100) (Scheme 29).[158,159] This is an intriguing result, because the enzymatic acylation of the secondary nitrogen atom with high enantioselectivity has proved to be a difficult task.[160–166] The method was tried for extension to the homologous β-amino esters **45** and **46**, but these were found not to be substrates for CAL-A.[167]

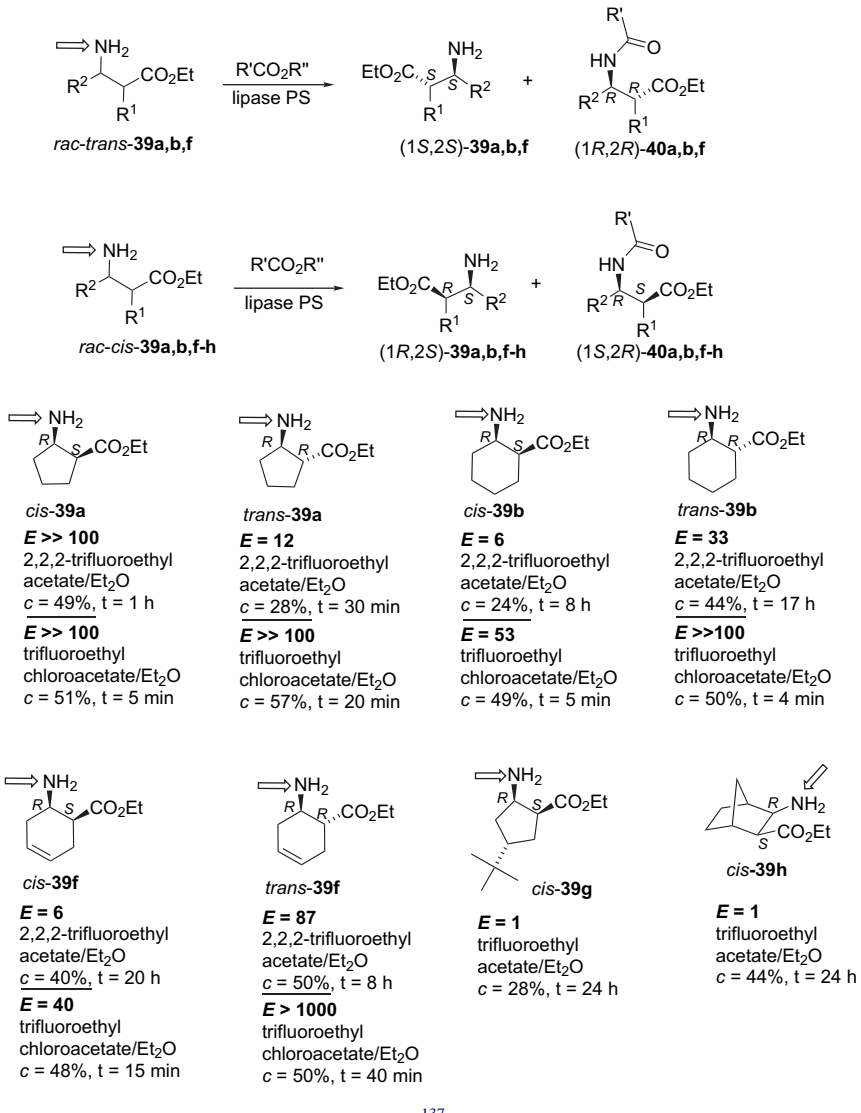


Scheme 29. N-Acylation of α- and β-amino esters **43**–**46**. More reactive enantiomers have been presented.[158,159,167]

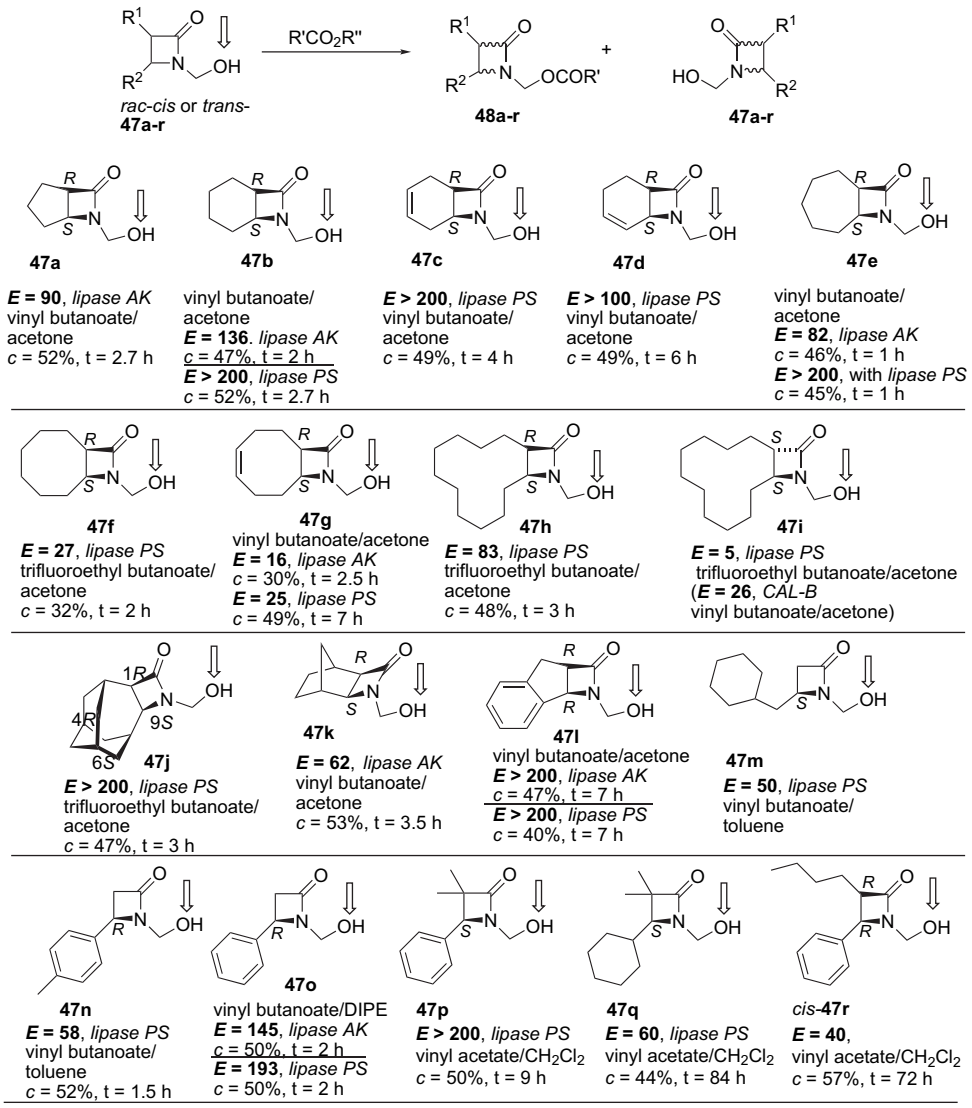
The reported results suggest CAL-A to be the most useful enzyme for the preparation of various highly enantiopure β^3- and $\beta^{2,3}$-amino acids by N-acylation. Even though further scale up of the substrate concentration to over 0.1 M has not been studied, the method conceals a very high synthetic potential. Combined with CAL-B catalysis, CAL-A is also important for the preparation of the enantiomers of *rac*-**41** as the only β^2-amino ester resolved enzymatically so far.

2.2.4. Lipases from *Pseudomonas* species and *Burkholderia cepacia*. Concerning the enzymatic kinetic resolution of β-amino acids and their precursors, three lipases have been reported to catalyse these reactions in a rather similar manner. The most common are lipase PS (from *B. cepacia*, formerly *Pseudomonas cepacia*) and lipase AK (from *Pseudomonas fluorescens*) from Amano, whilst lipase Amano P-30 from *P. cepacia* has been less frequently used. Concerning lipase PS, neither microorganism nor the lipase has been changed by the change in the name. The pH optimum for lipase PS is 7.0 and is 8.0 for lipase AK. The structure of lipase PS is well known,[168–175] with Ser87, His86 and Asp264 forming a catalytic triad. Three binding pockets constitute the active site, and two hydrophobic pockets are responsible for the enantiodiscrimination. Molecular modelling has not, however, been applied to β-amino acids.

Low enantioselectivity in the presence of lipase PS and AK has been reported for the reaction of acyclic *rac*-**27a** with 2,2,2-trifluoroethyl butanoate in DIPE.[119] On the other hand, the enzyme has been highly useful for the acylation of various hydroxymethylated β-lactams and $\beta^{2,3}$-amino esters (Schemes 30 and 31).[137,154,155,176–183] Thus, with racemic $\beta^{2,3}$-amino esters **39a**–**h** lipase PS displays excellent enantioselectivity towards the N-acylation of trans-compounds (Scheme 30) in particular, whereas CAL-A favours



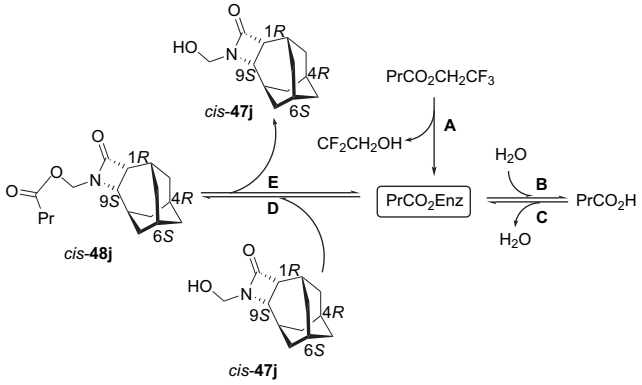
Scheme 30. Kinetic resolution of racemic *cis*- and *trans*-**39a**–**h** by lipase PS.[137] More reactive enantiomers are presented.



Scheme 31. Kinetic resolution of N-hydroxymethylated β-lactams by lipase PS and AK in organic solvents.[154,155,176–183] More reactive enantiomers are presented.

the acylation of cis-compounds (Scheme 27), the two lipases thus showing a nice complementary behaviour.[137] It has been observed that, for lipase PS catalysis, enantioselectivity and reactivity decrease when the acyl part of the achiral acyl donor becomes more hydrophobic, i.e., from Ac to PrCO. Accordingly, 2,2,2-trifluoroethyl chloroacetate has been, surprisingly, the best acyl donor for these N-acylations.

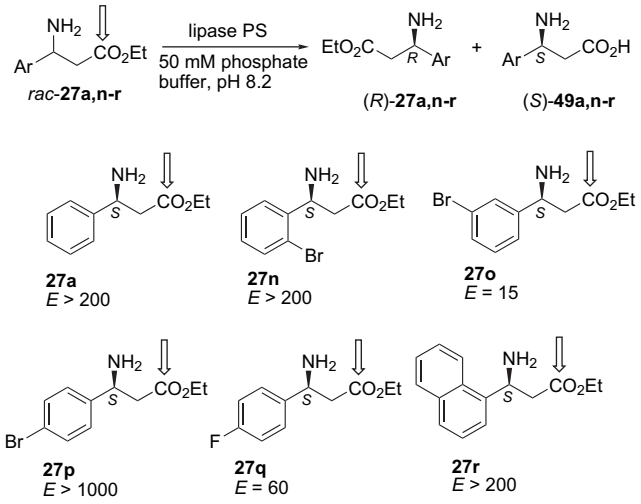
As shown by the data in Scheme 31, the lipase-catalysed acylation of N-hydroxymethylated β-lactams by lipase AK and PS is a highly valuable kinetic resolution method. The produced resolution products **47a–r** and **48a–r** can be easily transformed into the corresponding β-lactams and β-amino acids or β-amino esters.[183,184] As a drawback of this method, the drop in ee of the unreacted substrate enantiomer through enzymatic hydrolysis seems sometimes to hinder the total applicability of the method. This is suggested to be due to a complicated equilibrium in the system where the ester product e.g., **48j** produced through steps A+D and an achiral acyl donor are hydrolysed by the water in the seemingly dry enzyme preparation (steps A+B and E+B, Scheme 32).[155] On the other hand, the esterification of the acid (step C) acts as a continuous source of new water. It was also shown that, under strongly acidic conditions, the hydrolysis of an *N*-hydroxymethyl β-lactam and its ester into the corresponding β-amino acid results in the formation of a dimer.[155] For this reason, the hydrolysis through the corresponding β-lactam (cleavage of the hydroxymethyl group by



Scheme 32. Equilibria in the mixture of *cis*-**47j**, 2,2,2-trifluoroethyl butanoate, butanoic acid and water in the presence of lipase PS in TBME.[155]

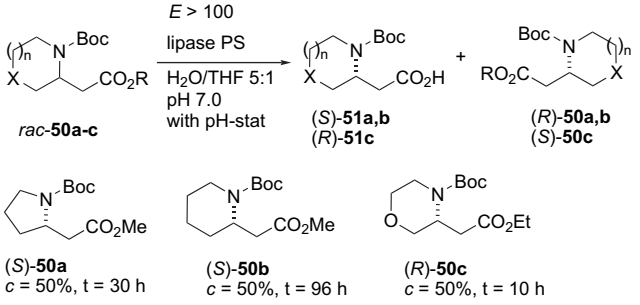
NH_4OH followed by hydrolysis of the β-lactam ring with HCl) can be recommended.[183]

As another strategy, lipase PS-catalysed hydrolysis at pH 8.2 has proved to be an excellent method for the resolution of 3-aryl-3-aminopropanoic acid esters **27a**,**n**–**r**, giving (*S*)-**49a**,**n**–**r** as resolution products (Scheme 33).[185] Thus, excellent enantioselectivities are observed with various aryl substituents. The reaction time (15 h) was mentioned only for **27a**. The method was reported to be scaleable to 200 g/dm^3 (1 M). A patent describing a closely similar system, however, reports solubility problems with **27a** (0.37 M) at pH 8.2 (no buffer).[186] This was overcome by using *tert*-butyl methyl ether as a cosolvent (1:1; pH 8.2 with a pH stat), allowing the use of 1.2 M of **27a**. Isolation of (*S*)-**49a** with 99.6% ee and a yield of 42% (t=15 h) were reported. The extendability of the method to other β-amino esters has not been studied.



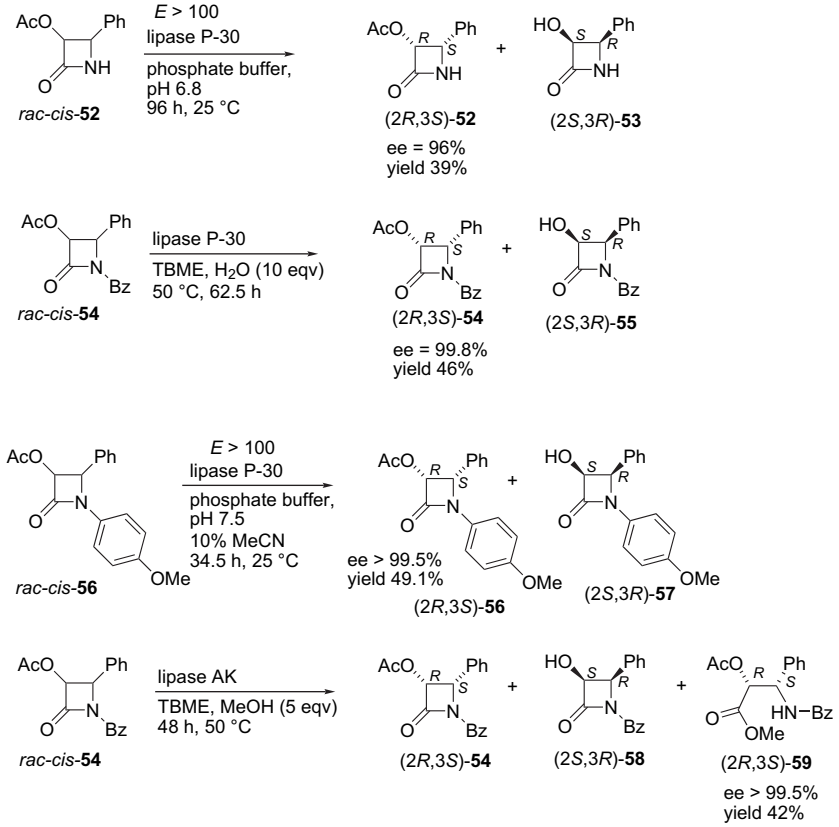
Scheme 33. Kinetic resolution of *rac*-**27a**,**n**–**r** by lipase PS.[185] More reactive enantiomers are presented.

Lipase PS has been successfully used in the kinetic resolution of *N*-Boc-protected heterocyclic β-amino esters **50a**–**c**, yielding highly enantiopure acids **51a**–**c** (Scheme 34).[187] Here, the β-amino functionality is a secondary nitrogen as part of the ring structure. Enantioselectivities of the resolutions of all tested compounds are excellent (E>100).



Scheme 34. Kinetic resolution of heterocyclic β-amino esters *rac*-**50a**–**c** by lipase PS.[187] More reactive enantiomers are presented.

Pseudomonas lipases have been efficiently used in the kinetic resolution of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, the Taxol C-13 side chain (Scheme 35).[188] Thus, lipases



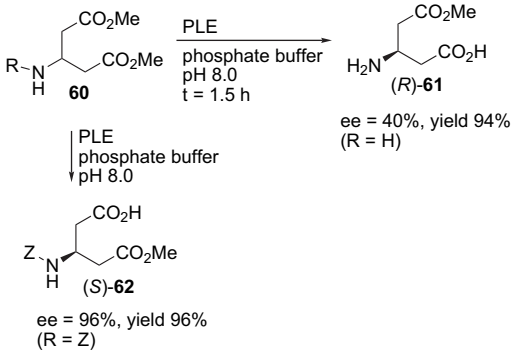
Scheme 35. Kinetic resolution of β-lactams by *Pseudomonas* lipases for the synthesis of Taxol C-13 side chain.[188]

P-30 and AK exhibit high enantioselectivity for the hydrolysis of the acetyl group of racemic *cis*-**52**, **54** and **56**, giving (2*S*,3*R*)-**53**, -**55** and -**57** as the hydrolysed product, respectively. In addition to this hydrolysis, β-lactam ring opening of *rac*-**54** with methanol is observed. This is possibly the first report on a lipase-catalysed β-lactam ring opening. The ring opening preferentially takes place with the (2*R*,3*S*)-enantiomer in the formation of (2*R*,3*S*)-**59**, simultaneously with the hydrolysis of the 3-acetoxy group of the (2*S*,3*R*)-enantiomer in the formation of (2*S*,3*R*)-**58**. When methanol is replaced by water, only hydrolysis of the C-3 acetoxy group is observed. Experiments on β-lactam ring opening with racemic *cis*-**52** and **56** were not reported.

For the resolution of the Taxol C-13 side chain, phenyl glycidic esters and 3-azido-2-hydroxy-3-phenylpropanoates have also been used as starting materials.[189,190] As another strategy, Baker's yeast and various microorganisms have also been used for the enantioselective reduction of the keto group of 3-amino-2-oxo-3-phenylpropanoic esters.[191,192]

2.2.5. Pig liver esterase. Pig liver esterase (PLE) [EC 3.1.1.1.] has been successfully used for the resolution of various prochiral dicarboxylic esters and acetylated prochiral diols.[50] With dicarboxylic esters, the reaction usually stops after the hydrolysis of the first ester group, which has been attributed to the charged carboxylate group. PLE is a serine esterase, which has been isolated with three different isoenzymes.[193–196] Even though the catalytic properties of the isoenzymes differ from each other, PLE has been commonly used as a crude mixture. The crystal structure of PLE has not been elucidated, but an empirical active site model has been developed, based on the hydrolysis of prochiral methyl esters.[197–199]

With prochiral **60** (R=H), enzymatic hydrolysis into (*R*)-**61** proceeds at low enantioselectivity (Scheme 36).[200] This is due to considerable chemical hydrolysis parallel to the enzymatic reaction. It was suggested that the amino group aids the reaction by hydrogen bonding to the carbonyl oxygen. Accordingly, *N*-benzyloxycarbonyl (Z) protection prevents hydrogen bonding, and (*S*)-**62** is produced with a high ee and yield (both 96%) with reversed enantiotopic selectivity. In order to find an enzyme of non-mammalian origin, the authors performed an extensive enzyme screening and reported *Flavobacterium lutescens* IFO 3084 as catalysing a highly regioselective hydrolysis of the pro-*R* ester group.[201] PLE



Scheme 36. PLE-catalysed hydrolysis of the prochiral **60**.[200]

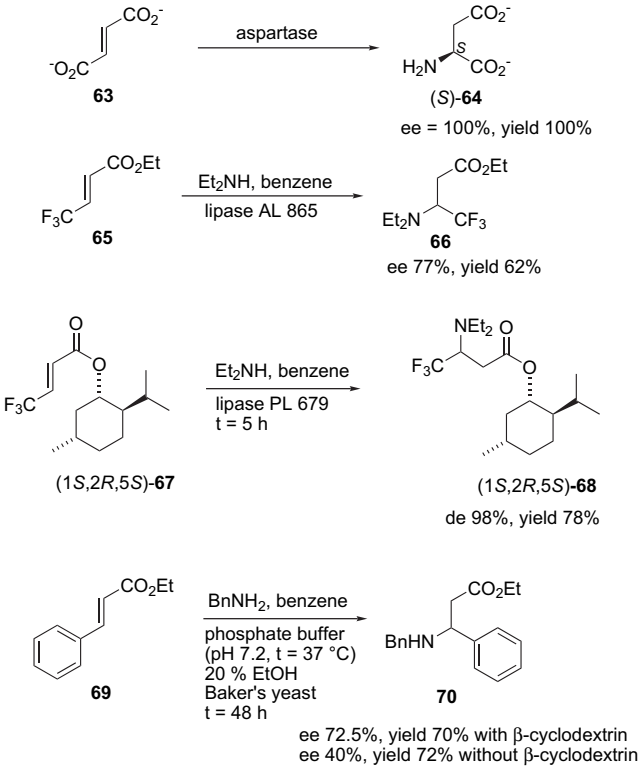
has also been observed to catalyse the ring opening of the methyl ester of penicillin G (**10**).[202]

PLE has limited use in the resolutions of β-amino acids. This can be seen in the hydrolysis of methyl *N*-benzoyl-3-aminobutanoic acid, which proceeds with low enantioselectivity.[203]

3. Other biotransformations

3.1. Michael-type additions

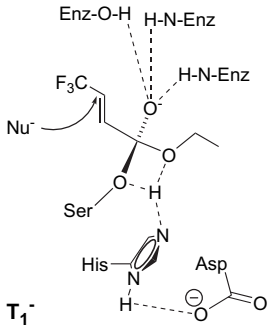
Lyases [EC 4.b.c.d] catalyse the addition of small molecules to C=C, C=N or C=O bonds, or the reverse reaction. Lyases may possess a high synthetic potential, but poor commercial availability hinders their use. As one of the most successful examples, the aspartase-catalysed [EC 4.3.1.1] addition of ammonia to fumaric acid **63** has been operated commercially for the production of (*S*)-aspartic acid, (*S*)-**64**, on a multithousand-ton scale by diverse producers (Scheme 37).[204,205] Even though the method utilising aspartase looks appealing, the enzyme has proved to be very substrate specific.



Scheme 37. Towards β^3-amino acids by Michael addition.[206–208]

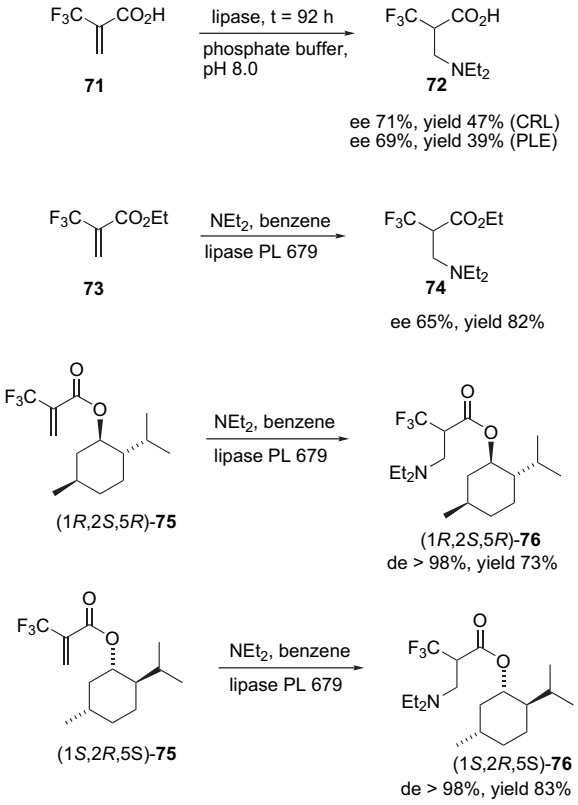
Another strategy is the use of lipase catalysis in the Michael-type additions. The method suffers from relatively low enantiopurities of the products, but is of high value in the future, in the expectation that more suitable lipases are found or developed. The Michael addition is not the natural reaction of lipases, but may take place if the first anionic tetrahedral intermediate serves as a template for the addition of a nucleophile (Scheme 38). Thus, the formation of **66** by the addition of diethylamine to ethyl (*E*)-4,4,4-trifluoro-2-butenoate **65** with various lipases has been tested (Scheme 37).[206,207] Lipase AL 865 from *Achromobacter* is one of

the best enzymes, with 77% product ee and 62% yield. The reaction has not been reported with ethyl (*E*)-2-butenoate. Thus, the necessity of fluorines as double-bond activators remains obscure. A further improvement has been achieved by using the (1*S*,2*R*,5*S*)-menthol ester **67** as a Michael acceptor (78% yield and 98% de of (1*S*,2*R*,5*S*)-**68**). Baker's yeast-catalysed Michael addition of various amines to ethyl *trans*-cinnamate **69** has also been reported.[208] The presence of β-cyclodextrin has been observed to increase the ee of the product **70** from 40 to 72.5%, the yields being around 70%. The absolute configurations were not determined, and the possible side products as a result of ester hydrolysis were not mentioned.



Scheme 38. Mechanism of Michael addition with lipases.

β²-Amino acids have also been obtained by the lipase-catalysed Michael addition (Scheme 39).[206,207,209] Lipases from *Candida rugosa* (CRL) and pig liver esterase (PLE) are able to catalyse the reaction of **71** with diethylamine, even though the enantiopurites and yields of the product **72** remain low.

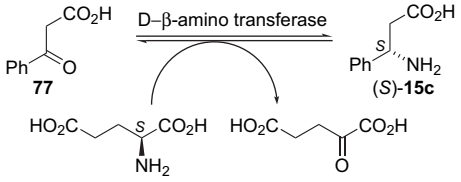


Scheme 39. Towards β²-amino acids by Michael addition.[206,207,209]

The use of lipase PL 679 and the esterified substrate **73** allows an improved yield of the product **74**. For the addition of diethylamine to 2-trifluoromethyl-2-propenoic acid menthol esters **75** catalysed by lipase PL 679, excellent diasteroselectivities (over 98% de) of the product **76** have been obtained with both enantiomers of menthol.

3.2. Transferases

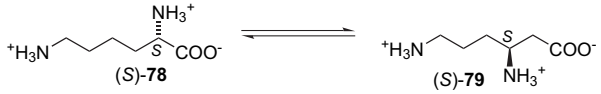
Transferases [EC 2.b.c.d] have not yet found widespread use in organic synthesis. Most aminotransferases (EC 2.6.1) require a cofactor that is often pyridoxal-5-phosphate. The use of β-aminotransferases has recently been introduced especially for the preparation of 3-amino-3-phenylpropanoic acid (Scheme 40).[210] D-β-Amino transferase from *Variovorax paradoxus* and L-β-amino transferase from *Alcaligenes eutrophus* catalyse the reductive amination of **77** into (*S*)- and (*R*)-β-amino acids **15c**, respectively. In this system, the inexpensive cofactors, (*S*)-glutamic acid and (*S*)-alanine, respectively, are oxidised into the corresponding keto acids. The reactions yield exclusively one enantiomer. For the reverse reaction, various racemic β-amino acids were subjected to enzymatic reaction conditions, and consumption of the other enantiomer was observed to take place typically within 24 h. Even though the exact conversion was not determined, the results suggest a wide substrate specificity. Gram-scale reactions were not performed.



Scheme 40. D-β-Amino transferase-catalysed reaction.[210]

3.3. Isomerases

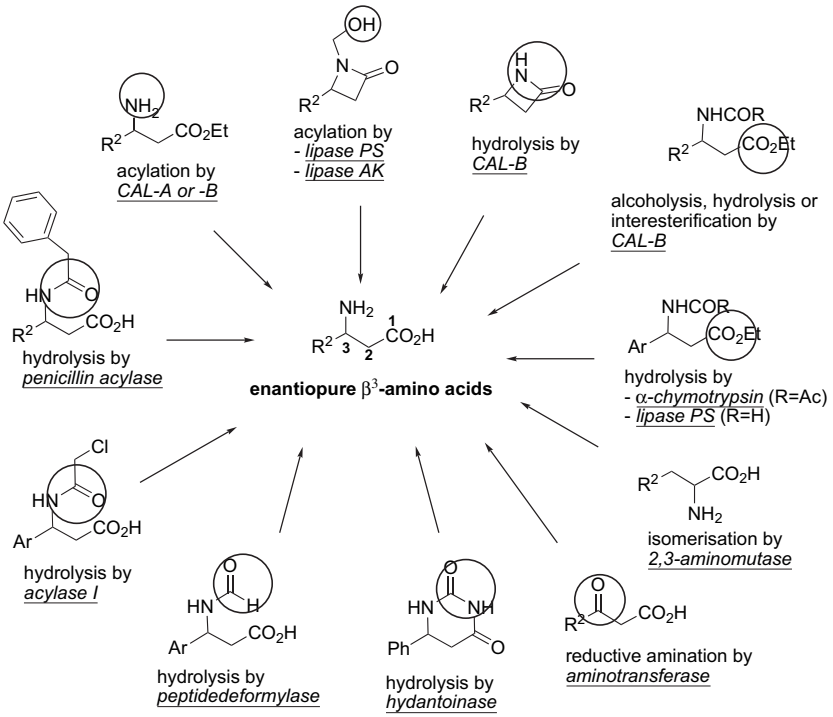
Enzymes in the class number five consist of isomerases. Their subclass [EC 5.4.3] encompasses enzymes transferring amino groups. Among these, enzymes capable of isomerisation of L-amino acids into L-β-amino acids may find synthetic use in the future, e.g., lysine 2,3-aminomutase catalyses the interconversion of L-lysine (*S*)-**78** and L-β-lysine (*S*)-**79** (Scheme 41).[211] This is the first step in the metabolism of lysine into acetate. Lysine 2,3-aminomutase has been claimed to accept also other substrates such as L-alanine, L-aspartate and L-glutamate.[212] At present, there is too little information available on aminomutases to assess their full synthetic potential.



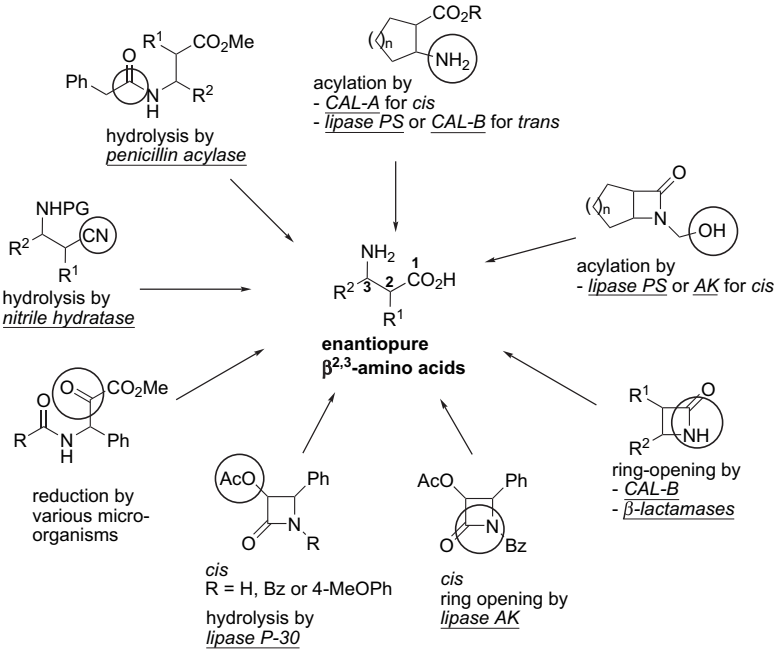
Scheme 41. Natural reaction of lysine 2,3-aminomutase.[212]

4. Conclusions

The enzymatic methods for the preparation of β³- and β²,³-amino acids have been summarised in Schemes 42 and 43,



Scheme 42. Synthesis of enantiopure β^3-amino acid derivatives by enzymatic resolution. The reactive functional group is circled.



Scheme 43. Preparation of enantiopure $\beta^{2,3}$-amino acid derivatives by enzymatic kinetic resolution. The reactive functional group is circled.

respectively. Thus far, the most frequently used methods are based on kinetic resolution with hydrolytic enzymes. The presence of amino and ester functionalities in the substrates enables the development of the various resolution methods. Thus, the highly enantioselective hydrolysis of a phenylacetyl group by penicillin acylase was the first successful approach that is applicable to the preparation of a wide range of enantiopure β^3- and $\beta^{2,3}$-amino acids. Other hydrolytic enzymes with relatively strictly targeted reaction possibilities are acylase I from porcine kidney and α-chymotrypsin. As recently introduced methods, the potency of peptide deformylase, hydantoinases, aminotransferases, 2,3-aminomutases and nitrilases/nitrile hydratases cannot be fully assessed at the present time. β-Lactamase-catalysed $\beta^{2,3}$-lactam ring opening proceeds with high enantioselectivity. Extendability of the method to β^3-amino acids is not known.

Lipases are the most utilised and also the most exploited enzymes for the preparation of β-amino acids and their analogues. Lipase PS from *B. cepacia* (lipase PS) and lipases A

and B from *C. antarctica* have proved to be the most prominent catalysts, indicating acceptance for a wide variety of substrates (β-amino acids, β-amino esters, β-amino nitriles, β-lactams and N-hydroxymethylated β-lactams). Generally, CAL-A catalysis allows the kinetic resolution of acyclic β^3-amino esters and alicyclic *cis*-$\beta^{2,3}$-amino esters of various types, whereas lipase PS is excellent for the kinetic resolution of alicyclic *trans*-$\beta^{2,3}$-amino esters. Noteworthy is the CAL-B-catalysed β-lactam ring opening, even though the problems of long reaction times and the control of water activity still need to be solved. CAL-B-catalysed N-acylation is, however, less useful than CAL-A- and lipase PS-catalysed N-acylation of amino esters. The reason is the low chemoselectivity of CAL-B, i.e., simultaneous interesterification and N-acylation with achiral acyl donors. The use of isopropyl methoxyacetate as an acyl donor has allowed N-acylation without interesterification also with CAL-B. Lipases PS and AK have been especially useful for the acylation of N-hydroxymethylated β-lactams, even though the method is sometimes hampered by reverse hydrolysis.

Lipases P-30 and AK exhibit high enantioselectivity in the resolution of *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine, the Taxol C-13 side chain. The resolutions are based on hydrolysis of acetyl groups or lipase AK-catalysed β-lactam ring opening. Enantioselective reduction of keto groups has also been used for obtaining the product.

The applicability of the above-mentioned methods to the preparation of enantiopure β^2-amino acids has not been extensively studied, even though they are also valuable synthons. Thus far, α-methyl-β-alanine is the only β^2-amino acid the enantiomers of which have been prepared by kinetic resolution. CAL-A and -B display low enantioselectivities in the kinetic resolution. The high chemoselectivity of CAL-A (allowing N-acylation) and low chemoselectivity of CAL-B (allowing interesterification) with carboxylic acid esters have been exploited in two successive kinetic resolutions on a gram scale.

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Biographical sketch

Arto Liljeblad was born in 1974 in Pori, Finland. He graduated with an M.Sc. in organic chemistry from the University of Turku in 2000. He received his PhD under the supervision of Professor Liisa T. Kanerva in February 2005 in the same University. His research focuses on the enzymatic kinetic and dynamic kinetic resolution of non-natural α- and β-amino acids.

Professor Liisa T. Kanerva was born in Salo, Finland in 1947. She received her M.Sc. in organic chemistry from the University of Turku in 1973 and her PhD in 1983. In 1987, she was appointed as a docent in physical organic chemistry in the University of Turku. In 1988–89 she spent a period in M.I.T. with Professor Alexander M. Klibanov. Since returning to the University of Turku, her group has been active in research where enzymes have been used for the preparation of enantiopure compounds, lipase-catalysed kinetic resolution of amino esters being one of the main fields. In 1992, she was appointed as a Professor of Medical Chemistry and, in 2000, Professor of Synthetic Drug Chemistry.

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Development of highly fluorescent photochromic material with high fatigue resistance

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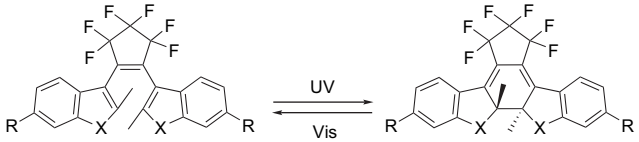
Abstract—Efficient and reversible fluorescence modulation with excellent photo-stability was achieved from a sulfone form of diacetyl diarylethene, 1,2-bis(6-acetyl-2-methyl-1-benzothiophene-1,1-dioxide-3-yl)perfluorocyclopentene (DABTFO4). The DABTFO4 emits strong fluorescence in the closed-ring isomer even in the absence of extra fluorophores. The fluorescence quantum yield, fatigue resistance, and photo-cyclization yield of DABTFO4 were significantly improved compared with the unsubstituted 1,2-bis(2-methyl-1-benzothiophene-1,1-dioxide-3-yl)perfluorocyclopentene (BTFO4) and the sulfide analogue, 1,2-bis(6-acetyl-2-methyl-1-benzothiophene-3-yl)perfluorocyclopentene (DABTF6).

1. Introduction

Photochromic materials have attracted extensive attention due to their potential applications in photonics such as photo-switching and optical memory systems.[1] Thermal stability and fatigue resistance are important considerations in the design of photochromic systems and in this consideration, diarylethenes (Scheme 1) are one of the most promising candidate for the systems.[2] According to Irie et al.,[3] 1,2-bis(2-methyl-1-benzothiophene-3-yl)perfluorocyclopentene (BTF6) is highly fatigue resistant and can carry out write/erase cycles more than 10,000 times without significant loss of performance. Nondestructive readout is another consideration to avoid interference with the photochromism. Among nondestructive readout methods, measuring fluorescence changes upon photochromic reaction is the promising method due to its single molecular detection sensitivity.[4] Previous works on the fluorescence based photochromic readout system adopted PPV,[5] porphyrin,[6] Lucifer yellow,[7] and metal complexes[8] as a fluorescence chromophore, rather than photochromic diarylethenes themselves. Those systems have the fluorescence changes upon photo-reaction based on energy transfer.[9] To utilize the photochromic diarylethene as the fluorophore, it is important to develop the system, which emits light in the closed-ring isomer and ideally enables the infinite signal change. However, in the diarylethene system, the fluorescence was observed when the molecule exists in the form of open-ring isomer, in general. Therefore, the sensitivity obtained in the system depends on the photo-cyclization yield because the unreacted open-ring isomer still emits fluorescence. There have been reports on the fluorescence of the closed-ring isomer by Lehn and Fernández-Acebes[10a] and Irie et al.[10b] However, Lehn and Fernández-Acebes adapted a tungsten metal complex as an emitter, which resulted in only fivefold signal change upon photo-cyclization due to same spectral features in open- and closed-ring isomer. Irie et al. reported a diarylethene derivative, which emits fluorescence upon photo-cyclization, but the fluorescence intensity of the closed-ring isomer is still weaker than that of the open-ring isomer.



***o*-BTF6** X = S, R = H
***o*-DABTF6** X = S, R = acetyl
***o*-BTFO4** X = SO_2, R = H
***o*-DABTFO4** X = SO_2, R = acetyl

***c*-BTF6** X = S, R = H
***c*-DABTF6** X = S, R = acetyl
***c*-BTFO4** X = SO_2, R = H
***c*-DABTFO4** X = SO_2, R = acetyl

Scheme 1. Photochromic reaction of diarylethene derivatives.

Keywords: Photochromic reaction; Diarylethene; Fluorescence modulation; Fatigue resistance.
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In our previous study, we found that 1,2-bis(2-methyl-1-benzothiophene-1,1-dioxide-3-yl)perfluorocyclopentene (BTFO4) is very suitable for the nondestructive fluorescence readout application because of the high fluorescence intensity of the closed-ring isomer.[11] However, the photo-stability of BTFO4 is rather worse compare with unoxidized diarylethene, BTF6. As part of a program for the design of an efficient and highly fluorescent photochromic material with high photo-stability, we report herein a new diarylethene molecule, 1,2-bis(6-acetyl-2-methyl-1-benzothiophene-3-yl)-perfluorocyclopentene (DABTFO4), a modified structure of the BTFO4, which demonstrates good fluorescence and photochromic properties with excellent photo-stability eligible for the nondestructive readout.

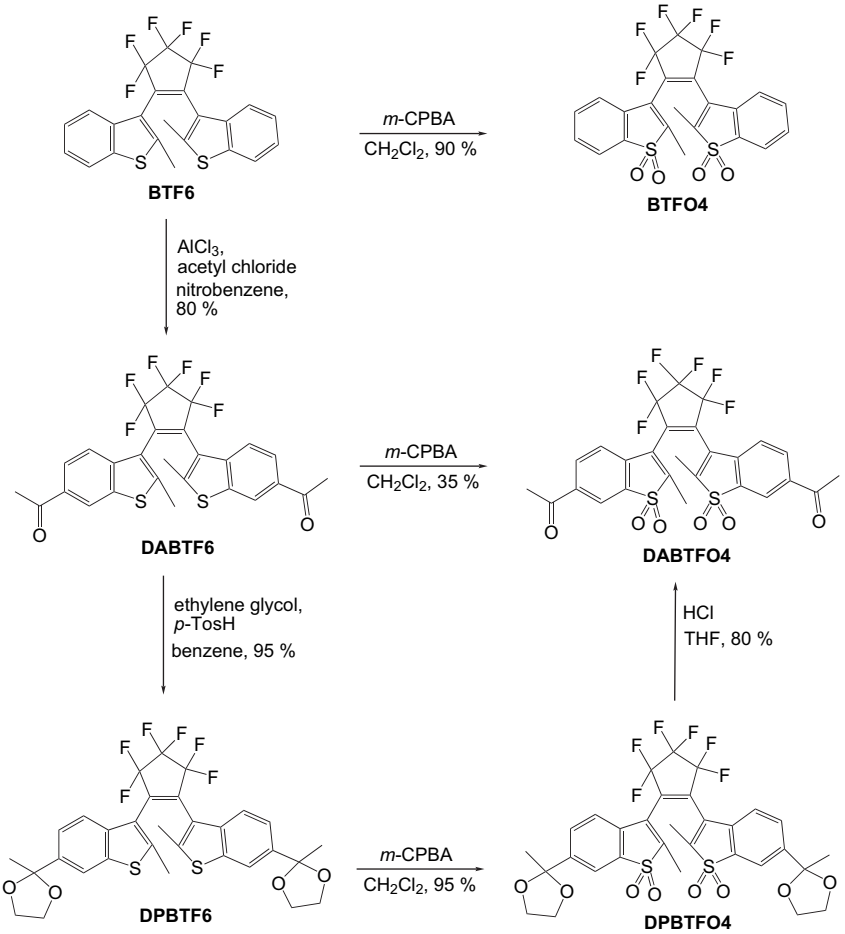
2. Results and discussion

2.1. Synthesis

Diarylethenes were prepared according to Scheme 2. The syntheses of 1,2-bis(2-methyl-1-benzothiophene-3-yl)perfluorocyclopentene (BTF6) and 1,2-bis(6-acetyl-2-methyl-1-benzothiophene-3-yl)perfluorocyclopentene (DABTF6) were previously described in the literature.[12] The direct oxidation of BTF6 and DABTF6 using 3-chloroperbenzoic acid gave BTFO4 (90%)[11] and DABTFO4 (35%), respectively. It was thought that the low yield obtained in the DABTF6 oxidation might be due to the Baeyer–Villiger oxidation type side reaction. Thus, to increase the yield of DABTFO4 formation, the carbonyl group of DABTF6 was converted to 1,3-dioxolane group[13] (DPBTF6) before the oxidation. The subsequent oxidation of DPBTF6 using *m*-CPBA followed by deprotection of the dioxolane group gave DABTFO4 in high yield (72% in three steps).

^{1}H NMR of the open-ring isomer of DABTFO4 (o-DABTFO4) showed two methyl peaks at 2.26 and 2.11 ppm corresponding to parallel (p-) and anti-parallel (ap-) form of o-DABTFO4, respectively. The relative population between the p- and ap-conformer calculated from the integration of the two peaks was determined to be 50:50, which is similar to that of o-BTFO4, however, quite different from that of o-BTF6 and o-DABTF6 (35:65).[14]

The photo-cyclization process of DABTFO4 under UV light (312 nm) was followed using ^{1}H NMR in $CDCl_3$ (5×10^{-3} M). Interestingly, a new singlet peak at 1.87 ppm, which may correspond to the closed-ring isomer of DABTFO4 (c-DABTFO4) was appeared along with decreasing intensities of o-DABTFO4 signals. At the photostationary state, the signals of o-DABTFO4 were almost disappeared indicating that the photo-cyclization yield of the reaction is higher than 99%, which is far better than that of other diarylethenes such as BTFO4 (80%), DABTF6 (73%), and BTF6 (43%).



Scheme 2. Synthesis of BTFO4, DABTF6, and DABTFO4.

2.2. Photophysical properties

2.2.1. Absorption spectra. Ground-state absorption spectra of (A) o-BTF6, (B) o-BTFO4, (C) o-DABTF6, and (D) o-DABTFO4 in ethyl acetate (1.0×10^{-5} M) at room temperature are shown in Figure 1 (solid line). The dashed line in Figure 1 represents the absorption spectra of the photostationary state of (A) BTF6, (B) BTFO4, (C) DABTF6, and (D) DABTFO4 in ethyl acetate at room temperature following UV illumination for 10 min. Photo-cyclization upon UV exposure, yielding the closed-ring isomer leads to spectral change toward longer wavelength compared to the corresponding open-ring isomer. A key finding is that the absorption maximum (λ_{max}) of the closed-ring isomer of the oxidized BTF6 derivatives (c-BTFO4 and c-DABTFO4) substantially deviate from that of the corresponding BTF6 derivatives (c-BTF6 and c-DABTF6). The c-DABTF6 showed two absorption bands at 370 and 552 nm, whereas the c-DABTFO4 showed only one absorption band at 412 nm. The spectral feature of the c-DABTFO4 is similar to that of previously reported c-BTFO4 molecule, except the slight red-shift of the absorption maximum from 398 to 412 nm and increase in molar absorption extinction coefficient from 21,000 to 27,900 $M^{-1}\,cm^{-1}$ in c-DABTFO4. Table 1 summarizes the photophysical properties of diarylethene derivatives.

2.2.2. Fluorescence spectra. Steady-state fluorescence spectra of o-DABTF6 and o-DABTFO4 with 315 nm photo-excitation in ethyl acetate (1.0×10^{-5} M) are shown in Figure 2A and B (solid line), respectively. Upon photocyclization, the fluorescence intensity of c-DABTF6 (λ_{ex} 552 nm) was decreased, whereas that of c-DABTFO4 (λ_{ex} 412 nm) was significantly increased as shown in Figure 2A and B (dashed line), respectively. The inset of Figure 2B shows the fluorescence spectra of c-DABTFO4 and c-BTFO4 (λ_{ex} 398 nm), indicating that the fluorescence intensity of c-DABTFO4 is five times stronger than that of

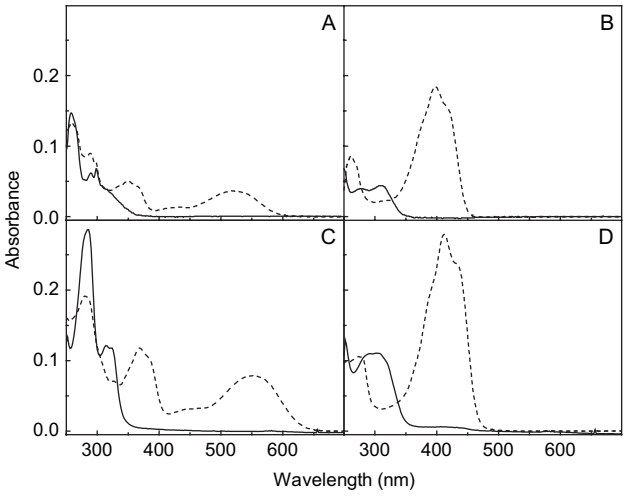


Figure 1. Absorption spectra of (A) BTF6, (B) BTFO4, (C) DABTF6, and (D) DABTFO4 in ethyl acetate (1.0×10^{-5} M) at room temperature; open-ring isomer (solid line), photostationary state (dashed line).

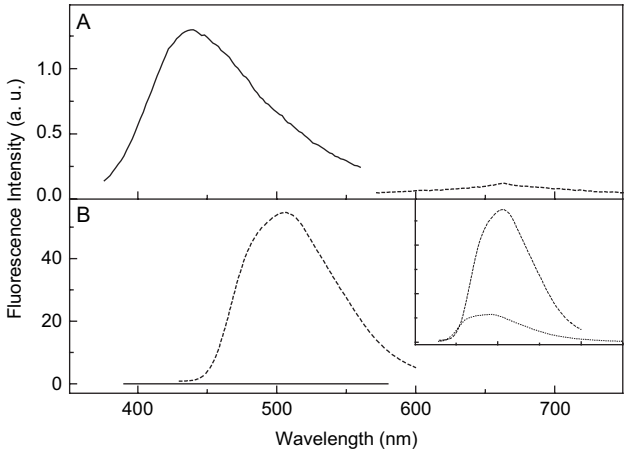


Figure 2. Steady-state fluorescence spectra upon photo-excitation at absorption maximum for (A) o-DABTF6 (solid line) and c-DABTF6 (dashed line), (B) o-DABTFO4 (solid line) and c-DABTFO4 (dashed line) in ethyl acetate (1×10^{-5} M) at room temperature. The inset shows the fluorescence spectra of c-DABTFO4 (dashed) and c-BTFO4 (dotted line).

Table 1. Photophysical properties of diarylethene derivatives

	Absorption λ_{max} (nm)/ ε (10^3 $M^{-1}\,cm^{-1}$)		Emission λ_{max} (nm)/ fluorescence quantum yield (Φ_{em})		Fluorescence intensity ratio (Δ_{fl}) between open-ring and closed-ring isomer[a]	
	Open-ring isomer	Closed-ring isomer[b]	Open-ring isomer[c]	Closed-ring isomer[d]	Δ_{fl} (315 nm excitation)	Δ_{fl} (excitation at λ_{max} of closed-ring isomer)
BTF6	258/16.0 290/6.2 299/6.8	276/14.0 352/12.0 523/10.0	436/0.012	—[e]	1.4	—[e]
DABTF6	286/28.6 316/12.0 324/12.8	276/16.2 368/16.0 552/10.8	430/0.0055	—[e]	2.9	—[e]
BTFO4	276/3.7 308/4.1	262/9.1 398/21.0	464/0.025	492/0.011	2.7	12
DABTFO4	302/11.1	274/10.6 412/27.9	484/0.0027	506/0.036	0.34	58

[a] Determined at photostationary state.
[b] Calculated from UV spectra by using Eq. $[A]_{PSS}=[A]_{open}\times(1-\text{conversion})+[A]_{closed}\times(\text{conversion})$. Ignored the shoulder peak.[18]
[c] Determined using fluoranthene as the reference (0.30:312 nm photo-excitation in cyclohexane).
[d] Determined using 3-aminofluoranthene as the reference (0.53:400 nm photo-excitation in cyclohexane).
[e] Not determined due to weak signal.

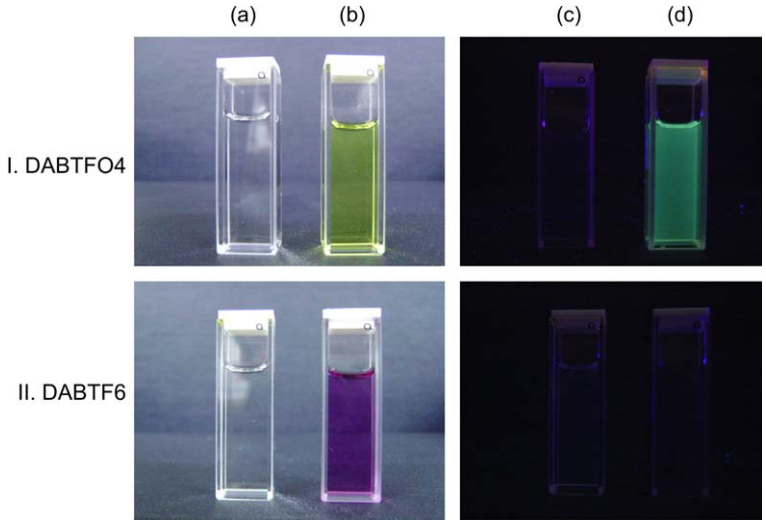


Figure 3. Photographs of solutions containing DABTFO4 (1.0×10^{-4} M in ethyl acetate) (I): color of (a) o-DABTFO4 (before UV irradiation under room light) and (b) c-DABTFO4 (under photostationary state after UV irradiation); fluorescence (photo-excitation with 365 nm UV lamp) of (c) o-DABTFO4 (no emission), and (d) c-DABTFO4 (green emission), as compared to those of o-DABTF6 and c-DABTF6 (no emission) in II, respectively.

c-BTFO4. The fluorescence quantum yield of c-BTFO4 and c-DABTFO4 is determined to be 0.011 and 0.036, respectively, using 3-aminofluoranthene (0.53 in cyclohexane) as the reference upon 400 nm photo-excitation (Table 1). Thus, it is clear that the introduction of acetyl group at 6 and 6′ positions as well as sulfonyl group at 1 and 1′ positions of the benzothiophene ring in diarylethene unit significantly enhances the fluorescence quantum yield of the closed-ring isomer and leads spectral shift to red (14 nm). Such a high fluorescence quantum yield of the c-isomer is unique to the oxidized diarylethenes. Diarylethenes have been known to exhibit fluorescence only in open-ring isomer. Upon oxidation of sulfide to sulfone, however, they show high fluorescence in the closed-ring isomer even though they do not contain extra fluorophore, as we reported before for BTFO4.[11] As a result of increasing fluorescence quantum yield, the photochromism and photo-induced fluorescence modulation of DABTFO4 could be easily observable with naked eyes. Figure 3 shows photographs exhibiting color change and emission of the solution containing DABTFO4 and DABTF6 (1.0×10^{-4} M in ethyl acetate). The colorless solution containing o-DABTFO4 (no emission) changed to yellow upon exposure to a UV light to form c-DABTFO4, which emits strong green light upon 365 nm photo-excitation. On the other hands, DABTF6 shows color change to a reddish purple upon photo-cyclization, which doesn't have any emission under the same condition.

2.3. Photochromic properties

2.3.1. Ring closing and ring opening quantum yield. Figure 4 represents the photochromic change of BTF6 (open square), DABTF6 (open circle), BTFO4 (closed square), and DABTFO4 (closed circle) by alternating UV and visible illumination as a function of time. The absorption change was monitored at absorption maximum of the closed-ring isomer (542 nm for DABTF6, 412 nm for DABTFO4, 524 nm for BTF6, and 398 nm for BTFO4). Upon 312 nm irradiation, the absorbance at λ_{max} of the samples was increased, while it was decreased upon visible light

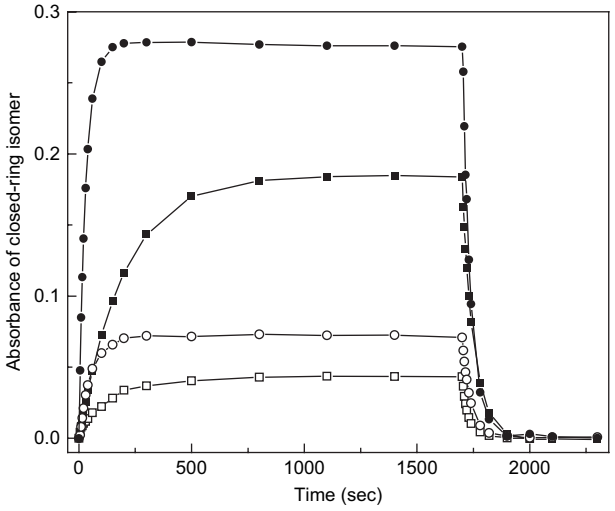


Figure 4. Photochromic behavior of BTF6 (open square), DABTF6 (open circle), BTFO4 (closed square), and DABTFO4 (closed circle) in ethyl acetate solution (1×10^{-5} M) at room temperature upon alternating 312 nm and visible illumination (BTF6: 523 nm, DABTF6: 552 nm, BTFO4: 398 nm, DABTFO4: 412 nm) using Xenon lamp as a function of time.

illumination using Xenon lamp. The cyclization and ring opening quantum yield of DABTF6, DABTFO4, and BTFO4 were determined using Eqs. 1 and 2, respectively.[15] BTF6 was used as a reference.[16]

$$\ln\frac{\mathrm{Abs}(\infty)-\mathrm{Abs}(0)}{\mathrm{Abs}(\infty)-\mathrm{Abs}(t)} = 2.303\times10^{3}\times I_0\times\varepsilon_0\times\Phi_{o-c}\frac{C_0}{C_c(\infty)}t \quad (1)$$

$$\ln\frac{\mathrm{Abs}(0)}{\mathrm{Abs}(t)} = 2.303\times10^{3}\times I_0\times\varepsilon_0\times\Phi_{c-o}t \quad (2)$$

Where Abs(∞) is the photostationary state, Abs(t) is the absorbance at λ_{max} of closed-ring isomer at time t. I_0 is the irradiation light intensity, and ε_o and ε_c are molar extinction coefficients of open and closed-ring isomer at the irradiation

Table 2. Photochromic properties of diarylethene derivatives in ethyl acetate

	Quantum yield		By-product formation time constant (min)[c]
	Cyclization[a]	Ring opening[b]	
BTF6	0.31[d]	0.28[d]	1300±100
DABTF6	0.46	0.15	11,000±1000
BTFO4	0.22	0.061	900±50
DABTFO4	0.40	0.055	3300±200

[a] Measured at 312 nm.
[b] Measured at λ_{max}.
[c] Fitted with exponential decay.
[d] Taken from Ref. 16.

wavelength, respectively. Φ_{o-c} and Φ_{c-o} are cyclization and ring opening quantum yield and C_0 and C_c are the total concentration and the concentration of closed-ring isomer at the photostationary state, respectively. The cyclization and ring opening quantum yield are summarized in Table 2.

2.3.2. Fluorescence modulation. We also investigated the photochromic properties of DABTFO4 in ethyl acetate (1.0×10^{-5} M) at room temperature by modulating the fluorescence intensity using alternating UV and visible light irradiation. Figure 5 illustrates the photochromically driven fluorescence modulation recorded at 505 nm with 412 nm photo-excitation as a function of time. Upon UV irradiation, the fluorescence intensity was increased (unshaded regions), whereas upon visible light illumination, it was decreased to the original intensity (shaded regions). For comparison, the photochromically driven fluorescence modulation of BTFO4 are also shown in Figure 5.

We have found two important features for DABTFO4 compared with the unsubstituted BTFO4 system. First, the photo-induced fluorescence change (Δ_{fl}) is much significant in DABTFO4 (Δ_{fl}=58) than in BTFO4 system (Δ_{fl}=12), as determined from the ratio of the maximum (closed-ring isomer) and minimum (open-ring isomer) fluorescence intensity (Table 1). It is desirable to have high fluorescence contrast (Δ_{fl}) for signal readout, which is essential for nondestructive photochromic readout application. Second, as mentioned before in Figure 4, the photo-cyclization rate is much improved in DABTFO4 and the ring opening rate is slightly improved compared with BTFO4, which is related to the writing (recording) and erasing speed in the erasable optical memory application. In addition, we have not observed significant fluorescence intensity decay while reading the signal with 412 nm light for longer than 1 h, indicating that DABTFO4 can be applied as an active media for a nondestructive optical readout system in the optical memory or all-optical switching device.

2.3.3. Fatigue properties. Finally, we investigated the fatigue properties of various types of diarylethenes in ethyl acetate (1.0×10^{-5} M) at room temperature by UV light irradiation for 500 min. Figure 6 illustrates the absorbance changes of diarylethenes (BTF6, open square; DABTF6, open circle; BTFO4, closed square; and DABTFO4, closed circle) at λ_{max} of closed-ring isomer as a function of UV illumination time. Initially, the absorbance was increased to A_t (t=0) as a result of photo-cyclization from open-ring isomer to closed-ring isomer and then decreased probably due to an irreversible photo-reaction (Scheme 3), which is strongly related with fatigue property.[17] Interestingly, as shown in Figure 6, the substitution of acetyl group at 6-position of benzothiophene subunit leads to a significant improvement in the photo-stability of the oxidized diarylethene (DABTFO4) as compared with BTFO4 (3300 vs 900 min). Similar effect was observed for DABTF6 and BTF6 (DABTF6: 11,000 min vs BTF6: 1300 min). Table 2 summarizes the by-product formation rate constant of diarylethene derivatives. Considering the photo-cyclization rate (DABTFO4: 0.5 min and BTFO4: 3.5 min) and the photo-induced fluorescence change (DABTFO4: Δ_{fl}=58 and BTFO4: Δ_{fl}=12) of the oxidized diarylethenes, the overall fatigue property of DABTFO4 have improved more than 140 times compared with BTFO4. This result suggests that DABTFO4 is an ideal material for photo-induced fluorescence modulation and other applications based on photochromism with high fatigue resistance.

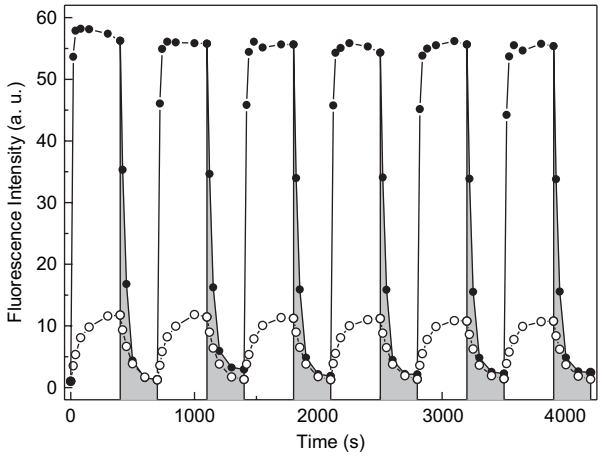


Figure 5. Modulation of fluorescence intensity of BTFO4 (open circle, λ_{ex}=398 nm, λ_{em}=492 nm) and DABTFO4 (closed circle, λ_{ex}=412 nm, λ_{em}=505 nm) in ethyl acetate (1×10^{-5} M) upon alternating 312 nm UV lamp (unshaded areas) and visible light (shaded areas) illumination.

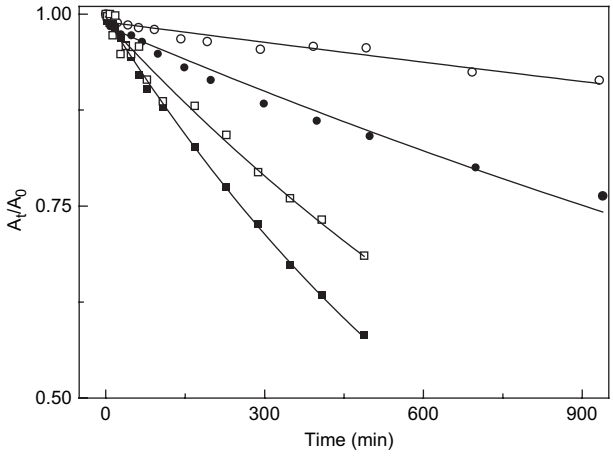
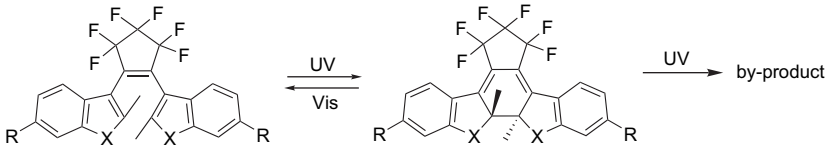


Figure 6. The absorbance changes of BTF6 (open square), DABTF6 (open circle), BTFO4 (closed square), and DABTFO4 (closed circle) at absorption maximum of closed-ring isomer as a function of UV illumination time in ethyl acetate (1×10^{-5} M). The data are fitted with exponential decay (line) and the fitting data (photo-reaction time) represent the time to reach 37% of its initial absorbance following UV illumination.



Scheme 3. Photochromic reaction and the by-products formation of diarylethene derivatives.

3. Conclusion

In summary, by diacetylation and oxidation of BTF6, we have synthesized highly fluorescent photochromic material with high fatigue resistance. The fluorescence quantum yield of c-DABTFO4 was enhanced significantly, and the photochromic properties such as cyclization yield and the photostability of DABTFO4 were greatly improved compared with unsubstituted BTFO4. Overall, the results suggest that DABTFO4 is a challenging material to realize a photo-induced fluorescence modulation applicable for non-destructive fluorescence readout memory and switch applications based on a reversible photochromic conversion.

4. Experimental

4.1. General

Octafluorocyclopentene was purchased from TCI. All other reagents and spectrograde solvents were purchased from Aldrich. Melting points were determined with Laboratory Devices Mel-Temp 3.0 melting point apparatus. The ^{1}H and ^{13}C NMR spectra were obtained using JEOL JNM-AL300 spectrometer at 300 and 75 MHz in $CDCl_3$, respectively, with tetramethylsilane as the internal reference. HRMS spectra were obtained with JEOL JMS-700 spectrometer. FTIR measurements were performed using a JASCO FTIR-430 instrument. UV absorption spectra were recorded on a Shimadzu UV-3100 spectrophotometer in spectroscopy grade ethyl acetate. Fluorescence spectra were collected in spectroscopy grade ethyl acetate on Fluoro Max-2 spectrophotometer equipped with a 150 W ozone-free xenon lamp. UV and visible irradiations were performed with standard lamps used for visualizing TLC plates (VL6L; 312 nm, 8 mW cm^{-2}) and a 100 W tungsten lamp and the samples were placed in a glass chamber maintained at room temperature. The photochromic changes as a function of time were carried out using 500 W Xe lamp (Newport 74000) equipped with a monochromator (Newport 66921) (312 nm–408–410 μW, 398 nm–1.3 mW, 412 nm–1.5 mW, 406 nm–1.4 mW, 524 and 528 nm–2.6 mW, and 550 nm–2.8 mW). Then, photochromic reaction quantum yields were determined according to the method described in Ref. 15. Flash column chromatography was performed with Merck silica gel 60 (70–230 mesh). BTF6 and DABTF6 were synthesized according to the literature procedure.[12] ^{1}H NMR (5×10^{-3} M, $CDCl_3$) of closed-ring isomer and conversion were determined after irradiation at 312 nm using UV lamp until reached photostationary state.

4.1.1. 1,2-Bis(2-methyl-1-benzothiophene-1,1-dioxide-3-yl)perfluorocyclopentene (BTFO4). A mixture of o-BTF6 (1.0 g, 2.1 mmol), and 70% 3-chloroperbenzoic acid (2.9 g, 11.8 mmol) in dichloromethane (50 mL) was stirred for 24 h at room temperature. The solution was washed with a saturated solution of Na_2SO_4. The organic layer was separated and dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (silica gel) yielded o-BTFO4 in 90% yield. Mp 294 °C (decomp.); ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.78 (d, J=7.2 Hz, ap-2H), 7.72 (d, J=7.2 Hz, p-2H), 7.66–7.55 (m, ap-4H), 7.50–7.41 (m, p-4H), 7.15 (d, J=7.2 Hz, ap-2H and p-2H), 2.20 (s, p-6H), 2.06 (s, ap-6H), ap:p=50:50; FTIR (KBr-cast): 2995, 2952, 2927, 2851, 1459, 1451, 1433, 1312, 1278, 1248, 1225, 1205, 1172, 1144, 1114, 1081, 1060, 1040, 991, 963, 946, 849, 836, 825, 770, 762, 744, 736, 690, 558, 541, 525 cm^{-1}; HRMS (70 eV, EI) *m/z* calcd for $C_{23}H_{14}F_6O_4S_2$: 532.0244; found: 532.0237; ^{1}H NMR (300 MHz, $CDCl_3$) of the closed-ring isomer (c-BTFO4): δ=8.26 (d, J=7.5 Hz, 2H), 8.04 (d, J=7.5 Hz, 2H), 7.88–7.71 (m, 4H), 1.85 (s, 6H).

4.1.2. 1,2-Bis[6-{1′-(1″,3″-dioxolanyl)ethyl}-2-methyl-1-benzothiophene-3-yl]perfluorocyclopentene (DPBTF6). A mixture of o-DABTF6 (0.88 g, 1.6 mmol), ethylene glycol (2 mL, 32 mmol), and *p*-toluenesulfonic acid monohydrate (61 mg, 0.32 mmol) in benzene (300 mL) was refluxed for two day with a Dean–Stack condenser. The solution was washed with a saturated solution of $NaHCO_3$. The organic layer was separated and dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (silica gel) yielded o-DPBTF6 in 95% yield. Mp 87–89 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.81 (s, ap-2H), 7.71 (s, p-2H), 7.59 (d, J=8.4 Hz, ap-2H), 7.49–7.44 (m, ap-2H and p-2H), 7.27 (d, J=8.4 Hz, p-2H), 4.05–3.99 (m, ap-4H and p-4H), 3.80–3.75 (m, ap-4H and p-4H), 2.47 (s, p-6H), 2.20 (s, ap-6H), 1.67 (s, ap-6H), 1.54 (s, p-6H), ap:p=70:30; HRMS (70 eV, EI) *m/z* calcd for $C_{31}H_{26}F_6O_4S_2$: 640.1177; found: 640.1171; ^{1}H NMR (300 MHz, $CDCl_3$) of the closed-ring isomer (c-DPBTF6): δ=7.82 (d, J=8.1 Hz, 2H), 7.36 (d, J=1.5 Hz, 2H), 7.25 (dd, J_1=8.1 Hz, J_2=1.5 Hz, 2H), 4.06–3.99 (m, 4H), 3.81–3.77 (m, 4H), 1.99 (s, 6H), 1.63 (s, 6H).

4.1.3. 1,2-Bis[6-{1′-(1″,3″-dioxolanyl)ethyl}-2-methyl-1-benzothiophene-1,1-dioxide-3-yl]perfluorocyclopentene (DPBTFO4). The o-DPBTFO4 was prepared in 95% yield using the method to prepare o-BTFO4. Mp 117–119 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=7.89 (s, ap-2H), 7.83 (s, p-2H), 7.70 (d, J=7.8 Hz, ap-2H), 7.50 (d, J=6.9 Hz, p-2H), 7.10–7.04 (m, ap-2H and p-2H), 4.06–3.81 (m, ap-4H and p-4H), 3.77–3.61 (m, ap-4H and p-4H), 2.17 (s, p-6H), 2.04 (s, ap-6H), 1.63 (s, ap-6H), 1.56 (s, p-6H), ap:p=60:40; HRMS (70 eV, EI) *m/z* calcd for $C_{31}H_{26}F_6O_8S_2$: 704.0973; found: 704.0978; ^{1}H NMR (300 MHz, $CDCl_3$) of the closed-ring isomer (c-DPBTFO4): δ=8.19 (d, J=8.5 Hz, 2H), 8.12 (s, 2H), 7.92 (d, J=8.5 Hz, 2H), 4.09

(t, J=7.0 Hz, 4H), 3.80 (t, J=7.0 Hz, 4H), 1.82 (s, 6H), 1.67 (s, 6H).

4.1.4. 1,2-Bis(6-acetyl-2-methyl-1-benzothiophene-1,1-dioxide-3-yl)perfluorocyclopentene (DABTFO4). A solution of o-DPBTFO4 (0.46 g, 0.65 mmol) in THF (25 mL) was added 37% HCl (1 mL). The solution was stirred for 3 h at room temperature. After completion of reaction, H_2O (50 mL) was added, extracted with CH_2Cl_2 (2×50 mL), and washed with aqueous Na_2CO_3 (2×50 mL). The organic layer were dried $MgSO_4$, filtered, and the solvent was removed. The residue was purified by chromatography on silica gel to give o-DABTFO4 (0.32 g) with 80% yield. Mp 128–130 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=8.31 (s, ap-2H), 8.25 (s, p-2H), 8.22 (d, J=8.5 Hz, ap-2H), 8.06 (d, J=8.5 Hz, p-2H), 7.27–7.23 (m, ap-2H and p-2H), 2.67 (s, ap-6H), 2.62 (s, p-6H), 2.26 (s, p-6H), 2.11 (s, ap-6H); FTIR (KBr-cast): 3098, 9067, 3049, 3004, 2923, 1695, 1600, 1569, 1436, 1413, 1318, 1276, 1246, 1202, 1151, 1077, 1043, 994, 956, 913, 844, 805, 734, 682, 667, 643, 612, 601, 570, 537 cm^{-1}; HRMS (70 eV, EI) m/z calcd for $C_{27}H_{18}F_6O_6S_2$: 616.0449; found: 616.0452; ^{1}H NMR (300 MHz, $CDCl_3$) of the closed-ring isomer (c-DABTFO4): δ=8.52 (d, J=1.3 Hz, 2H), 8.41 (dd, J_1=8.5 Hz, J_2=1.3 Hz, 2H), 8.35 (d, J=8.5 Hz, 2H), 2.75 (s, 6H), 1.87 (s, 6H).

4.1.5. Synthesis of DABTFO4 from DABTF6. A mixture of o-DABTF6 (1.0 g, 1.8 mmol) and 70% 3-chloroperbenzoic acid (2.5 g, 10 mmol) in dichloromethane (50 mL) was stirred for 24 h at room temperature. The solution was washed with a saturated solution of Na_2SO_4. The organic layer was separated and dried over $MgSO_4$ and concentrated in vacuo. Flash chromatography (silica gel) yielded o-DABTFO4 in 35% yield.

Acknowledgements

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A new, direct, and efficient synthesis of benzonaphthyridin-5-ones

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Abstract—Microwave-assisted Suzuki cross-coupling reaction of 2-fluorophenylboronic acid with all orthochlorocyanopyridine isomers allowed the rapid syntheses of key intermediates for anionic ring closure, which was performed using potassium hydroxide under microwave irradiation to give benzonaphthyridin-5-ones in high yields.

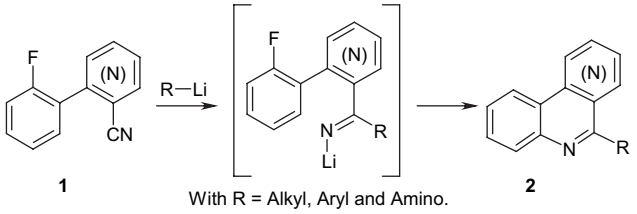
1. Introduction

Benzonaphthyridines are of great interest regarding to their diverse biological activities[1] and as 'aza-analogues' of phenanthridines, which have been widely studied in the field of medicinal chemistry.[2] However their syntheses are not scalable and suffer from a lack of diversity. To our point of view, benzonaphthyridin-5-ones could be useful scaffolds for the syntheses of diverse 5-substituted compounds. In this paper, we wish to report a new and an efficient two-step synthesis of the four benzonaphthyridin-5-one isomers **5a**–**d**. Three of them have already been reported generally with poor to low yield: 6*H*-benzo[*f*][1,7]naphthyridin-5-one **5a**,[3] 6*H*-benzo[*c*][2,7]naphthyridin-5-one **5b**,[3a,4] and 6*H*-benzo[*h*][1,6]naphthyridin-5-one **5c**.[3a,5] The synthesis of 6*H*-benzo[*c*][2,6]naphthyridin-5-one **5d** has not been reported yet.

2. Results and discussion

2.1. Strategy

We hypothesized that a two-step procedure including an anionic ring closure and Suzuki cross-coupling could lead directly to benzonaphthyridinone systems. This strategy was supported by the work of the Begtrup's team[6,7] who demonstrated that anionic ring closure could be a powerful method to synthesize 6-substituted phenanthridines and 5-substituted benzonaphthyridines **2** by the attack of a lithiated species on the nitrile function of biaryl **1** and subsequent intramolecular nucleophilic aromatic substitution of the fluorine atom (Scheme 1).



Scheme 1. Anionic ring closure.

However, the scope of this sequence was still limited to the variety of organometallic derivatives employed to achieve the second step: alkyllithium and lithium amide reagents mainly. In the benzonaphthyridine series, this reaction had only been reported using lithium morpholide as a nucleophile.[7] This is the reason why in order to enlarge the scope of this methodology we planned to prepare the lactam moieties using, this time, the hydroxide ion as the nucleophile.

Before considering the improvement of the anionic ring closure, it was necessary to have an easy access to biaryl systems bearing a cyano group in position 2 and a fluorine atom in position 2′. These biaryl structures could be obtained using the Suzuki–Miyaura cross-coupling reaction.[8] Meanwhile four different partnerships were possible to achieve the cross-coupling (Table 1). The pathway A using orthofluoropyridylboronic derivatives was not usable for two reasons. First these species, for which we described a synthesis,[9] remain very expensive. Second, no synthesis for a 4-fluoro-3-pyridylboronic or 3-fluoro-2-pyridylboronic species is available. The B pathway using orthofluorobenzene halides and orthocyanopyridylboronic acids or esters had already been reported by Hansen and co-workers.[7] But these orthocyanopyridylboronic species are quite unstable[10] and no 2-pyridyl derivative has been described yet. The pathway C was also limited (as pathways A and B) because of the

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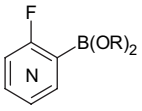
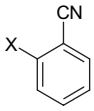
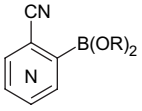
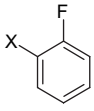
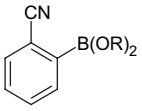
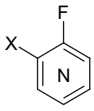
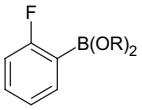
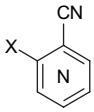
Table 1. Cross-coupling partnerships

Boronics	Halides	Cross-coupling partnerships
		A
		B
		C
		D

expensiveness of fluoropyridine derivatives and the instability of orthocyanophenylboronic species during the cross-coupling reaction.[11] The last partnership D consisted in fusing 2-fluorophenylboronic and orthochlorocyanopyridine **3**. Since we had described a general method for the ortholithiation of cyanopyridines[12] that permitted to synthesize all isomers of orthochlorocyanopyridine **3**, we first decided to apply this last strategy using commercial 2-fluorophenylboronic acid, which was able to furnish the four isomers of benzonaphthyridin-5-one **5a–d** in good conditions.

2.2. Cross-coupling reaction of orthochlorocyanopyridines with 2-fluorophenylboronic acid

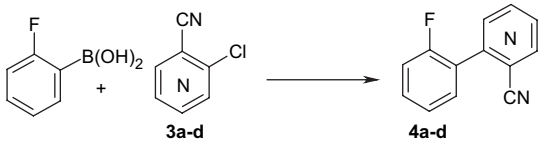
Our first attempt of cross-coupling at 100 °C in DMF with K_3PO_4 and $Pd(PPh_3)_4$ starting from **3b** was disappointing. However, using 2 equiv of 2-fluorophenylboronic acid in order to compensate the protodeboronation side reaction and increasing the reaction time from 24 to 36 h, we obtained a 80% yield. Finally, taking into account the recent results of several groups[13] who had demonstrated that the use of microwave energy could shorten the reaction time in this reaction, we conducted an assisted microwave reaction in a sealed tube. These latter conditions permitted the isolation of **4b** with a good 85% yield after 30 min at 150 °C (Table 2).

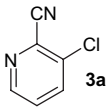
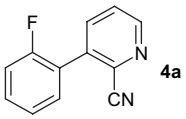
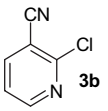
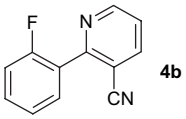
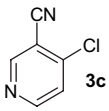
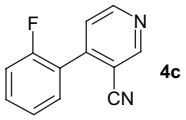
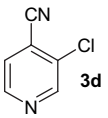
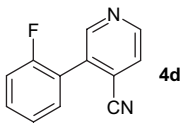
We then applied these reaction conditions to the isomers **3a** and **3d**, which gave **4a** and **4d** with 67 and 77% yield, respectively. In the case of **3c** it was necessary to avoid the side reaction of the chlorine atom in aromatic nucleophilic substitutions, we therefore replaced the K_3PO_4 by CsF to obtain **4c** with a 71% yield.

2.3. Anionic ring closure

To achieve the second step we first evaluated the feasibility of the anionic ring closure with KOH from 4-cyano-3-(2-fluorophenyl)pyridine **4d**. The first attempt with 5 equiv of KOH in refluxing methanol for 24 h only led to the carboxamide **6**. When the temperature was raised to 150 °C in a sealed tube for 1 h, the benzonaphthyridin-5-one **5d** was

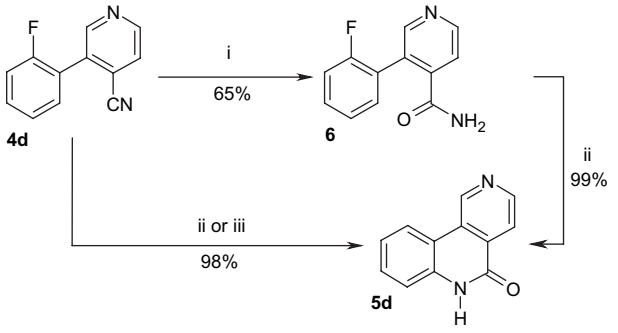
Table 2. Microwave-assisted cross-coupling reaction[a]



Starting materials	Products	Yields (%)[b]
 **3a**	 **4a**	67
 **3b**	 **4b**	85
 **3c**	 **4c**	71[c]
 **3d**	 **4d**	77

[a] Reaction conditions: 1 equiv of aromatic halide, 2 equiv of 2-fluorophenylboronic acid, 5% mol of $Pd(PPh_3)_4$, 2.5 equiv of K_3PO_4, DMF, 150 °C, microwave heating, sealed tube, 30 min.
[b] Isolated yields.
[c] CsF (2.5 equiv) was used instead of K_3PO_4.

obtained in 98% yield. The use of microwave heating conditions reduced the reaction time to 10 min maintaining the same yield (Scheme 2). We then tested the reactivity of the carboxamide **6** under our microwave conditions. Its total conversion into the benzonaphthyridin-5-one **5d** was observed, with no formation of the corresponding carboxylic acid. In the absence of KOH, the carboxamide **6** did not react and only the starting material was recovered. Therefore these experiments showed that the formation of an anion intermediate was needed to achieve the cyclization.



Scheme 2. Anionic ring closure using various temperatures under microwave or conventional heating conditions (isolated yields): (i) KOH 5 equiv, MeOH, reflux, conventional heating, 24 h, (ii) KOH 5 equiv, MeOH, 150 °C, conventional heating, sealed tube, 1 h, and (iii) KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 10 min.

We further investigated this reaction regarding the quantity and the nature of the base employed (Table 3). With 1 equiv

Table 3. Microwave-assisted anionic ring closure varying nature and quantity of base[a]

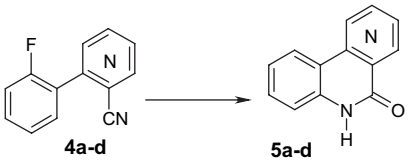
Bases	Equivalents	Reaction times (min) μW	Products molar ratio[b]		
			4d	**6**	**5d**
KOH	1	10	23	47	30
KOH	1	20	16	42	42
KOH	3	10	3	9	88
KOH	3	20	3	3	94
KOH	5	10	0	0	100
NaOH	5	10	4	1	95

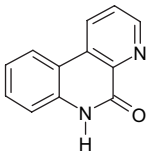
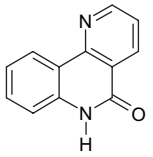
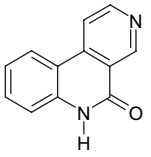
[a] Reaction conditions: MeOH, 150 °C, microwave heating, and sealed tube.
[b] Molar ratio determined by analysis of the crude ^{1}H NMR spectra.

of KOH, the reaction was not completed even after increasing the reaction time from 10 to 20 min. With 3 equiv of KOH the ratio of the benzonaphthyridin-5-one **5d** was increased, but the reaction was still not finished yet after 10 min. The same reaction conducted within 20 min did not allow a total conversion of **4d** into **5d**. The use of 5 equiv of KOH in a 10 min experiment showed us a total conversion of **4d** into **5d** without formation of **6**. The same reactive conditions conducted with NaOH appeared to be less efficient for this reaction. Finally, the best conditions to achieve the reaction were: 5 equiv of KOH, 150 °C, and 10 min under microwave heating.

Then, the three fluorophenylcyanopyridines **4a–c** were subjected to these best conditions to give the three corresponding benzonaphthyridin-5-ones **5a–c** in nearly quantitative yields (Table 4).

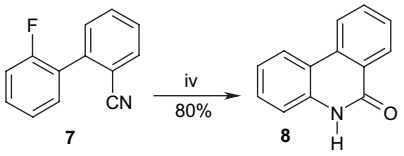
Table 4. Microwave-assisted anionic ring closure[a]



Starting materials	Products	Yields[b] (%)	Product number
4a		95	**5a**
4b		99	**5b**
4c		95	**5c**

[a] Reaction conditions: KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 10 min.
[b] Isolated yields.

Because our methodology was not described in the corresponding phenanthridinic system our anionic ring closure was finally tested on the 2′-fluorobiphenyl-2-carbonitrile **7** (Scheme 3). The 5*H*-phenanthridin-6-one **8** was obtained in a good 80% yield but the reaction time has to be increased to 30 min. The π-deficient nature of the pyridine nucleus could explain the milder condition needed to achieve the transformation in benzonaphthyridin-5-one.



Scheme 3. Anionic ring closure using 2′-fluorobiphenyl-2-carbonitrile **7** (isolated yields): (iv) KOH 5 equiv, MeOH, 150 °C, microwave heating, sealed tube, 30 min.

3. Conclusion

In conclusion, we have developed a very efficient microwave-assisted synthesis of the benzonaphthyridin-5-ones **5a–d** in a two-step procedure involving Suzuki cross-coupling reaction followed by original KOH promoted anionic ring closure. The benzonaphthyridin-5-ones **5a–d** were obtained in 63–84% overall yields starting from **3a–d**. Both nitrile and carboxamide groups were reactive under these conditions and could allow an easy scalable access to benzonaphthyridine scaffolds with a potential interest in the field of medicinal chemistry. Finally, a new access to the 5*H*-phenanthridin-6-one enlarges the scope of our reaction to benzenic derivatives. Furthermore, we are currently exploring the use of our approach to synthesize aza-heterocyclic systems.

4. Experimental

4.1. General

All commercial reagents were used as received except THF, which was distilled from Na/benzophenone. Melting points were determined on a kofler melting point apparatus. IR spectra were recorded with a Perkin–Elmer BX FTIR. ^{1}H and ^{13}C NMR spectra were recorded, respectively, at 400 and 100 MHz with a Jeol Lambda 400 NMR spectrometer. The microwave reactions were performed using a Biotage Initiator microwave oven. Temperatures were measured with an IR-sensor and the reactions are given as hold times.

4.2. General procedure for the synthesis of ortho-chlorocyanopyridines (3a, 3c, and 3d)

To a stirred solution under N_2 of 2,2,6,6-tetramethylpiperidine (20.2 mmol, 3.4 mL) in THF (40 mL) was added at −30 °C 2.5 M *n*-butyllithium (19.2 mmol, 7.7 mL). The solution was allowed to reach 0 °C, kept under stirring during 15 min and cooled to −80 °C. A solution of the chosen cyanopyridine (9.6 mmol, 1 g) in THF (20 mL) was slowly added to the mixture over 15 min. After stirring 30 min at −80 °C, a solution of hexachloroethane (20.2 mmol, 4.78 g) in THF (10 mL) was slowly added over 15 min and

the resulting mixture was stirred for 30 min. The solution was then allowed to warm slowly to room temperature. The mixture was quenched with 40 mL of a saturated NH_4Cl solution. The solution was extracted with EtOAc (3×100 mL), the combined organic layers were washed with brine (2×100 mL), dried with $MgSO_4$, filtered, and evaporated under reduced pressure. The products were purified by silica gel chromatography using EtOAc/cyclohexane (1/4) as eluent.

4.2.1. 3-Chloropyridine-2-carbonitrile 3a. Starting from 2-cyanopyridine and following the general procedure, the product was obtained as a pale yellow powder (0.99 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (dd, ^3J=4.6 Hz, ^3J=8.5 Hz, 1H), 7.88 (dd, ^4J=1.4 Hz, ^3J=8.5 Hz, 1H), 8.63 (dd, ^4J=1.4 Hz, ^3J=4.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=114.6, 127.5, 133.5, 135.9, 137.6, 148.7; IR (KBr) 3437, 3049, 2970, 2238 (CN), 1563, 1421, 1062, 1041, 813, 746, 676, 559, 507 cm^{-1}; mp 84 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.39; H, 1.95; N, 19.98.

4.2.2. 4-Chloronicotinonitrile 3c. Starting from 3-cyanopyridine and following the general procedure, the product was obtained as a pale yellow powder (0.5 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.51 (d, ^3J=5.3 Hz, 1H), 8.71 (d, ^3J=5.3 Hz, 1H), 8.86 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=111.4, 113.8, 124.6, 146.5, 153.4, 153.8; IR (KBr) 3426, 3091, 2926, 2236 (CN), 1572, 1549, 1473, 1404, 1291, 1187, 1101, 844, 798, 728, 700, 571, 476 cm^{-1}; mp 86 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.31; H, 2.07; N, 19.93.

4.2.3. 3-Chloroisonicotinonitrile 3d. Starting from 4-cyanopyridine and following the general procedure, the product was obtained as pale orange needles (0.99 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.56 (d, ^3J=4.8 Hz, 1H), 8.68 (d, ^3J=4.8 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=113.7, 120.9, 126.3, 133.1, 148.1, 150.4; IR (KBr) 3016, 2953, 2475, 2238 (CN), 1573, 1471, 1401, 1384, 1280, 1162, 1036, 840, 795, 708, 576 cm^{-1}; mp 80 °C. Anal. Calcd for $C_6H_3ClN_2$ (%): C, 52.01; H, 2.18; N, 20.22. Found: C, 52.39; H, 2.37; N, 20.32. Lit.[14]

4.3. General procedure for the microwave Suzuki cross-coupling synthesis of 4a–d and 7

In a microwave vial with a magnetic stir bar was introduced K_3PO_4 (18 mmol, 3.8 g), 2-fluorophenylboronic acid (14 mmol, 2 g), and $Pd(PPh_3)_4$ (5%, 0.4 g). The vial was sealed and purged with argon through the septum inlet. A solution of orthochlorocyanopyridine **3a–d** (7 mmol, 1 g) in DMF (15 mL) was degassed with argon and added with a syringe through the vial's septum. The suspension was then heated at 150 °C under microwave irradiation for half an hour. The resulting mixture was poured into 100 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The products were purified by silica gel chromatography using EtOAc/cyclohexane (1/4) as eluent.

4.3.1. 3-(2-Fluorophenyl)pyridine-2-carbonitrile 4a. Starting from **3a** and following the general procedure, the product was obtained as a white powder (0.96 g, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.23 (m, 1H), 7.31 (td, J=7.5 and 1.2 Hz, 1H), 7.43–7.55 (m, 2H), 7.60 (dd, ^3J=8.0 Hz, ^3J=4.6 Hz, 1H), 7.88 (dd, ^3J=8.0 Hz, ^4J=1.4 Hz, 1H), 8.73 (dd, ^3J=4.7 Hz, ^4J=1.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.3 (d, J_{C-F}=22 Hz), 116.5, 123.1 (d, J_{C-F}=15 Hz), 124.8 (d, J_{C-F}=4 Hz), 126.4, 131.2 (d, J_{C-F}=2 Hz), 131.8 (d, J_{C-F}=8 Hz), 133.5, 136.6, 138.7 (d, J_{C-F}=2 Hz), 150.0, 159.5 (d, J_{C-F}=248 Hz); IR (KBr) 3066, 3050, 2236 (CN), 1835, 1615, 1579, 1496, 1457, 1416, 1217, 1111, 1001, 811, 775, 689, 551 cm^{-1}; mp 88 °C. Lit.[7]

4.3.2. 2-(2-Fluorophenyl)nicotinonitrile 4b. Starting from 2-chloro-3-cyanopyridine and following the general procedure, the product was obtained as a white powder (1.22 g, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.21 (m, 1H), 7.25 (td, J=7.5 and 1.1 Hz, 1H), 7.38 (dd, ^3J=4.8 Hz, ^3J=7.8 Hz, 1H), 7.41–7.47 (m, 1H), 7.52 (td, J=7.5 and 1.7 Hz, 1H), 8.02 (dd, ^3J=7.8 Hz, ^4J=1.7 Hz, 1H), 8.85 (dd, ^3J=4.8 Hz, ^4J=1.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=110.4, 116.3 (d, J_{C-F}=21 Hz), 116.4, 122.1, 124.5 (d, J_{C-F}=4 Hz), 125.5 (d, J_{C-F}=14 Hz), 131.2 (d, J_{C-F}=2.5 Hz), 132.1 (d, J_{C-F}=8 Hz), 140.7, 152.6, 157.3, 159.7 (d, J_{C-F}=249 Hz); IR (KBr) 3066, 2226 (CN), 1613, 1577, 1556, 1493, 1459, 1433, 1219, 1110, 835, 809, 760, 687, 621, 552 cm^{-1}; mp 76 °C. Lit.[7]

4.3.3. 4-(2-Fluorophenyl)nicotinonitrile 4c. Starting from **3c** according to the general procedure and replacing K_3PO_4 by CsF (18 mmol, 2.73 g), the product was obtained as a white powder (1.01 g, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.32 (td, J=9.0 and 0.8 Hz, 1H), 7.32 (td, J=7.6 and 0.8 Hz, 1H), 7.45–7.55 (m, 3H), 8.86 (d, J=4.8 Hz, 1H), 9.00 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=110.1, 115.9, 116.5 (J_{C-F}=21 Hz), 123.2 (J_{C-F}=13 Hz), 124.9 (J_{C-F}=4 Hz), 125.0, 130.6 (J_{C-F}=2 Hz), 132.2 (J_{C-F}=7 Hz), 147.1, 152.6, 153.5, 159.1 (J_{C-F}=249 Hz); IR (KBr), 3056, 2233 (CN), 1615, 1585, 1474, 1447, 1398, 1257, 1210, 1109, 1040, 846, 826, 775, 756, 620, 587, 551, 529; mp 101 °C. Lit.[7]

4.3.4. 3-(2-Fluorophenyl)isonicotinonitrile 4d. Starting from **3d** and following the general procedure, the product was obtained as a white powder (1.10 g, 77%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.25–7.27 (m, 1H), 7.32 (td, J=7.5 and 1.1 Hz, 1H), 7.46 (td, J=7.5 and 1.8 Hz, 1H), 7.49–7.52 (m, 1H), 7.65 (d, ^3J=5.1 Hz, 1H), 8.80 (d, ^3J=5.1 Hz, 1H), 8.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=115.7, 116.4 (d, J_{C-F}=22 Hz), 120.5, 122.3 (d, J_{C-F}=15 Hz), 124.7 (d, J_{C-F}=4 Hz), 125.6, 131.1 (d, J_{C-F}=2 Hz), 131.8 (d, J_{C-F}=8 Hz), 133.3, 149.4, 151.6 (d, J_{C-F}=2 Hz), 159.5 (d, J_{C-F}=248 Hz); IR (KBr) 3064, 2233 (CN), 1614, 1577, 1500, 1472, 1450, 1402, 1260, 1219, 1199, 1074, 841, 828, 785, 763, 752, 586, 555 cm^{-1}; mp 50 °C. Lit.[7]

4.3.5. 2′-Fluorobiphenyl-2-carbonitrile 7. Starting from 2-bromobenzonitrile and following the general procedure, the product was obtained as a white powder (0.92 g, 88%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=7.19–7.30 (m, 2H), 7.40–7.52 (m, 4H), 7.66 (ddd, J=8.0, 7.3, and 1.3 Hz, 1H), 7.78 (ddd, J=7.6, 1.5, and 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=112.9, 116.2 (d, J_{C-F}=22 Hz), 118.1, 124.3 (d, J_{C-F}=4 Hz), 125.8 (d, J_{C-F}=14.8 Hz), 128.2, 130.8

(d, J_{C-F}=8 Hz), 131.0 (d, J_{C-F}=2.5 Hz), 131.2 (d, J_{C-F}=3.0 Hz), 132.5, 133.3, 139.6, 159.6 (J_{C-F}=248 Hz). Lit.[6a]

4.4. Synthesis of 3-(2-fluorophenyl)isonicotinamide 6

3-(2-Fluorophenyl)isonicotinonitrile **4d** (1 mmol, 0.2 g) and KOH (5 mmol, 0.28 g) were solubilized in MeOH (5 mL) in a sealed tube. The mixture was then heated at 65 °C for 24 h. The resulting solution was poured into 20 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated. The crude product was purified by silica gel chromatography using CH_2Cl_2/EtOAc (1/1) and EtOAc as eluents to give 3-(2-fluorophenyl)isonicotinamide **6** as a yellow powder (0.14 g, 65%).^{1}H NMR (400 MHz, $CDCl_3$) δ=5.72 (br s, 1H), 5.98 (br s, 1H), 7.17 (t, J=8.5 Hz, 1H), 7.26 (t, J=7.6 Hz, 1H), 7.37–7.48 (m, 2H), 7.61 (d, ^3J=4.8 Hz, 1H), 8.63 (s, 1H), 8.71 (d, ^3J=4.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ=116.1 (d, J_{C-F}=21 Hz), 121.8, 124.0 (d, J_{C-F}=15 Hz), 124.8 (d, J_{C-F}=3 Hz), 128.4, 130.8 (d, J_{C-F}=8 Hz), 131.1 (d, J_{C-F}=15 Hz), 132.1 (d, J_{C-F}=10 Hz), 142.0, 149.8, 151.6, 159.7 (d, J_{C-F}=247 Hz), 168.5; IR (KBr) 3312 (NH), 3045, 1666 (CO), 1582, 1477, 1451, 1388, 1257, 1203, 1111, 1082, 849, 763, 625 cm^{-1}; mp 174 °C; HRMS/ESI (g mol^{-1}) Calcd for $C_{12}H_{10}FN_2O$ $[M+H]^+$ 217.0777; found 217.072.

4.5. General procedure for microwave anionic ring closure synthesis of 5a–d

A biaryl **4a–d** (2.4 mmol, 0.49 g) and KOH (12 mmol, 0.69 g) were solubilized in MeOH (7 mL) in a microwave vial. The suspension was then heated at 150 °C under microwave irradiation for 10 min. The resulting mixture was poured into 20 mL of water and extracted three times with EtOAc. The combined organic layers were dried with $MgSO_4$, filtered, and evaporated to give analytically pure products **5a–d**.

4.5.1. 6*H*-Benzo[*f*][1,7]naphthyridin-5-one 5a. Starting from **4a** and following the general procedure, the product was obtained as a white powder (0.46 g, 95%). ^{1}H NMR (400 MHz, DMSO) δ=7.28 (td, J=7.3 and 1.2 Hz, 1H), 7.37 (dd, J=8.2 and 0.7 Hz, 1H), 7.52 (td, J=8.2 and 1.2 Hz, 1H), 7.83 (dd, ^3J=4.4 Hz, ^3J=8.3 Hz, 1H), 8.40 (d, J=7.3 Hz, 1H), 8.88 (dd, ^4J=1.5 Hz, ^3J=4.4 Hz, 1H), 8.95 (dd, ^4J=1.5 Hz, ^3J=8.3 Hz, 1H), 11.97 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.9, 116.5, 122.3, 123.7, 127.0, 130.3, 130.8, 131.4, 136.4, 141.6, 150.1, 159.4; IR (KBr) 3178, 3127, 3043, 2857, 1677 (CO), 1588, 1549, 1460, 1270, 1221, 1158, 867, 809, 160, 751, 671, 629 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.22; H, 3.85; N, 14.30. Lit.[3a]

4.5.2. 6*H*-Benzo[*h*][1,6]naphthyridin-5-one 5b. Starting from **4b** and following the general procedure, the product was obtained as a white powder (0.48 g, 99%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.3 Hz, 1H), 7.58 (td, J=1.5 and 7.3 Hz, 1H), 7.66 (dd, ^3J=4.6 Hz, ^3J=8.1 Hz, 1H), 8.56–8.62 (m, 2H), 9.05 (dd, ^4J=1.7 Hz, ^3J=4.6 Hz, 1H), 11.87 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.9, 118.8, 121.2, 122.4, 123.3, 124.0, 131.2, 135.7, 137.9, 150.5, 154.1, 160.8; IR (KBr) 3033, 2983, 2873, 1678 (CO), 1604, 1585, 1455, 1406, 1361, 1204, 1151, 884, 762, 731, 711, 668, 617, 496 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.19; H, 4.11; N, 14.08. Lit.[3a]

4.5.3. 6*H*-Benzo[*c*][2,7]naphthyridin-5-one 5c. Starting from **4c** and following the general procedure, the product was obtained as a white powder (0.46 g, 95%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.1 Hz, 1H), 7.38 (d, J=8.2 Hz, 1H), 7.68 (t, J=7.1 Hz, 1H), 8.41 (d, J=5.7 Hz, 1H), 8.45 (d, J=8.2 Hz, 1H), 8.90 (d, J=5.7 Hz, 1H), 9.41 (s, 1H), 11.94 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.7, 116.1, 116.4, 120.3, 122.6, 124.0, 131.2, 138.2, 140.6, 150.2, 151.8, 160.2; IR (KBr) 3016, 2887, 1682 (CO), 1603, 1476, 1417, 1357, 1180, 1041, 1018, 752, 730, 667 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.36; H, 4.08; N, 14.36. Lit.[3a,5]

4.5.4. 6*H*-Benzo[*c*][2,6]naphthyridin-5-one 5d. Starting from **4d** and following the general procedure, the product was obtained as a white powder (0.475 g, 98%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.3 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.54 (t, J=7.3 Hz, 1H), 8.10 (d, ^3J=5.1 Hz, 1H), 8.56 (d, J=8.0 Hz, 1H), 8.80 (d, ^3J=5.1 Hz, 1H), 9.88 (s, 1H), 12.07 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=115.7, 116.4, 119.6, 122.8, 123.0, 128.5, 130.4, 130.8, 136.9, 146.5, 147.8, 159.7; IR (KBr) 3024, 2997, 2874, 1669 (CO), 1609, 1549, 1469, 1432, 1411, 1368, 878, 748, 687, 639, 620, 508 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.13; H, 4.08; N, 13.96.

4.5.5. 5*H*-Phenanthridin-6-one 8. Starting from **7** and following the general procedure, the product was obtained as a white powder (0.39 g, 80%). ^{1}H NMR (400 MHz, DMSO) δ=7.30 (t, J=7.5 Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.53 (t, J=7.5 Hz, 1H), 7.69 (t, J=7.5 Hz, 1H), 7.90 (t, J=7.5 Hz, 1H), 8.37 (d, J=8.0 Hz, 1H), 8.42 (d, J=8.0 Hz, 1H), 8.54 (d, J=8.0 Hz, 1H) 11.73 (br s, 1H); ^{13}C NMR (100 MHz, DMSO) δ=116.1, 117.5, 122.2, 122.6, 123.2, 125.6, 127.4, 127.9, 129.5, 132.7, 134.2, 136.5, 160.8; IR (KBr) 3435, 3047, 1663 (CO), 1608, 1557, 1510, 1469, 1424, 1369, 1153, 1037, 943, 748, 726 cm^{-1}; mp>260 °C. Anal. Calcd for $C_{12}H_8N_2O$ (%): C, 79.98; H, 4.65; N, 7.17. Found: C, 79.84; H, 4.52; N, 6.72. Lit.[15]

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Microwave assisted synthesis and crystal structures of 2-imidazolines and imidazoles

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Abstract—A series of 2-imidazolines and imidazoles has been synthesized using green synthetic methodologies. The preparation of 2-imidazolines was performed by cyclization of nitriles with ethylenediamine. The use of microwave irradiation in solvent-free conditions enabled 2-imidazolines to be obtained in high yields within short reaction times. Aromatization of imidazoles was performed under microwave irradiation in toluene and using Magtrieve™ as the oxidant. The X-ray structures for five of these derivatives are provided. In all cases, the molecules are assembled into chains through N–H···N hydrogen bonds.

1. Introduction

The preparation of 2-substituted imidazolines and imidazoles is of increasing interest because of their applications as disinfectants, pharmaceuticals or as starting materials for these fine chemicals.[1] In supramolecular chemistry these systems have found multiple applications, for example, in the preparation of molecular tectonics through the formation of intermolecular hydrogen bonds,[2] in the formation of a helical assembly through triple hydrogen bonds in tris(oxazoline)-tris(imidazoline) benzene,[3] in the preparation of triple-stranded helices and zig-zag chains by coordination with copper(I),[4] in the synthesis of palladium complexes with pyridine/imidazoline ligands that have been shown to react readily with carbon monoxide,[5] and in the preparation of supramolecular structures by self assembly using π–π stacking and hydrogen bonding interactions.[6]

We became interested in the synthesis of azolyl-substituted imidazolines and imidazoles for possible use in the formation of supramolecular structures by coordination with transition metals or by the formation of intermolecular hydrogen bonds. In this regard, we recently described the synthesis and self-association of azolyl-substituted pyrimidine and 1,3,5-triazine derivatives.[7]

In consequence, we have considered the preparation of pyrazolylimidazolines and imidazoles under green synthetic conditions, using microwave irradiation as the energy source, solvent-free conditions, and green oxidants.

2. Results

2.1. Synthesis of imidazolines 3, 5, and 7

The imidazoline ring was built by cyclization of the appropriate nitrile with ethylenediamine in the presence of sulfur and under solvent-free conditions (Scheme 1).

The preparation of imidazolines has previously been performed by electrophilic diamination of functionalized alkenes,[8] reaction of aziridines with platinum(II) nitriles,[9] and reaction of aromatic nitriles with ethylenediamines by the action of elemental sulfur,[10] copper salts,[11] phosphates or silica.[12]

We consider the reaction with ethylenediamine in the presence of elemental sulfur as the most suitable because of the simplicity of the method and the easy work-up procedure, which makes this method a green synthetic procedure.

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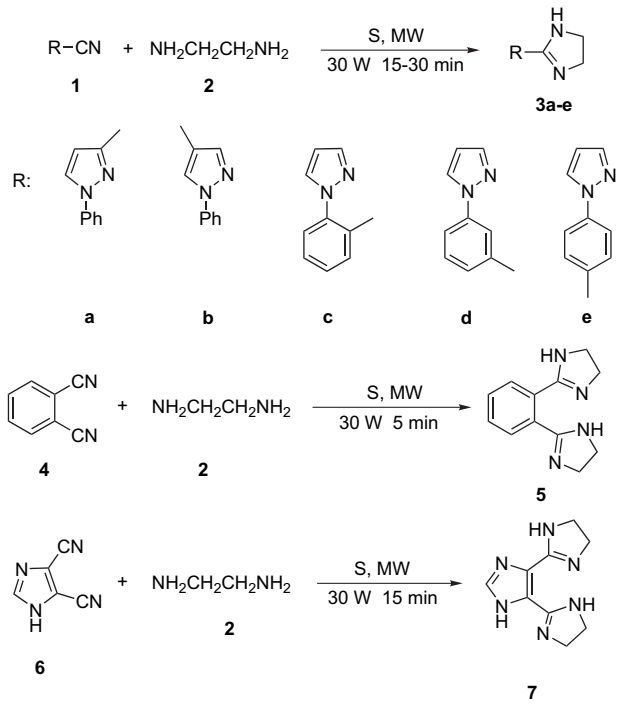


Scheme 1.

Reactions were performed under solvent-free conditions; a mixture of the nitrile, sulfur, and an excess of ethylenediamine was irradiated at 30 W for 3–30 min. Reaction times were optimized for every nitrile considering that in solvent-free conditions absorption of microwave irradiation, and in consequence the temperature reached during the reaction, strongly depends on the polarity of the starting material. The crude product was washed with cold water and, in most cases, the pure product crystallized. Good-to-excellent yields (Table 1) of the corresponding imidazolines were obtained using this approach.

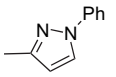
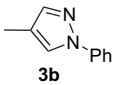
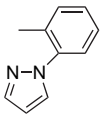
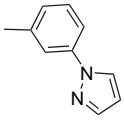
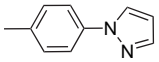
The ^{1}H NMR spectra of compounds **3**, **5**, and **7** contain the characteristic signals of the pyrazole and phenyl rings and two or three broad singlets for the imidazoline protons, one for the NH group, and one or two for the CH_2 groups. A similar situation is also found in the ^{13}C NMR spectra in which the CH_2 carbons are not observed even with a long relaxation time. The presence of broad signals for the CH_2 groups indicates the occurrence of a tautomeric equilibrium in the imidazoline ring. However, the free energy of activation could not be calculated as these signals remain as broad singlets over a broad temperature range (from 223 to 413 K). A similar observation has been previously described for aminopyrazolines.[13]

2.2. Aromatization of imidazolines 3, 5, and 7

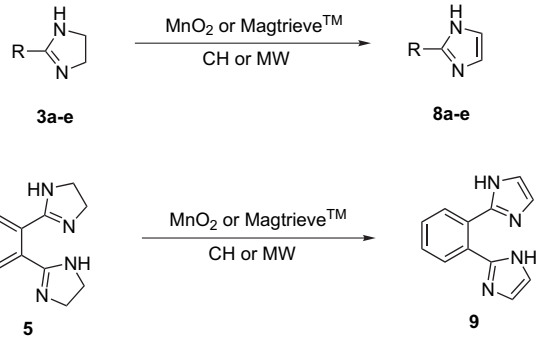
Aromatization of imidazolines to the corresponding imidazoles has been performed by reaction with DMSO,[14] dehydrogenation with Pd/C[14,15] in toluene, by Swern oxidation,[16] and by reaction with trichloroisocyanuric acid[17] in acetonitrile.

We performed the aromatization of imidazolines using Magtrieve™, which is an environmentally friendly oxidant because it can be used under mild conditions, removed magnetically, and recycled (Scheme 2). Magtrieve™ is a chromium dioxide-based reagent that has been used in the oxidation of alcohols[18–20] and thiols,[21] side chain oxidation of arenes,[22] deprotection of acetals,[23] and aromatization of Hantzsch dihydropyridines.[24] Magtrieve™ is polar and can be heated efficiently under microwaves; the material reaches temperatures up to 360 °C within 2 min of irradiation, but is not distributed uniformly and is very difficult to control. When toluene was introduced into the reaction vessel, the temperature of Magtrieve™ reached ca. 140 °C within 2 min and the temperature was more uniformly distributed.[20]

Table 1. Reaction conditions and yields for the preparation of imidazolines **3a–e**, **5**, and **7**

R	Power (W)	*t* (min)	*T* (K)	Yield (%)
 **3a**	30	15	383	74
 **3b**	30	30	383	98
 **3c**	30	30	373	98
 **3d**	30 —	30 30	373 373	82 68[a]
 **3e**	30	15	383	91
 **5**	30 30	5 3	353 353	42 18[b]
 **7**	30 30 30	5 15 25	368 368 368	68 89 95

[a] Conventional heating in an oil bath.
[b] Traces of impurities.



Scheme 2.

Table 2. Aromatization of imidazoline **3b** in toluene solution at reflux (383 K)

Entry	Oxidant	*t* (min)	Power (W)	Yield (%)
1	Magtrieve™	75	120	54
2	Magtrieve™	105	120	64
3	$BaMnO_4$	105	120	21
4	MnO_2	75	120	56
5	MnO_2	105	120	61

As a consequence we decided to study the aromatization of imidazolines **3**, **5**, and **7** using Magtrieve™ under microwave irradiation in toluene solution.

In an effort to show the potential of Magtrieve™ we performed the aromatization of imidazoline **3b** and compared the results with other oxidizing reagents such as MnO_2 and $BaMnO_4$ (Table 2) under microwave irradiation. The results obtained with Magtrieve™ (entries 1 and 2) were comparable to those obtained with MnO_2 (entries 4 and 5) and better than with $BaMnO_4$ (entry 3).

The use of conventional heating with MnO_2 meant that longer reaction times (24–48 h) were required to obtain good results (Table 3).

Under microwave irradiation the reaction times can be shortened to 75–105 min (Table 4) and better yields are obtained in comparison to conventional heating under comparable reaction conditions of temperature and time (see, for example, entries 2 vs 3 and 4 vs 5). Compound **7** with two imidazoline rings did not afford any oxidation product and the starting material was recovered along with the oxidizing agents. This can be a consequence of the acidic imidazole NH interfering with the oxidants. Similarly, compound **5** gave low yield (entry 8) even after increasing the temperature using refluxing xylene as the solvent (entry 9), and only conventional heating in long reaction time gave acceptable results (entry 10).

Table 3. Aromatization of imidazolines **3** with MnO_2 in $CHCl_3$ at reflux under conventional heating

Entry	Imidazoline	*t* (h)	Yield (%)
1	**3a**	24	92
2	**3b**	48	76
3	**3c**	24	93
4	**3d**	24	81
5	**3e**	24	89

Table 4. Aromatization of imidazolines **3** and **5** with Magtrieve™ in toluene at reflux

Entry	Imidazoline	*t* (min)	Power (W)	Yield (%)
1	**3a**	105	120	77
2	**3b**	105	120	64
3	**3b**	105	[a]	16
4	**3c**	75	270	88
5	**3c**	75	[a]	56
6	**3d**	75	270	70
7	**3e**	105	270	77
8	**5**	105	90	26[b]
9	**5**[c]	105	120	20[b]
10	**5**	24 h	[a]	65

[a] Conventional heating.
[b] Yield of compound **9**.
[c] Solvent: xylene.

2.3. Solid-state structure determination

The structures of compounds **3d**, **3e**, **5**, **9**, and **10** were characterized by X-ray crystallography. The crystal structure of compound **5** has been reported previously,[25] but the atomic coordinates were not deposited in the Cambridge Crystallographic Data Centre[26] (CSD refcode IMYLBZ) and so the structure was determined in this work for the sake of comparison.

In all compounds, the supramolecular structure is dominated by one-dimensional chains formed through N–H···N interactions, as illustrated in Figures 1 and 2. Compounds **3d** and **3e** differ in the conformation of the molecule and in the bond distances and angles involving the NH–C=N and C–N=N fragments in the imidazoline and pyrazole rings. In **3e**, the imidazoline ring is almost coplanar with

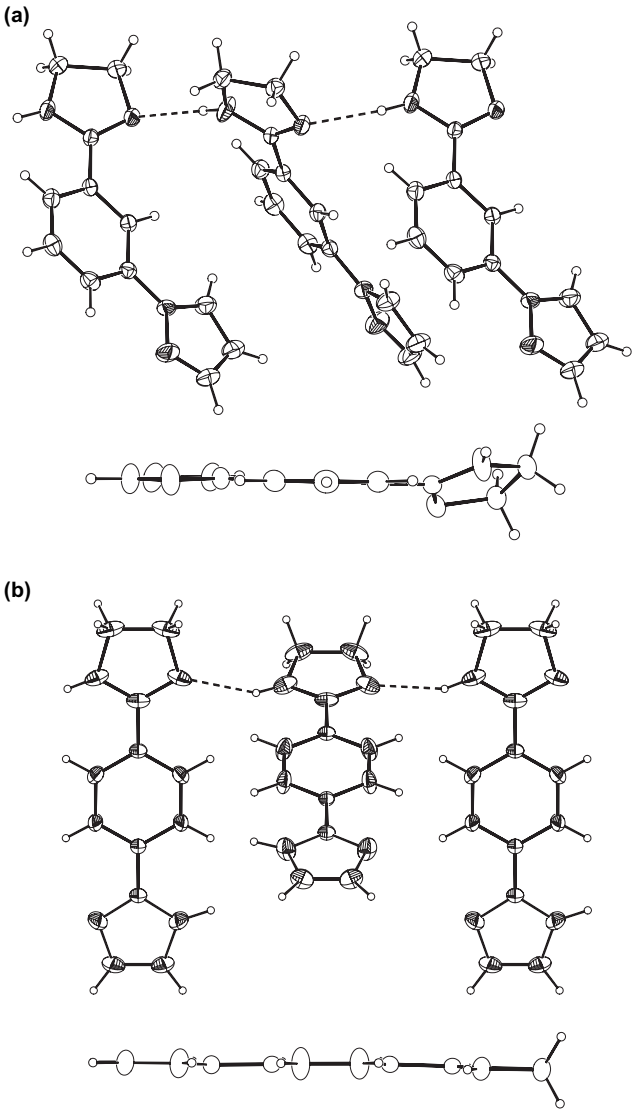


Figure 1. (a) Hydrogen bonding network in **3d** and a perspective view showing the molecular conformation. (b) Same for **3e**. The disorder has been omitted for clarity [N···N intermolecular distances of 2.943(2) and 2.990(6) Å for **3d** and **3e**, respectively].

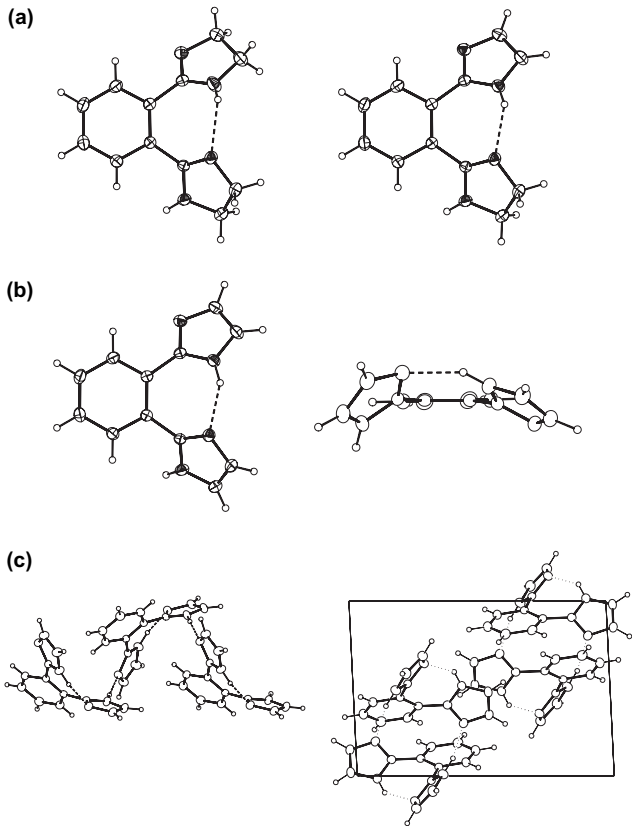


Figure 2. (a) Molecular structures of **5** and **10**. (b) Two views of the molecular structure of **9** showing the disposition of the azoles. (c) 1D structure and crystal packing of **9** along the *b* axis [N···N intra- and intermolecular distances of 2.752(2), 2.935(2); 2.753(2), 2.853(2) and 2.706(2), 2.924(2) Å for **5**, **9**, and **10**, respectively].

the phenyl ring (Fig. 1) and the C═N and N═N bonds are delocalized.

The molecular structure of compounds **5**, **9**, and **10** are shown in Figure 2a, b. The crystal structures of these compounds are isomorphous with one another and so only the supramolecular structure of one compound (**9**) and its crystal packing is illustrated in Figure 2c. In all cases, the analysis reveals a combination of intra- and intermolecular N–H···N hydrogen bonds leading to the formation of helical chains. The main differences between the three compounds concern the conformation of the azoles, imidazoline and/or imidazole, and the type of interactions in which they are involved. The imidazole is, as expected, close to planar, but the imidazoline displays an almost undistorted envelope conformation. In all cases, the azoles are twisted with respect to the phenyl rings, as illustrated in Figure 2b. In compound **10**, where both types of rings are present in the molecular structure, the acidic N–H of the imidazole ring acts as a hydrogen-bond donor to the basic imidazoline N atom in the intramolecular interaction (Fig. 2a) with the shortest N···N distance.

3. Conclusions

The preparation of 2-imidazolines and imidazoles has been performed using green synthetic procedures, i.e., microwave irradiation, solvent-free conditions, and an environmentally friendly oxidant. Microwave irradiation under solvent-free conditions allows the preparation of 2-imidazolines in high yield in a short reaction time. Aromatization of the imidazoles was carried out in solution in order to moderate the absorption of microwave energy by Magtrieve™. Comparison with MnO_2 shows that this oxidant gives similar results under similar conditions but in an environmentally friendly procedure.

The solid-state structures of 2-imidazolines and imidazoles show the formation of one-dimensional chains in compounds with one imidazoline ring (**3d** and **3e**) through intermolecular N–H···N interactions. In compounds with two imidazole or imidazoline rings, a combination of intra- and intermolecular N–H···N interactions leads to the formation of helical chains.

4. Experimental

4.1. General

Melting points were determined using a Gallenkamp melting point apparatus and are uncorrected. NMR spectra were recorded on Varian Unity 300 and 500 spectrometers with TMS as the internal standard. The IR spectra were obtained with a Nicolet-550 FTIR spectrophotometer. The mass spectra were recorded on a VG AutoSpec apparatus using electron impact at 70 eV and Atmospheric pressure Chemical Ionization (ApCI). Flash column chromatography was performed on silica gel 60 (Merck, 230–400 mesh). All compounds gave satisfactory elemental analysis (±0.3%).

Reactions under microwave irradiation were performed in a modified PROLABO MAXIDIGEST MX350. Reactions were performed at the power indicated in Tables 1, 2, and 4. The temperature was measured with an IR pyrometer and controlled using a computer with PACAM MPX-2 software. When the temperature exceeded the programed value, the power was reduced to 10 W.

4.2. General procedure for the synthesis of 4,5-dihydroimidazolylpyrazoles 3 and 7 and bis-4,5-dihydroimidazolylbenzene (5)

A mixture of sulfur (1.95 mmol, 0.062 g), the appropriate nitrile (3.9 mmol), and ethylenediamine (75 mmol, 4.5 g, 5 mL) was introduced into a Pyrex flask and irradiated as described in Table 1. The cold crude mixture was suspended in water and filtered. The solid was washed with water (2×5 mL) to afford the pure imidazoline.

4.2.1. 3-(4,5-Dihydro-1*H*-imidazol-2-yl)-1-phenylpyrazole (3a). From 3-cyano-1-phenylpyrazole **1a** (3.99 mmol, 0.66 g). The mixture was irradiated for 15 min at 30 W. The ethylenediamine was removed in vacuo and the crude mixture was suspended in water and filtered. The solid was washed with water (2×5 mL) to yield 0.67 g (74%). Mp 128–129 °C. IR (KBr) 3450, 3220, 1600, 1521 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.50 (br s, 2H), 4.00 (br s, 2H), 5.47 (br s, 1H), 6.98 (d, *J* 2.7, 1H), 7.32 (t, *J* 7.6, 1H), 7.47 (dd, *J* 7.8, 7.6, 2H), 7.70 (d, *J* 7.8, 2H), 7.92 (d, *J* 2.7, 1H); ^{13}C NMR ($CDCl_3$) δ 107.53, 119.35, 127.02, 128.23,

129.50, 139.76, 145.01, 159.65; MS (ApCI/MeOH) 213.1 (M+H).

4.2.2. 4-(4,5-Dihydro-1*H*-imidazol-2-yl)-1-phenylpyrazole (3b). From 4-cyano-1-phenylpyrazole **1b** (3.99 mmol, 0.66 g). The mixture was irradiated for 30 min at 30 W. Yield 0.814 g (98%). Mp 187–188 °C. IR (KBr) 3444 (ν N–H), 3155, 1630, 1560 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (br s, 4H), 7.33 (t, *J* 7.3, 1H), 7.47 (dd, *J* 7.7, 7.3, 2H), 7.69 (dd, *J* 7.7, 2H), 7.98 (s, 1H), 8.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 115.52, 119.28, 126.59, 127.18, 129.57, 139.54, 139.66, 158.52; MS (ApCI/MeOH) 213.1 (M+H).

4.2.3. 1-[2-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl]pyrazole (3c). From 2-(pyrazol-1-yl)benzonitrile **1c** (3.9 mmol, 0.66 g). The mixture was irradiated for 30 min at 30 W. After cooling, the crude mixture was suspended in water and extracted with CH_2Cl_2 (3×10 mL). The organic solution was dried over anhydrous magnesium sulfate, filtered and the solvent removed in vacuo to give the pure imidazoline. Yield 0.811 g (98%). Mp 102–104 °C. IR (KBr) 3100 (ν N–H), 1590, 1510 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.59 (s, 4H), 4.5 (br s, 1H), 6.44 (dd, *J* 2.4, 1.6, 1H), 7.41–7.43 (m, 2H), 7.51 (td, *J* 8.5, 2.0, 1H), 7.69 (d, *J* 2.4, 1H), 7.71 (d, *J* 1.6, 1H), 7.83 (dd, *J* 9.3, 2.0, 1H); ^{13}C NMR ($CDCl_3$) δ 50.21, 107.05, 126.23, 127.44, 128.45, 130.54, 130.65, 131.44, 138.46, 140.93, 163.51; MS (ApCI/MeOH) 213.1 (M+H).

4.2.4. 1-[3-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl]pyrazole (3d). From 3-(pyrazol-1-yl)benzonitrile **1d** (3.9 mmol, 0.66 g). The mixture was irradiated for 30 min at 30 W. Yield 0.67 g (82%). Mp 127–128 °C. IR (KBr) 3440 (ν N–H), 1580, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.5 (br s, 2H), 4.01 (br s, 2H), 4.89 (br s, 1H), 6.48 (dd, *J* 2.4, 1.5, 1H), 7.49 (t, *J* 7.8, 1H), 7.98 (d, *J* 7.8, 1H), 7.73 (d, *J* 1.5), 7.84 (dt, *J* 7.9, 1H), 8.00 (d, *J* 2.4, 1H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 42.0, 56.0, 107.92, 117.38, 121.24, 124.76, 126.85, 129.66, 131.88, 140.31, 141.31, 163.98; MS (ApCI/MeOH) 213.1 (M+H).

4.2.5. 1-[4-(4,5-Dihydro-1*H*-imidazol-2-yl)phenyl]pyrazole (3e). From 4-(pyrazol-1-yl)benzonitrile **1e** (3.9 mmol, 0.66 g). The mixture was irradiated during 15 min at 30 W. Yield 0.765 g (91%). Mp 230–231 °C. IR (KBr) 3140 (ν N–H), 1620, 1530 cm^{-1}; ^1H NMR (DMSO) δ 3.61 (br s, 4H), 6.57 (t, *J* 2.19, 1H), 6.92 (br s, 1H), 7.78 (d, *J* 1.95, 1H), 7.93 and 7.90 (AA′XX′, *J* 8.3, 4H), 8.57 (d, *J* 2.44, 1H); ^{13}C NMR (DMSO) δ 108.19, 117.68, 127.86, 128.25, 128.33, 140.73, 141.35, 162.80; MS (ApCI/MeOH) 213.1 (M+H).

4.2.6. 1,2-Bis-(4,5-dihydro-1*H*-imidazol-2-yl)benzene (5). From phthalodinitrile **4** (3.9 mmol, 0.511 g). The mixture was irradiated for 5 min at 30 W. Yield 0.362 g (42%). Mp 171–172 °C. IR (KBr) 3090 (ν N–H), 1580, 1490 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.72 (s, 8H), 6.05 (br s, 2H), 7.42 (m, 2H), 7.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 51.70, 129.41, 129.72, 130.47, 166.01; EM (ApCI/MeOH) 215.1 (M+H).

4.2.7. 4,5-Bis-(4,5-dihydro-1*H*-imidazol-2-yl)imidazole (7). From 4,5-dicyanoimidazole **6** (3.9 mmol, 0.471 g). The mixture was irradiated for 25 min at 30 W. The crude mixture was suspended in water and filtered. The solid was washed with ethanol (2×5 mL) and diethyl ether (2×5 mL). Yield 0.832 g (96%). Mp >260 °C. IR (KBr) 3120 cm^{-1} (ν N–H); ^1H NMR (D_2O+HCl) δ 3.92 (s, 8H), 7.99 (s, 1H); ^{13}C NMR (D_2O+HCl) δ 123.36, 142.37, 158.07; MS (ESI/MeOH+0.1% TFA) 206.1 (M+H) and 205.1 (M).

4.3. General procedure for the synthesis of imidazolylpyrazoles 8 and bisimidazolylbenzene (9)

Method A. Aromatization under conventional heating

(A1) *Manganese(IV) oxide*. In a round-bottomed flask fitted with a reflux condenser, imidazoline **3** (1.16 mmol), active manganese(IV) oxide (0.976 g, 0.011 mmol), and chloroform (5 g, 6 mL) were introduced and the mixture was heated under reflux for 24 h (Table 3). The solution was filtered through a Whatman paper and the solvent evaporated in vacuo. The product was purified by column chromatography on silica gel using ethanol as the eluent.

(A2) *Magtrieve*™. In a round-bottomed flask fitted with a reflux condenser, imidazoline **3** or **5** (0.707 mmol), Magtrieve™ (0.750 g, 8.9 mmol), and toluene (6 mL) were introduced and the mixture was heated under reflux for 24 h (Table 4). The work-up was performed as for method A1.

Method B. Aromatization under microwave irradiation

(B1) *Manganese(IV) oxide*. A mixture of imidazoline **3b** (0.707 mmol), active manganese(IV) oxide (0.75 g, 8.6 mmol), and toluene (6 mL) was introduced into a Pyrex flask fitted with a reflux condenser and irradiated under the conditions indicated in Table 2. The work-up was performed as for method A1.

(B2) *Barium manganate*. A mixture of imidazoline **3b** (0.707 mmol), barium manganate (0.75 g, 2.9 mmol), and toluene (6 mL) was introduced into a Pyrex flask fitted with a reflux condenser and irradiated under the conditions indicated in Table 2. The work-up was performed as for method A1.

(B3) *Oxidation with Magtrieve*™. A mixture of imidazoline **3** or **5** (0.707 mmol), Magtrieve™ (0.75 g, 8.9 mmol), and toluene (6 mL) was introduced into a Pyrex flask fitted with a reflux condenser and irradiated under the conditions indicated in Tables 2 and 4. The work-up was performed as for method A1.

4.3.1. 3-(1*H*-Imidazol-2-yl)-1-phenylpyrazole (8a). *Method B3*. From **3a** (0.150 g, 0.7 mmol). The mixture was irradiated for 105 min at 90 W and the temperature reached 100 °C. The product was purified by column chromatography using hexane/ethyl acetate 1:1, gradient ethyl acetate, as the eluent. Yield 0.082 g (57%). Mp 160–161 °C. IR (KBr) 3060 (ν N–H), 1600, 1520 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (d, *J* 2.4, 1H), 7.11 (s, 2H), 7.22 (t, *J* 7.3, 1H), 7.36 (dd, *J* 8.3, 7.3, 2H), 7.61 (d, *J* 8.3, 2H), 7.84 (d, *J* 2.44, 1H); ^{13}C NMR ($CDCl_3$) δ 105.99, 118.99, 122.73, 126.54, 128.21, 129.31, 139.62, 141.49, 145.25; MS (ApCI/MeOH) 211.1 (M+H).

4.3.2. 4-(1*H*-Imidazol-2-yl)-1-phenylpyrazole (8b). *Method B3*. From **3b** (0.150 g, 0.7 mmol). The mixture

was irradiated for 105 min at 120 W and the temperature reached 105 °C. The product was purified by column chromatography using ethyl acetate as the eluent. Yield 0.107 g (64%). Mp 209–211 °C. IR (KBr) 3100 (ν N–H), 1600, 1500 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (s, 2H), 7.28 (t, *J* 7.8, 1H), 7.41 (dd, *J* 7.8, 7.3, 2H), 7.61 (d, *J* 7.3, 2H), 8.03 (s, 1H), 8.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 115.49, 119.06, 122.04, 124.68, 126.96, 129.52, 138.23, 139.52, 140.49; MS (ApCI/MeOH) 211.1 (M+H).

4.3.3. 1-[2-(1*H*-Imidazol-2-yl)phenyl]pyrazole (8c). *Method B3*. From **3c** (0.150 g, 0.7 mmol). The mixture was irradiated for 75 min at 270 W and the temperature reached 95 °C. The product was purified by column chromatography using hexane/ethyl acetate 1:1, gradient ethyl acetate, as the eluent. Yield 0.128 g (88%). Mp 139.4–140.1 °C. IR (KBr) 3400 (ν N–H), 1390, 1100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.48 (dd, *J* 2.6, 1.8, 1H), 7.04 (s, 2H), 7.31 (dd, *J* 7.7, 1.5, 1H), 7.43 (td, *J* 7.7, 1.5, 1H), 7.55 (td, *J* 7.7, 1.3, 1H), 7.58 (d, *J* 2.6, 1H); 7.85 (d, *J* 1.8, 1H); 8.27 (dd, *J* 7.7, 1.3, 1H); ^{13}C NMR ($CDCl_3$) δ 107.50, 127.55, 127.74, 128.93, 129.54, 130.56, 132.97, 136.75, 141.33, 143.62; MS (ApCI/MeOH) 212.1 (M+H).

4.3.4. 1-[3-(1*H*-Imidazol-2-yl)phenyl]pyrazole (8d). *Method B3*. From **3d** (0.150 g, 0.7 mmol). The mixture was irradiated for 75 min at 270 W and the temperature reached 95 °C. The product was purified by column chromatography using hexane/ethyl acetate 1:1, gradient ethyl acetate, as the eluent. Yield 0.104 g (70%). Mp 154–155 °C. IR (KBr) ν_{max} 3400 (ν N–H), 1590, 1525 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.42 (dd, *J* 2.4, 1.9, 1H), 7.17 (s, 2H), 7.40 (t, *J* 7.8, 1H), 7.64 (dd, *J* 7.8, 1.9, 1H), 7.70 (d, *J* 1.9, 1H), 7.76 (d, *J* 7.8, 1H), 7.83 (d, *J* 2.4, 1H), 8.14 (t, *J* 1.9, 1H), 11.30 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 107.83, 115.78, 119.07, 123.22, 126.2, 130.05, 131.56, 140.52, 141.19, 146.05; MS (ApCI/MeOH) 211.2 (M+H).

4.3.5. 1-[4-(1*H*-Imidazol-2-yl)phenyl]pyrazole (8e). *Method B3*. From **3e** (0.150 g, 0.7 mmol). The mixture was irradiated for 105 min at 270 W and the temperature reached 100 °C. The product was purified by column chromatography using ethyl acetate as the eluent. Yield 0.115 g (77%). Mp 260 °C (decomp.). IR (KBr) 3400 (ν N–H), 1620, 1525 cm^{-1}; ^1H NMR (DMSO) δ 6.56 (dd, *J* 2.4, 1.5, 1H), 7.04 and 7.26 (br s, 2H), 7.77 (d, *J* 1.5, 1H), 7.92 (d, *J* 8.8, 2H), 8.04 (d, *J* 8.8, 2H), 8.54 (d, *J* 2.4, 1H), 12.56 (s, 1H); ^{13}C NMR (DMSO) δ 107.97, 117.78, 118.47, 125.79, 127.66, 128.65, 129.06, 139.02, 141.07, 144.88; MS (ApCI/MeOH) 211.1 (M+H).

4.3.6. 1,2-Bis-(1*H*-imidazol-2-yl)benzene (9) and 1-(1*H*-imidazol-2-yl)-2-(4,5-dihydro-1*H*-imidazol-2-yl)-benzene (10). *Method B3*. From **5** (0.150 g, 0.7 mmol), Magtrieve™ (0.75 g, 0.0089 mol), and toluene (6 mL). The mixture was irradiated for 105 min at 120 W. Product **9** was purified by column chromatography using ethyl acetate with 1% diethylamine as the eluent. Yield 0.029 g (20%). Mp 230 °C. IR (KBr) 3050 (ν N–H), 2600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.01 (AA′XX′, J_{AX} 7.9, $J_{AA'}$ 7.3, $J_{AX'}$ 1.4, 2H), 7.17 (s, 4H), 7.57 (AA′XX′, J_{AX} 7.9, $J_{AA'}$ 7.3, $J_{AX'}$ 1.4, 2H); ^{13}C NMR ($CDCl_3$) δ 122.45, 126.84, 127.73, 130.15, 146.62; EIMS 210 (M), 156.

The same eluent gave traces of product **10**. Mp 189–190 °C. IR (KBr) ν_{max} 3105 (ν N–H), 2865, 1585 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.86 (s, 4H), 7.15 (s, 2H), 7.32 (ddd, *J* 7.8, 7.3, 1.5, 1H), 7.50 (ddd, *J* 8.0, 7.3, 1.5, 1H), 7.61 (dd, *J* 7.8, 1.5, 1H), 8.4 (dd, *J* 8.0, 1.5, 1H); ^{13}C NMR ($CDCl_3$) δ 49.95, 122.95, 126.95, 127.56, 129.08, 129.82, 130.55, 130.61, 146.62, 166.83; EIMS 212 (M), 211, 182, 156.

4.4. X-ray analysis

Crystals of **3d**, **5**, **9**, and **10** were obtained by crystallization from solutions in ethyl acetate and those of **3e** were obtained from a solution in methanol. The intensity data for all compounds were recorded at room temperature on a Nonius Kappa CCD diffractometer [λ(Mo Kα)=0.7107 Å] driven by DENZO[27] and COLLECT[28] software. Crystals of **5**, **9**, and **10** are isomorphous. All structures were solved by direct methods[29] and refined based on F^2 using SHELXL97,[30] both programs operating under the WinGx program package.[31] All hydrogen atoms were located on difference Fourier maps and were allowed to ride on the respective bonded atoms. Structural illustrations have been drawn with PLATON[32] under WinGx.

3d: $C_{12}H_{12}N_4$, *M*=212.26, monoclinic, space group *P*2/*c*, *a*=20.4378(63), *b*=5.5678(7), *c*=9.6300(13) Å, β=103.320(6)°, *Z*=4, D_c=1.322 g cm^{-3}, final *R*=0.053 and R_w=0.118 for 1693 observed reflections ($I>2\sigma(I)$).

3e: $C_{12}H_{12}N_4$, *M*=212.26, orthorhombic, space group *Pcam*, *a*=15.781(6), *b*=6.372(8), *c*=10.309(9) Å, *Z*=4, D_c=1.360 g cm^{-3}, final *R*=0.080 and R_w=0.223 for 824 observed reflections ($I>2\sigma(I)$). The systematic absences permitted $Pca2_1$ and *Pcam* as possible space groups. The solution of the structure and the refinement in $Pca2_1$ gave similar results as in *Pcam* with missing symmetry strongly indicated.[32]

The molecule almost exhibits C_s symmetry and, in *Pcam*, lies on a crystallographic mirror plane perpendicular to the phenyl ring. Therefore, and due to the lack of symmetry of the azoles, the molecule is disordered over two positions with distinct sites for the –N= atoms and the associated H atoms.

5: $C_{12}H_{14}N_4$, *M*=214.27, monoclinic, space group $P2_1/n$, *a*=9.0190(7), *b*=9.2100(5), *c*=13.1630(16) Å, β=93.575(5)°, *Z*=4, D_c=1.304 g cm^{-3}, final *R*=0.060 and R_w=0.155 for 2155 observed reflections ($I>2\sigma(I)$).

9: $C_{12}H_{10}N_4$, *M*=210.24, monoclinic, space group $P2_1/n$, *a*=8.7990(5), *b*=9.0830(10), *c*=12.9030(10) Å, β=92.762(6)°, *Z*=4, D_c=1.356 g cm^{-3}, final *R*=0.051 and R_w=0.145 for 1868 observed reflections ($I>2\sigma(I)$).

10: $C_{12}H_{12}N_4$, *M*=212.26, monoclinic, space group $P2_1/n$, *a*=8.8890(7), *b*=9.1110(7), *c*=13.0610(7) Å, β=93.558(4)°, *Z*=4, D_c=1.335 g cm^{-3}, final *R*=0.058 and R_w=0.160 for 2063 observed reflections ($I>2\sigma(I)$).

CCDC reference numbers 296364–296368 for compounds **10**, **3d**, **3e**, **5**, and **9**, respectively.

See http://www.rsc.org/suppdata/ … for crystallographic files in .cif format.

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Reactions of salicyl *N*-tosylimines or salicylaldehydes with diethyl acetylenedicarboxylate for the synthesis of highly functionalized chromenes

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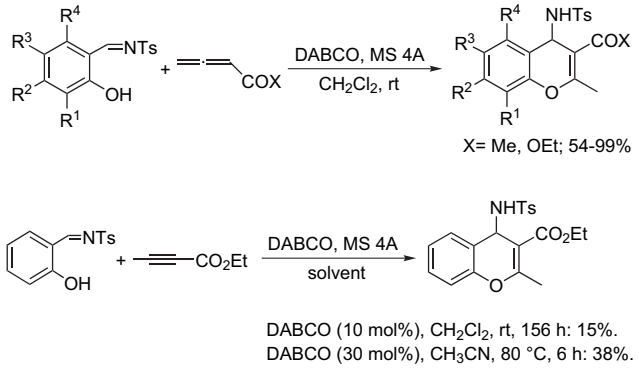
Abstract—Reactions of diethyl acetylenedicarboxylate with salicyl *N*-tosylimines or salicylaldehydes proceeded smoothly in the presence of DABCO or dimethylphenylphosphine under mild conditions to give the corresponding chromenes in excellent yields.

1. Introduction

Due to the unique biological and pharmacological activity, chromene derivatives have attracted considerable attention.[1] Different processes for the synthesis of chromenes have been reported during the past few years.[2] We have recently reported an efficient approach to substituted chromenes by amine-catalyzed reaction of allenic esters, allenic ketones or ethyl 2-butynoate with salicyl *N*-tosylimines (Scheme 1).[3] However, the reaction between ethyl 2-butynoate and salicyl *N*-tosylimine did not give the corresponding chromene in satisfactory yield under various reaction conditions (Scheme 1). During our continuing research in this area, we found that diethyl acetylenedicarboxylate showed higher reactivity than ethyl 2-butynoate for this reaction. In this paper, we report the reactions of salicyl *N*-tosylimines or salicylaldehydes with diethyl acetylenedicarboxylate to give the corresponding chromenes in excellent yields in the presence of DABCO or dimethylphenylphosphine under mild conditions.



Scheme 1. Reaction of allenes or ethyl 2-butynoate with salicyl *N*-tosylimines.

2. Results and discussion

Different solvents and catalysts were first examined using the reaction of salicyl *N*-tosylimine **1a** (1.0 equiv) with diethyl acetylenedicarboxylate **2a** (1.2 equiv) as a model. The results are summarized in Table 1. Using 1,4-diazabicyclo[2,2,2]octane (DABCO) (10 mol %) as the catalyst and performing the reaction in dichloromethane did not give the corresponding chromene and alternatively, acyclic product **3a** was obtained in 50% yield (Table 1, entry 1). Compound **3a** is confirmed to be a mixture of *E:Z* isomers (12:1) by comparison of the ^{1}H NMR chemical shifts of the olefinic protons with those of similar known compounds.[4] Then, several other solvents were examined under the similar conditions (Table 1, entries 2–6). As a consequence, DMSO was found to be the best solvent. Under the catalysis of DABCO, the reaction could be completed in DMSO within 2 h giving the corresponding chromene **4a** in 98% yield (Table 1, entry 6). Other amine or phosphine

Keywords: Salicyl *N*-tosylimines; Salicylaldehydes; DABCO; $PPhMe_2$; Diethyl acetylenedicarboxylate; Chromenes.
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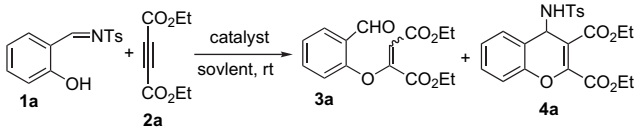
Table 1. Reactions of salicyl *N*-tosylimine **1a** (1.0 equiv) with diethyl acetylenedicarboxylate **2a** (1.2 equiv) in the presence of 10 mol % of catalyst in various solvents



Entry	Solvent	Time (h)	Catalyst	Yield (%)[a]	
				3a	**4a**
1	CH_2Cl_2	25	DABCO	50	—
2	THF	25	DABCO	43	—
3	PhMe	25	DABCO	—	33
4	CH_3CN	25	DABCO	—	60
5	DMF	25	DABCO	—	95
6	DMSO	2	DABCO	—	98
7	DMSO	0.5	DBU	—	94
8	DMSO	0.5	DMAP	—	90
9	DMSO	1	Et_3N	—	91
10	DMSO	0.5	PMe_3	—	92
11	DMSO	2.5	PPh_2Me	—	89
12	DMSO	2	$PPhMe_2$	—	88
13	DMSO	1	PBu_3	—	85
14	DMSO	1	PPh_3	—	90
15	DMSO	3	$^iPr_2NEt$	—	72
16	DMSO	2	K_2CO_3	—	72

[a] Isolated yields.

catalysts also showed catalytic activity for the reaction in DMSO while the yields of **4a** were slightly lower (Table 1, entries 7–14). It should be noted that the weak nucleophile ethyldiisopropylamine ($^iPr_2NEt$) and inorganic catalyst K_2CO_3 could also promote this reaction to give the corresponding chromene **4a** in moderate yields (72%) (Table 1, entries 15 and 16). Thus, we established the optimal reaction conditions for this reaction using DABCO as catalyst and performing the reaction in DMSO.

Under these optimized reaction conditions, the reaction of several other salicyl *N*-tosylimines **1** with **2a** was also examined. Both electron-withdrawing and electron-donating substituents were tolerated at various positions on the benzene rings in the imines. The corresponding chromenes **3** were obtained in good yields (Table 2, entries 1–5).

In the previous study, we found that weak nucleophilic catalysts showed no catalytic activity for the reaction between

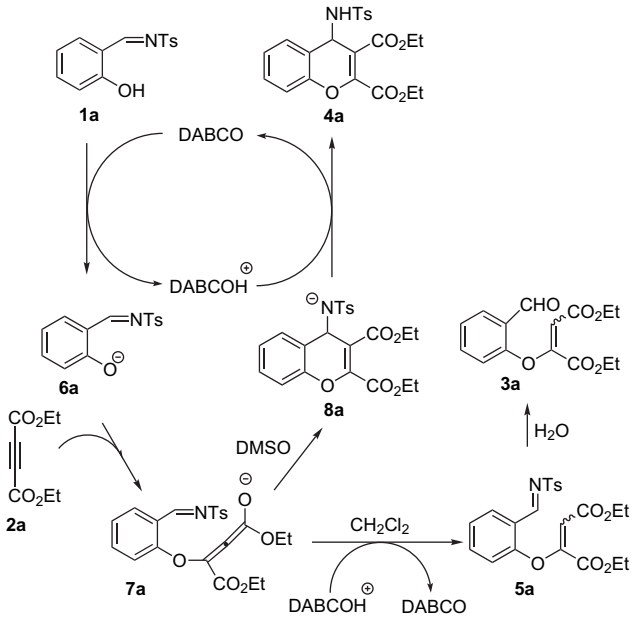
Table 2. Reactions of other salicyl *N*-tosylimines **1** (1.0 equiv) with diethyl acetylenedicarboxylate **2a** (1.2 equiv) in the presence of 10 mol % of DABCO

Entry	R^1	R^2	R^3	Time (h)	Yield of **4** (%)[a]
1	OMe	H	H	1	**4b**: 97
2	H	OMe	H	1	**4c**: 98
3	H	H	OMe	1	**4d**: 90
4	H	H	Cl	2	**4e**: 94
5	Cl	H	Cl	24	**4f**: 83

[a] Isolated yields.

allenic esters and salicyl *N*-tosylimines.[3] While now weak nucleophilic catalyst ethyldiisopropylamine ($^iPr_2NEt$) or K_2CO_3 can also promote the reaction of salicyl *N*-tosylimine **1a** with diethyl acetylenedicarboxylate **2a** effectively. Thus, the reaction was most likely to proceed through a different pathway.

On the basis of the above results, one reasonable mechanism is shown in Scheme 2.[5,6] DABCO first abstracts a proton from imine **1a** to generate anion **6a** and release $DABCOH^+$. Then, Michael addition occurs between intermediate **6a** and **2a** to give intermediate **7a**. Then, the reaction follows different pathways depending on the solvent. In DMSO, intramolecular Mannich reaction occurs in intermediate **7a** to afford intermediate **8a** and subsequent protonation gives product **4a** and regenerates DABCO. In CH_2Cl_2, intermediate **7a** abstracts a proton from $DABCOH^+$ to give compound **5a**, which is hydrolyzed to **3a** upon work up. The reason why the reaction proceeds through different pathways in different solvents has not been fully understood. Based on the previous reports,[7] one reasonable explanation is the medium effect in which the ionic intermediate 8a can be stabilized in the solvent such as DMSO better than in CH_2Cl_2 so that intramolecular Mannich reaction readily occurs in DMSO rather than in CH_2Cl_2. Another explanation is that the proton transfer step for the conversion of intermediate 8a to 4a is rate determining[7,8] and the intramolecular Mannich reaction is a reversible one. Proton transfer in DMSO is much faster, which allows the Mannich reaction to be predominant, while in CH_2Cl_2 the proton transfer is slower and retro-Mannich reaction effectively competes to give the starting anionic intermediate **7a** and subsequent protonation gives **5a**.



Scheme 2. Possible mechanism for the formation of **3a** and **4a**.

To confirm, compound **5a** was indeed obtained during the reaction, we monitored the reaction process of **1a** and **2a** in $CDCl_3$ by ^1H NMR spectra. Molecular sieves 4 Å were added to prevent the decomposition of **1a** during the spectroscopic trace process. Some selected spectra are shown in Figures 1–3. As can be seen from Figure 3, intermediate

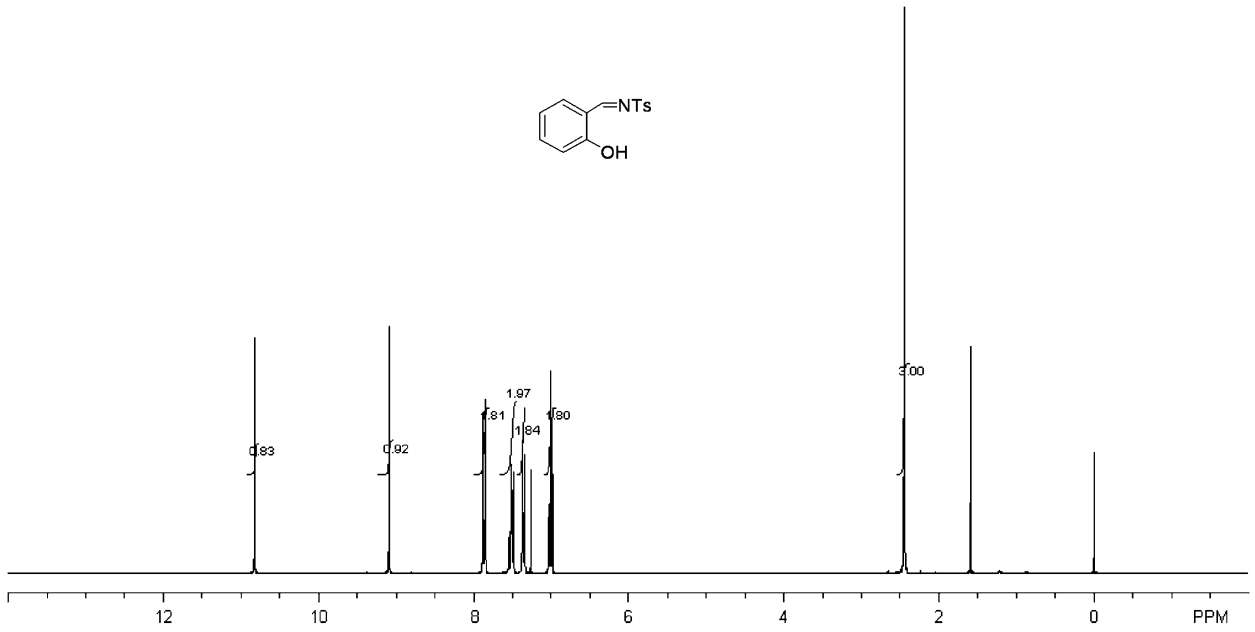


Figure 1. ^{1}H NMR spectroscopy of **1a** in $CDCl_3$.

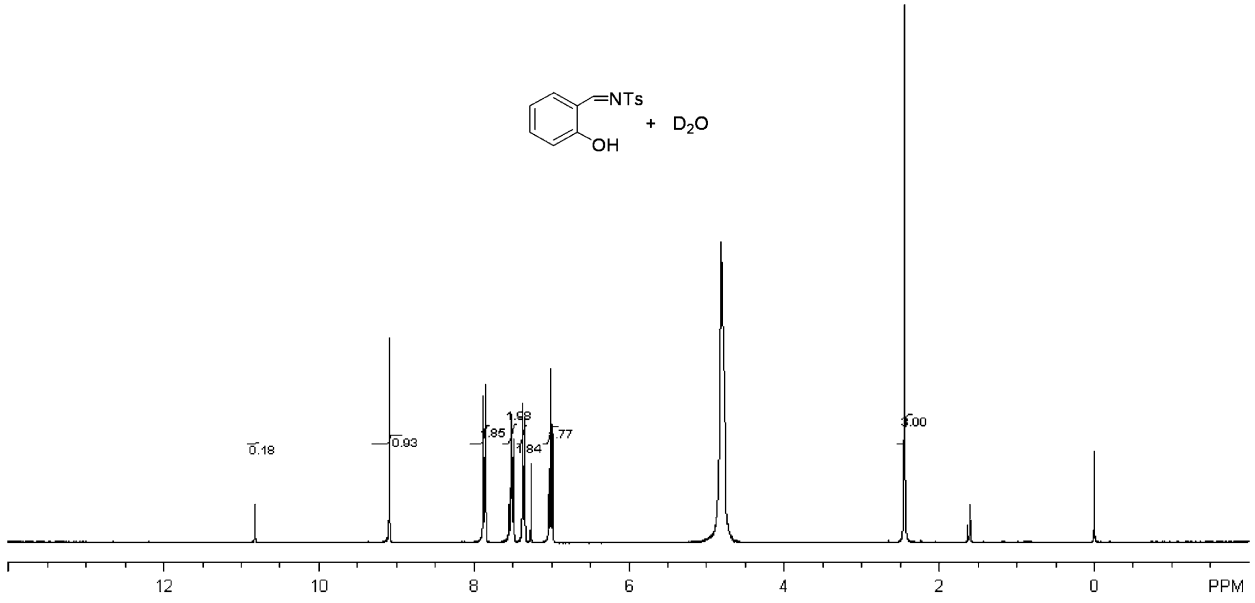


Figure 2. D_2O was added to the solution of **1a** in $CDCl_3$.

5a was indeed observed and the specific peaks for iminium proton and olefinic proton were assigned. Therefore, the reaction is most likely to proceed via the pathway shown in Scheme 2.

When the strongly nucleophilic and weakly basic phosphine is used as the catalyst, the reaction might proceed through an alternative pathway as shown in Scheme 3. The phosphine first attacks **2a** to generate a zwitterionic intermediate **7b**. Then, Mannich reaction between **7b** and **1a** followed by proton transfer provides intermediate **8b**. Subsequent cyclization of **8b** yields product **4a** and regenerates the catalyst.

Since the reaction between salicyl *N*-tosylimine **1a** and diethyl acetylenedicarboxylate **2a** proceeded effectively, we further attempted to know whether the less reactive salicylaldehyde could also react with **2a** to give the corresponding chromene under the similar conditions. Although the reaction of dimethyl acetylenedicarboxylate with salicylaldehyde was reported in the literature, yet the yield of the corresponding chromene was rather low (22%).[4] Thus, it is necessary to study the reaction of salicylaldehyde and **2a** systematically.

The optimization for the reaction conditions of salicylaldehyde **9a** and **2a** is shown in Table 3. Under the same optimal reaction conditions for **1a** and **2a**, the corresponding chromene **10a** could be obtained in 93% yield in 24 h (Table 3, entry 1). Several other catalysts were also screened (Table 3, entries 2–11) and $PPhMe_2$ was found to be the most

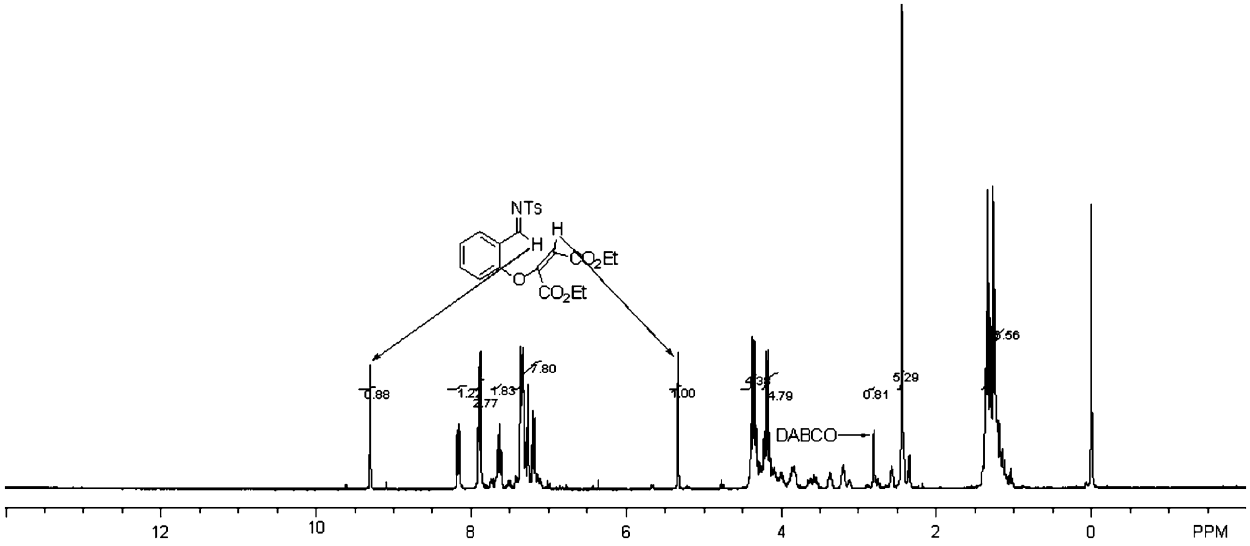
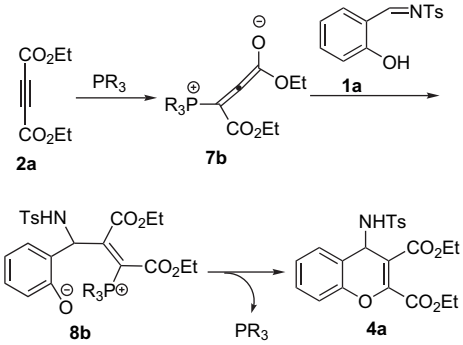
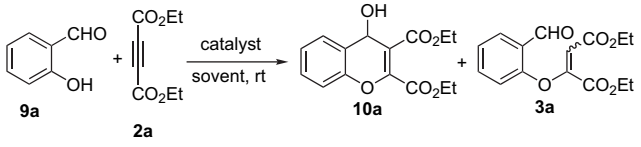


Figure 3. Twelve hours after DABCO was added to the solution of **1a** and **2a** in $CDCl_3$.



Scheme 3. An alternative pathway for the formation of **4a** under the catalysis of phosphine.

Table 3. Reactions of salicylaldehyde **9a** (1.0 equiv) with diethyl acetylenedicarboxylate **2a** (1.2 equiv) in the presence of 10 mol % of catalyst



Entry	Solvent	Time (h)	Catalyst	Yield (%)[a]	
				10a	**3a**
1	DMSO	24	DABCO	93	—
2	DMSO	11	DBU	87	—
3	DMSO	4	Et_3N	82	—
4	DMSO	1	DMAP	74	—
5	DMSO	30	PPh_3	93	—
6	DMSO	7	PBu_3	85	—
7	DMSO	2	PMe_3	95	—
8	DMSO	4	PPh_2Me	88	—
9	DMSO	2	$PPhMe_2$	97	—
10	DMSO	1	$^iPr_2NEt$	73	—
11	DMSO	13	K_2CO_3	77	—
12	CH_3CN	25	$PPhMe_2$	40	—
13	DMF	25	$PPhMe_2$	20	—
14	CH_2Cl_2	25	$PPhMe_2$	—	24
15	THF	25	$PPhMe_2$	—	22
16	PhMe	100	$PPhMe_2$	—[b]	

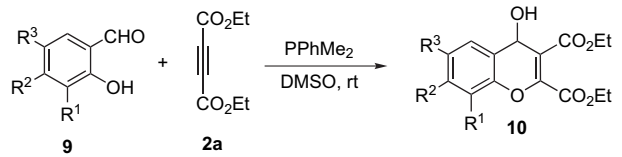
[a] Isolated yields.
[b] Disordered reaction.

effective catalyst (Table 3, entry 9). Using $PPhMe_2$ as the catalyst, solvent effect was also examined (Table 3, entries 12–16). Performing the reaction in acetonitrile and *N*,*N*-dimethylformamide (DMF), both provided **10a** in low yields (Table 3, entries 12 and 13). When carrying out the reaction in CH_2Cl_2 or THF, acyclic product **3a** was obtained as well (Table 3, entries 14 and 15). Changing the solvent to toluene, the reaction became disordered and from which no products could be identified (Table 3, entry 16). Thus, these optimized reaction conditions for this reaction were using $PPhMe_2$ as the catalyst and DMSO as the solvent.

Under the above optimal reaction conditions, several other salicylaldehydes (**9**) can also react with **2a** to give the corresponding chromenes **10** in excellent yields (Table 4, entries 1–5). Therefore, the reaction of salicylaldehyde **9** with **2a** has been significantly improved in comparison with the previous synthetic procedures.[4]

With the acyclic compound **3a** in hand, we further attempted to know if **3a** could be cyclized to chromene **10a** by intramolecular Baylis–Hillman reaction.[9] To test this hypothesis, **3a** was treated with DABCO in DMSO. However, no reaction occurred within 48 h (Scheme 4). This result suggests

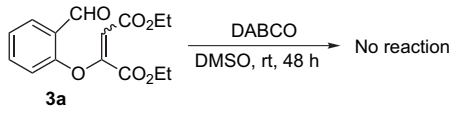
Table 4. Reactions of other salicylaldehydes **9** (1.0 equiv) with diethyl acetylenedicarboxylate **2a** (1.2 equiv) in the presence of 10 mol % of $PPhMe_2$



Entry	R^1	R^2	R^3	Time (h)	Yield of **10** (%)[a]
1	OMe	H	H	3	**10b**: >99
2	H	OMe	H	3	**10c**: 94
3	H	H	OMe	3	**10d**: 92
4	H	H	Cl	24	**10e**: 89
5	Cl	H	Cl	24	**10f**: 83

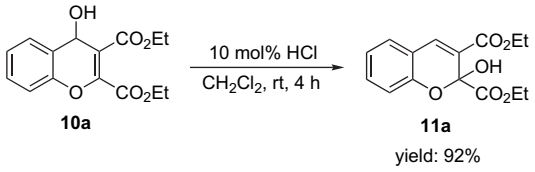
[a] Isolated yields.

again that chromenes **4** and **10** would be formed via the pathway shown in Scheme 2.



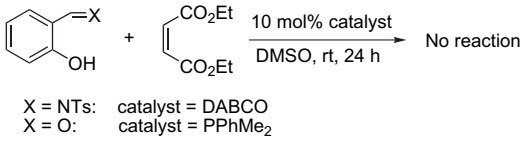
Scheme 4. The attempted intramolecular Baylis–Hillman reaction.

On the other hand, similar to the reported procedure,[4] compound **10a** could be converted to another type of chromene derivative **11a** in 92% yield via hydroxy migration simply by treating with catalytic amount of hydrochloric acid (Scheme 5).



Scheme 5. Transformation of product **10a**.

Since diethyl acetylenedicarboxylate shows excellent reactivity, we further envisioned whether diethyl maleate was also suitable substrate for this kind of reaction. To test this hypothesis, diethyl maleate was subjected to the reaction with salicyl *N*-tosylimine or salicylaldehyde under these above optimized conditions (Scheme 6). However, no reaction occurred presumably due to the reason that diethyl maleate is less electrophilic than diethyl acetylenedicarboxylate as a Michael acceptor.



Scheme 6. The attempted reaction of diethyl maleate with salicyl *N*-tosylimine or salicylaldehyde.

3. Conclusions

We have shown an efficient process for the synthesis of highly functionalized chromene derivatives by reaction of diethyl acetylenedicarboxylate with salicyl *N*-tosylimines or salicylaldehydes. The reaction proceeded smoothly under mild conditions in the presence of DABCO and $PPhMe_2$, respectively, and the corresponding chromenes were obtained in excellent yields. Further application of these products is under progress in our laboratory.

4. Experimental

4.1. General remarks

Mps were obtained with a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer for solution in $CDCl_3$ with tetramethylsilane (TMS) as internal standard; *J*-values are in Hertz. Mass spectra were recorded with a HP-5989 instrument and HRMS was measured by an Ion Spec 4.7 Tesla FTMS mass spectrometer. Some of the solid compounds reported in this paper gave satisfactory CHN microanalyses with a Carlo-Erba 1106 analyzer and other compounds reported in this paper gave satisfactory HRMS analytic data. Commercially obtained reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF_{254} silica gel coated plates. Flash column chromatography was carried out using 200–300 mesh silica gel at increased pressure. The starting materials such as salicylic aldehydes and diethyl acetylenedicarboxylate were bought from Aldrich Company. Salicyl *N*-tosylimines[10] were prepared according to the literature.

4.2. Typical procedure for the reaction of salicyl *N*-tosylimine with diethyl acetylenedicarboxylate catalyzed by DABCO in CH_2Cl_2

To a Schlenk tube with CH_2Cl_2 (1.0 mL) were added salicyl *N*-tosylimine (68.9 mg, 0.25 mmol), diethyl acetylenedicarboxylate (51 mg, 0.3 mmol) and DABCO (2.8 mg, 0.025 mmol). The solution was stirred for 25 h at room temperature. Then, the solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give **3a** (eluent: EtOAc/petroleum=1:6, 36.5 mg, yield 50%) as a colorless liquid. We obtained product **3a** as a mixture of *E*,*Z*-isomers (*E*/*Z*=12:1). The *E*,*Z*-isomers of **3a** could not be isolated by SiO_2 flash chromatography. The ratio of the two isomers was obtained based on ^{1}H NMR spectroscopic data and the corresponding ^{1}H NMR spectroscopic data for *E*-isomers of **3a** could be assigned.

4.2.1. 2-(2-Formyl-phenoxy)-but-2-enedioic acid diethyl ester (3a). A colorless liquid, IR (KBr) ν 1744, 1719, 1697, 1211, 1189 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.27 (t, *J*=7.2 Hz, 3H, CH_3), 1.35 (t, *J*=7.2 Hz, 3H, CH_3), 4.13 (q, *J*=7.2 Hz, 2H, CH_2), 4.37 (q, *J*=7.2 Hz, 2H, CH_2), 5.24 (s, 1H, CH), 7.21 (d, *J*=5.4 Hz, 1H, Ar), 7.40 (t, *J*=7.2 Hz, 1H, Ar), 7.66 (td, *J*=5.4, 1.8 Hz, 1H, Ar), 7.97 (dd, *J*=7.8, 1.8 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.9, 60.8, 62.5, 102.1, 121.5, 126.7, 127.7, 128.9, 135.9, 155.3, 159.6, 161.9, 164.6, 187.6; MS (EI) *m*/*z* 293 (M^+, 0.63), 342 (M^+−170, 53.58), 242 (M^+−270, 35.82), 270 (M^+−242, 12.05), 170 (M^+−342, 4.57), 155 (M^+−357, 11.84); HRMS calcd for $C_{15}H_{16}O_6$ requires 292.0947. Found: 292.0958.

4.3. Typical procedure for the reaction of salicyl *N*-tosylimine with diethyl acetylenedicarboxylate catalyzed by DABCO in DMSO

To a Schlenk tube with DMSO (1.0 mL) were added salicyl *N*-tosylimine (68.9 mg, 0.25 mmol), diethyl acetylenedicarboxylate (51 mg, 0.3 mmol) and DABCO (2.8 mg, 0.025 mmol). The solution was stirred for 2 h at room temperature. CH_2Cl_2 (40 mL) was added and the solution was washed with water (20 mL×3) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a silica gel column

chromatography to give **4a** (eluent: EtOAc/petroleum=1:4, 109.3 mg, yield 98%) as a white solid.

4.3.1. Diethyl 4-(4-methylphenylsulfonamido)-4*H*-chromene-2,3-dicarboxylate (4a). A white solid, mp: 148–150 °C; IR (KBr) ν 3270, 2988, 1712, 1275, 1224, 1158, 1102, 764, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.17 (t, J=7.2 Hz, 3H, CH_3), 1.37 (t, J=7.2 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.88–4.00 (m, 1H, CH_2), 4.32–4.39 (m, 1H, CH_2), 4.35 (q, J=7.2 Hz, CH_2), 5.08 (d, J=7.2 Hz, 1H, NH), 5.65 (d, J=7.2 Hz, 1H, CH), 7.08–7.12 (m, 2H, Ar), 7.22–7.29 (m, 3H, Ar), 7.40 (d, J=7.2 Hz, 1H, CH), 7.66 (d, J=8.1 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.8, 21.4, 46.80, 61.3, 62.5, 106.8, 116.6, 119.4, 125.5, 126.8, 129.2, 129.4, 129.7, 138.8, 142.9, 149.7, 149.8, 161.7, 164.6; MS (EI) m/z 371 (M^+−74, 3.68), 312 (M^+−133, 2.18), 244 (M^+−203, 4.07), 203 (M^+−244, 3.75), 133 (M^+−312, 87.98), 74 (M^+−371, 100.00); Anal. Calcd for $C_{22}H_{23}NO_7S$: C, 59.32; H, 5.20; N, 3.14%. Found: C, 59.43; H, 5.18; N, 2.96%.

4.3.2. Diethyl 8-methoxy-4-(4-methylphenylsulfonamido)-4*H*-chromene-2,3-dicarboxylate (4b). A white solid, mp: 118–122 °C; IR (KBr) ν 3728, 2983, 1718, 1649, 1303, 1214, 1100, 1025, 944, 860, 816, 563 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.17 (t, J=7.2 Hz, 3H, CH_3), 1.37 (t, J=7.2 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 3.86 (s, 3H, CH_3), 3.87–3.90 (m, 1H, CH_2), 3.98–4.00 (m, 1H, CH_2), 4.36 (q, J=7.2 Hz, 2H, CH_2), 4.86 (d, J=8.6 Hz, 1H, NH), 5.67 (d, J=8.6 Hz, 1H, CH), 6.85 (d, J=8.1 Hz, 1H, Ar), 7.01–7.06 (m, 2H, Ar), 7.24 (d, J=8.0 Hz, 2H, Ar), 7.69 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.8, 21.4, 46.8, 56.1, 61.4, 62.5, 106.8, 111.4, 120.5, 120.6, 125,4 126.9, 129.3, 138.8, 139.6, 142.9, 147.6, 149.7, 161.6, 164.6; MS (ESI) m/z 498 (M^++23); Anal. Calcd for $C_{23}H_{25}NO_8S$: C, 58.10; H, 5.30; N, 2.95%. Found: C, 58.05; H, 5.23; N, 2.61%.

4.3.3. Diethyl 7-methoxy-4-(4-methylphenylsulfonamido)-4*H*-chromene-2,3-dicarboxylate (4c). A white solid, mp: 136–140 °C; IR (KBr) ν 3261, 2908, 1725, 1574, 1224, 1492, 1276, 1209, 1156, 1024, 764 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.17 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.2 Hz, 3H, CH_3), 2.41 (s, 3H, CH_3), 3.79 (s, 3H, CH_3), 3.91–4.05 (m, 1H, CH_2), 4.33–4.37 (m, 1H, CH_2), 4.36 (q, J=7.2 Hz, 2H, CH_2), 4.85 (d, J=6.0 Hz, 1H, NH), 5.59 (d, J=6.0 Hz, 1H, CH), 6.60–6.68 (m, 2H, Ar), 7.20–7.40 (m, 3H, Ar), 7.67 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.8, 21.4, 46.8, 55.5, 61.4, 62.5, 100.8, 107.6, 111.5, 113.0, 126.9, 129.3, 130.4, 138.8, 142.9, 149.2, 150.5, 160.3, 161.7, 164.8; MS (EI) m/z 431 (M^+−44, 0.62), 319 (M^+−155,11.71), 245 (M^+−230, 4.57), 230 (M^+−245, 30.14); 155 (M^+−319, 22.77); Anal. Calcd for $C_{23}H_{25}NO_8S$: C, 58.10; H, 5.30; N, 2.95%. Found: C, 57.83; H, 5.33; N, 2.67%.

4.3.4. Diethyl 6-methoxy-4-(4-methylphenylsulfonamido)-4*H*-chromene-2,3-dicarboxylate (4d). A white solid, mp: 174–176 °C; IR (KBr) ν 3279, 2984, 1742, 1651, 1489, 1342, 1276, 1215, 1157 1101, 750 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.19 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.2 Hz, 3H, CH_3), 2.40 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 3.91–4.04 (m, 1H, CH_2), 4.32–4.37 (m, 1H, CH_2), 4.36 (q, J=7.2 Hz, 2H, CH_2), 4.97 (d, J=7.5 Hz, 1H, NH), 5.63 (d, J=7.5 Hz, 1H, CH), 6.82–6.86 (m, 2H, Ar), 7.04 (d, J=8.4 Hz, 1H, Ar), 7.23–7.27 (m, 2H, Ar), 7.66 (d, J=6.3 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.8, 21.4, 47.5, 55.4, 61.4, 62.5, 105.8, 111.9, 117.1, 117.9, 119.7, 126.9, 129.3, 138.9, 143.0, 143.9, 150.1, 156.9, 161.9, 164.8; MS (EI) m/z 431 (M^+−44, 1.82), 319 (M^+−155, 100), 245 (M^+−230, 37.21) 230 (M^+−245, 8.12); 155 (M^+−319, 1.48); Anal. Calcd for $C_{23}H_{25}NO_8S$: C, 58.10; H, 5.30; N, 2.95%. Found: C, 58.02; H, 5.26; N, 2.70%.

4.3.5. Diethyl 6-bromo-4-(4-methylphenylsulfonamido)-4*H*-chromene-2,3-dicarboxylate (4e). A white solid, mp: 160–162 °C; IR (KBr) ν 3250, 2985, 1722, 1479, 1346, 1276, 1158, 1030, 813 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.23 (t, J=7.2 Hz, 3H, CH_3), 1.39 (t, J=7.2 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3), 4.01–4.04 (m, 1H, CH_2), 4.07–4.09 (m, 1H, CH_2), 4.54 (q, J=7.2 Hz, 2H, CH_2), 5.13 (d, J=6.9 Hz, 1H, NH), 5.53 (d, J=6.9 Hz, 1H, CH), 6.98 (d, J=8.7 Hz, 1H, Ar), 7.22–7.26 (m, 3H, Ar), 7.36 (dd, J=8.7, 2.4 Hz, 1H, Ar), 7.61 (d, J=8.4 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.8, 21.5, 46.7, 61.7, 62.7, 106.9, 117.8, 118.6, 120.7, 126.8, 129.5, 132.3, 132.6, 138.5, 143.5, 148.9, 149.5, 161.5, 164.4; MS (EI) m/z 367 (M^+−155, 51.60), 352 (M^+−171,37.39), 171 (M^+−352, 4.76), 155 (M^+−367, 14.84); Anal. Calcd for $C_{22}H_{22}BrNO_7S$: C, 50.39; H, 4.23; N, 2.67%. Found: C, 50.41; H, 4.17; N, 2.49%.

4.3.6. 6,8-Dichloro-4-(toluene-4-sulfonylamino)-4*H*-chromene-2,3-dicarboxylic acid diethyl ester (4f). A white solid, mp: 136–140 °C; IR (KBr) ν 3281, 2984, 1745, 1654, 1587, 1489, 1302, 815, 765 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.21 (t, J=7.2 Hz, 3H, CH_3), 1.39 (t, J=7.2 Hz, 3H, CH_3), 2.42 (s, 3H, CH_3) 3.99–4.06 (m, 2H, CH_2), 4.37 (q, J=7.2 Hz, 2H, CH_2), 5.07 (d, J=7.6 Hz, 1H, NH), 5.65 (d, J=7.6 Hz, 1H, CH), 7.10 (s, 1H, Ar), 7.26–7.33 (m, 2H, Ar), 7.33 (s, 1H, Ar), 7.64 (d, J=7.5 Hz, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.80, 13.85, 21.5, 46.9, 61.8, 62.8, 107.4, 121.8, 123.0, 126.9, 127.8, 129.5, 130.0, 130.2, 138.3, 143.6, 144.7, 149.2, 160.9, 164.0; MS (EI) m/z 357 (M^+−155, 76.77), 342 (M^+−170, 53.58), 242 (M^+−270, 35.82), 270 (M^+−242, 12.05), 170 (M^+−342, 4.57), 155 (M^+−357, 11.84); Anal. Calcd for $C_{22}H_{21}Cl_2NO_7S$: C, 51.37; H, 4.12; N, 2.72%. Found: C, 51.07; H, 4.34; N, 2.45%.

4.4. Typical procedure for the reaction of salicylaldehyde with diethyl acetylenedicarboxylate catalyzed by $PPhMe_2$ in DMSO

To a Schlenk tube with DMSO (1.0 mL) were added salicylaldehyde (30.5 mg, 0.25 mmol), diethyl acetylenedicarboxylate (51 mg, 0.3 mmol) and $PPhMe_2$ (3.5 mg, 0.025 mmol). The solution was stirred for 2 h at room temperature. CH_2Cl_2 (40 mL) was added and the solution was washed with water (20 mL×3) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by a silica gel column chromatography to give **10a** (eluent: EtOAc/petroleum=1:4, 70.8 mg, yield 97%) as a white solid.

4.4.1. 4-Hydroxy-4*H*-chromene-2,3-dicarboxylic acid diethyl ester (10a). A white solid, mp: 63–64 °C; IR (KBr) ν 2985, 1746, 1654, 1275, 1587, 1488, 1301, 1222, 1045, 1015, 892, 759 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.32 (t, J=7.2 Hz, 3H, CH_3), 1.38 (t, J=7.2 Hz, 3H, CH_3), 3.11 (d, J=4.8 Hz, 1H, CH), 4.33 (q, J=7.2 Hz, 2H, CH_2), 4.39 (q, J=7.2 Hz, 2H, CH_2), 5.76 (d, J=4.8 Hz, 1H, OH), 7.15 (d, J=6.9 Hz, 1H, Ar), 7.25–7.54 (m, 2H, Ar), 7.56 (dd, J=7.5, 1.5 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.8, 14.0, 60.3, 61.5, 62.5, 107.4, 116.6, 120.8, 125.5, 129.6, 129.9, 149.0, 150.2, 162.3, 165.7; MS (EI) *m/z* 291 (M^+, 8.39), 191 (M^+-101, 8.49) 173 (M^+-118, 100), 118 (M^+-173, 6.78), 101 (M^+-191, 17.59); Anal. Calcd for $C_{15}H_{16}O_6$: C, 61.64; H, 5.52%. Found: C, 61.52; H, 5.56%.

4.4.2. Diethyl 4-hydroxy-8-methoxy-4*H*-chromene-2,3-dicarboxylate (10b). A white solid, mp: 100–102 °C; IR (KBr) ν 3270, 2988, 1712, 1275, 1224, 1158, 1102, 764, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.34 (t, J=7.2 Hz, 3H, CH_3), 1.39 (t, J=7.2 Hz, 3H, CH_3), 3.10 (d, J=5.1 Hz, 1H, CH), 3.89 (s, 3H, CH_3), 4.26 (q, J=7.2 Hz, 2H, CH_2), 4.35 (q, J=7.2 Hz, 2H, CH_2), 5.74 (d, J=5.1 Hz, 1H, OH), 6.90 (d, J=6.6 Hz, 1H, Ar), 7.10–7.27 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.8, 14.0, 56.1, 60.5, 61.5, 62.5, 107.3, 111.6, 120.8, 121.7, 125.4, 139.0, 147.6, 150.1, 162.3, 165.7; MS (EI) *m/z* 280 (M^+-43, 21.64), 235 (M^+-89, 10.16) 89 (M^+-235, 11.30), 43 (M^+-280, 8.81), 101 (M^+-191, 17.59); Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63%. Found: C, 59.52; H, 5.61%.

4.4.3. Diethyl 4-hydroxy-7-methoxy-4*H*-chromene-2,3-dicarboxylate (10c). A white solid, mp: 98–100 °C; IR (KBr) ν 3627, 2983, 1748, 1294, 1236, 1100, 1033, 858, 818, 775 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.31 (t, J=7.2 Hz, 3H, CH_3), 1.37 (t, J=7.2 Hz, 3H, CH_3), 3.59 (d, J=5.4 Hz, 1H, CH), 3.85 (s, 3H, CH_3), 4.27 (q, J=7.2, Hz, 2H, CH_2), 4.40 (q, J=7.2 Hz, 2H, CH_2), 5.69 (d, J=5.4 Hz, 1H, OH), 6.86 (dd, J=9.0, 2.0 Hz, 1H, Ar), 7.07–7.13 (m, 2H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.6, 13.8, 55.9, 60.1, 61.3, 62.3, 107.4, 111.3, 120.7, 121.8, 125.1, 138.8, 147.4, 149.8, 162.0, 165.6; MS (EI) *m/z* 203 (M^+-119, 100), 188 (M^+-133, 0.68) 119 (M^+-203, 16.24), 133 (M^+-188, 3.32); Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63%. Found: C, 59.45; H, 5.55%.

4.4.4. Diethyl 4-hydroxy-6-methoxy-4*H*-chromene-2,3-dicarboxylate (10d). A white solid, mp: 124–126 °C; IR (KBr) ν 3454, 2982, 1750, 1288, 1224, 1113, 1098, 974, 837, 755 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.32 (t, J=7.2 Hz, 3H, CH_3), 1.37 (t, J=7.2 Hz, 3H, CH_3), 3.40 (d, J=5.1 Hz, 1H, CH), 3.80 (s, 3H, CH_3), 4.26 (q, J=7.2 Hz, 2H, CH_2), 4.37 (q, J=7.2 Hz, 2H, CH_2), 5.71 (d, J=5.1 Hz, 1H, OH), 6.77 (dd, J=9.0, 2.4 Hz, 1H, Ar), 6.99 (d, J=2.4 Hz, 1H, Ar) 7.06 (d, J=8.7 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.9, 55.5, 60.6, 61.3, 62.3, 106.3, 112.3, 116.8, 117.6, 121.4, 143.0, 150.3, 156.7, 162.3, 165.7; MS (EI) *m/z* 203 (M^+-119, 100.00), 119 (M^+-203, 21.76); Anal. Calcd for $C_{16}H_{18}O_7$: C, 59.62; H, 5.63%. Found: C, 59.34; H, 5.53%.

4.4.5. Diethyl 6-chloro-4-hydroxy-4*H*-chromene-2,3-dicarboxylate (10e). A white solid, mp: 78–80 °C; IR (KBr) ν 3464, 2983, 1719, 1653, 1480, 1375, 1283, 860, 818, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.34 (t, J=7.2 Hz, 3H, CH_3), 1.42 (t, 3H, J=7.2 Hz, CH_3), 3.21 (d, J=6.0 Hz, 1H, CH), 4.31 (q, J=7.2 Hz, 2H, CH_2), 4.37 (q, J=7.2 Hz, 2H, CH_2), 5.76 (d, J=7.2 Hz, 1H, OH), 7.09 (d, J=9.0 Hz, 1H, Ar), 7.29 (dd, J=5.7, 2.4 Hz, 1H, Ar), 7.40 (d, J=2.4 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.8, 59.9, 61.5, 62.5, 107.4, 118.0, 122.4, 129.4, 129.7, 130.2, 147.4, 149.6, 161.9, 165.4; MS (EI) *m/z* 326 (M^+, 6.17), 207 (M^+-119, 100) 191 (M^+-135, 4.92); Anal. Calcd for $C_{15}H_{15}ClO_6$: C, 55.14; H, 4.63%. Found: C, 55.10; H, 4.56%.

4.4.6. Diethyl 6,8-dichloro-4-hydroxy-4*H*-chromene-2,3-dicarboxylate (10f). A white solid, mp: 96–100 °C; IR (KBr) ν 3458, 2984, 1721, 1656, 1578, 1461, 1305, 1206, 1051, 1014, 987 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz, TMS) δ 1.34 (t, J=7.2 Hz, 3H, CH_3), 1.41 (t, J=7.2 Hz, 3H, CH_3), 3.20 (d, J=6.0 Hz, 1H, CH), 4.32 (q, J=7.2 Hz, 2H, CH_2), 4.42 (q, J=7.2 Hz, 2H, CH_2), 5.71 (d, J=6.0 Hz, 1H, OH), 7.42 (d, J=1.2 Hz, 1H, Ar), 7.45 (d, J=1.2 Hz, 1H, Ar); ^{13}C NMR ($CDCl_3$, 75 MHz, TMS) δ 13.7, 13.8, 60.0, 61.7, 62.6, 108.2, 122.7, 123.7, 127.9, 129.9, 143.7, 148.9, 161.3, 165.1; MS (EI) *m/z* 286 (M^+-75, 100), 189 (M^+-173, 7.60), 173 (M^+-189, 16.32), 75 (M^+-286, 13.87); Anal. Calcd for $C_{15}H_{14}Cl_2O_6$: C, 49.88; H, 3.91%. Found: C, 49.80; H, 3.80%.

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A facile synthesis of fused aromatic spiroacetals based on the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) skeleton

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Abstract—The facile synthesis of a series of aromatic 6,6-spiroacetals based on the parent 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) heterocyclic system is reported. Key steps included the use of a Sonogashira coupling for the synthesis of an aryl acetylene that was coupled to an aryl aldehyde to form a propargyl alcohol intermediate. Hydrogenation of the alkynol followed by oxidation produced a masked dihydroxy ketone that upon treatment with trimethylsilyl bromide underwent deprotection and cyclisation to the fused aromatic spiroacetal.

1. Introduction

The presence of spiroacetals as key sub-units in a wide range of biologically active natural products has prompted a range of synthetic methods for their preparation largely based on the acid catalysed cyclisation of dihydroxyketones or compounds containing a masked carbonyl group.[1] However, the occurrence of spiroacetals in which the oxygen atoms are derived from two aromatic hydroxy groups is less common and therefore fewer methods have been reported for their synthesis. The rubromycins **1–3** (Fig. 1) are a class of antibiotics isolated from cultures of *Streptomyces*[2] that exhibit activity against Gram-positive bacteria. β-Rubromycin **2** and γ-rubromycin **3** exhibit potent inhibition of human telomerase[3] with IC_{50} values of 3 μM and are active against the reverse transcriptase of human immunodeficiency virus-1.[4] These compounds possess a unique aromatic spiroacetal ring system in which benzannelated furan and pyran rings share one carbon atom to form a spiroacetal system. The fact that α-rubromycin **1**, which lacks this aryl spiroacetal moiety, exhibits substantially decreased inhibitory potency towards telomerase (IC_{50}>200 μM), suggests that this

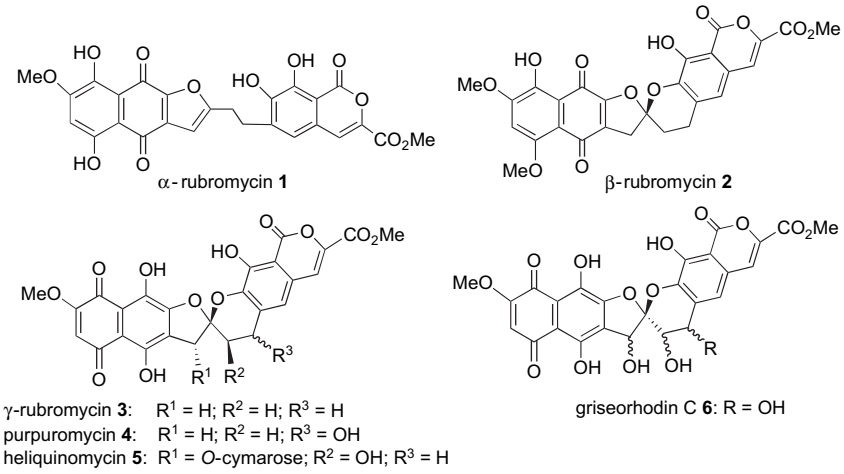

Figure 1. The rubromycin family of antibiotics.

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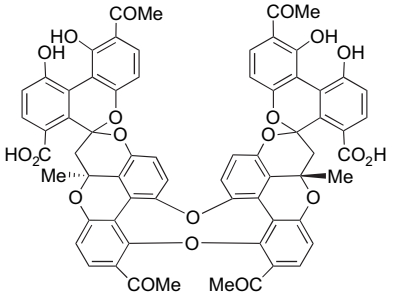
spiroacetal system plays an essential role in the observed inhibition of telomerase. Structurally related to the rubromycins are purpuromycin **4**,[5] a potential topical agent for vaginal infections,[6] heliquinomycin **5**,[7] an inhibitor of DNA helicase and griseorhodin C **6**.[8] All these compounds can act as bioreductive alkylating agents as postulated by Moore.[9]

To date the only synthesis of a naturally occurring bisbenzannelated spiroacetal is the elegant total synthesis of heliquinomycin **5** reported by Danishefsky et al.[10] In this case the key aromatic 5,6-spiroacetal ring system was assembled via electrophilic spiroacetalization of a naphthofuran bearing a phenolic hydroxyl group as the nucleophilic partner. The only other synthesis of the bisbenzannelated spiroacetal ring system present in γ-rubromycin **3** was reported by de Koning et al.[11] in which a Henry reaction allowed union of two aryl moieties and a Nef reaction was used to liberate the masked carbonyl group that induces the spiroacetalization step.

Our research group has also reported[12] the synthesis of several bisbenzannelated aromatic 5,6-spiroacetal analogues of the naturally occurring antibiotic γ-rubromycin **3**. We now herein report the synthesis of a series of aromatic 6,6-spiroacetals as found in the novel cytotoxic acetophenone, cynantetrone **7**.[13] These aryl 6,6-spiroacetals are homologous to the aryl 5,6-spiroacetal present in γ-rubromycin **3**. Extension of the central core spiroacetal ring system provides an opportunity to probe the effect of the conformation of the spiroacetal ring system on the inhibition of human telomerase. Previous syntheses of the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) heterocyclic system involved hydrogenation and acid catalysed cyclisation of a disalicylideneacetone,[14] acid catalysed reaction of resorcinol with 2,6-dimethyl-2,5-heptadien-4-one or 1,5-diphenyl-1,4-pentadien-3-one,[15] or Michael reaction between dimedone and a 1,5-diaryl-1,4-pentadien-3-one[16] followed by intramolecular cyclisation of the Michael 1:2 adduct. These latter approaches however, only afforded C_2-symmetric spirochromans where the oxygen atoms were derived from two aromatic hydroxy groups. Our strategy for the synthesis of the 3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) skeleton was amenable to the preparation of unsymmetrical analogues.

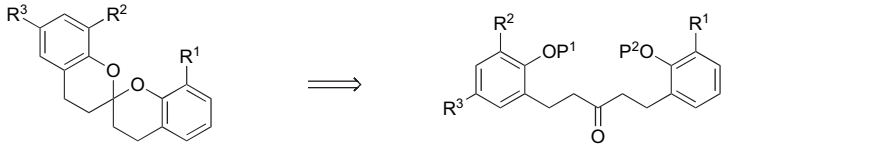


cynantetrone **7**

2. Results and discussion

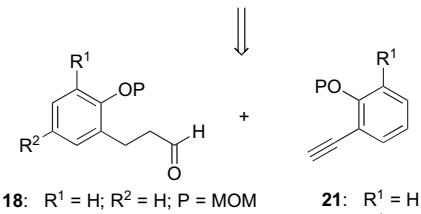
As a part of our synthetic programme directed towards the synthesis of bioactive spiroacetal-containing natural products we prepared the tetracyclic aryl spiroacetals **8**–**12** via disconnection to the protected diphenolic ketones **13**–**17** (Scheme 1). The strategy for assembly of these spiroacetal precursors **13**–**17** focussed on reaction of the aryl acetaldehydes **18**–**20** with the acetylides derived from acetylenes **21** and **22**.

The synthesis of the aryl aldehydes **18**–**20** required for coupling with the acetylenes **21**,**22** is outlined in Scheme 2. Aldehydes **18**–**20** were prepared from the readily available phenols **23**–**25** via Claisen rearrangement of the derived allylphenols **26**–**28**. After protection of the Claisen rearrangement products **29**–**31** as either a methoxymethyl (MOM), a methoxyethoxymethyl (MEM) or an ethoxymethyl (EM) ether, hydroboration of the alkenes **32**–**34** using borane–dimethylsulfide complex at 0 °C afforded the



8: R^1 = H; R^2 = H; R^3 = H
9: R^1 = H; R^2 = OMe; R^3 = H
10: R^1 = H; R^2 = H; R^3 = OMe
11: R^1 = OMe; R^2 = H; R^3 = OMe
12: R^1 = OMe; R^2 = OMe; R^3 = H

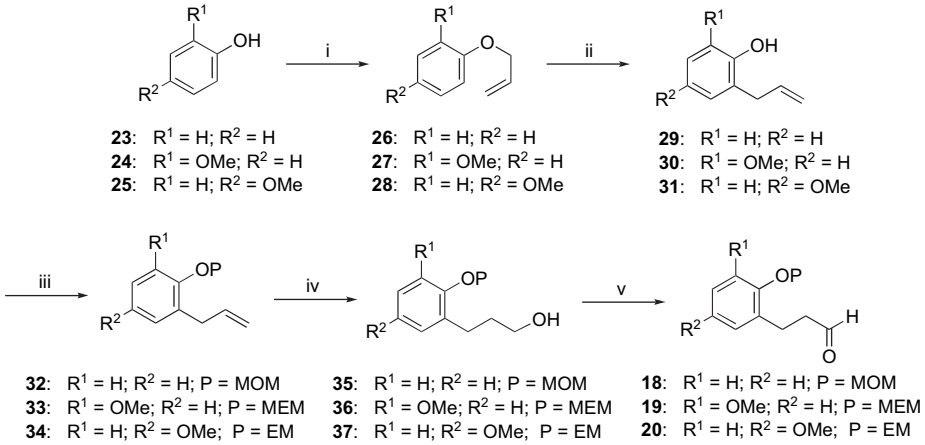
13: R^1 = H; R^2 = H; R^3 = H; P^1 = MOM; P^2 = MEM
14: R^1 = H; R^2 = OMe; R^3 = H; P^1 = MEM; P^2 = MEM
15: R^1 = H; R^2 = H; R^3 = OMe; P^1 = EM; P^2 = MEM
16: R^1 = OMe; R^2 = H; R^3 = OMe; P^1 = EM; P^2 = MOM
17: R^1 = OMe; R^2 = OMe; R^3 = H; P^1 = MEM; P^2 = MOM



18: R^1 = H; R^2 = H; P = MOM
19: R^1 = OMe; R^2 = H; P = MEM
20: R^1 = H; R^2 = OMe; P = EM

21: R^1 = H; P = MEM
22: R^1 = OMe; P = MOM

Scheme 1.



Scheme 2. Reagents, conditions and yields: (i) allyl bromide, K_2CO_3, acetone, reflux, **26**, 86%; **27**, 83%; **28**, 97%; (ii) 180 °C, N_2, **29**, 72%; **30**, 87%; **31**, 99%; (iii) MOMCl/MEMCl/EMCl, $^{i}Pr_2NEt$, CH_2Cl_2, 0 °C, **32**, 50%; **33**, 37%; **34**, 74%; (iv) $BH_3 \cdot SMe_2$, NaOH, H_2O_2, **35**, 60%; **36**, 55%; **37**, 70%; (v) TPAP, NMO, 4 Å MS, CH_2Cl_2, **18**, 51%; **19**, 70%; **20**, 40%.

primary alcohols **35**–**37** that underwent oxidation to the desired aldehydes **18**–**20** in moderate yield using tetrapropylammonium perruthenate (TPAP) and 4-methylmorpholine *N*-oxide (NMO).

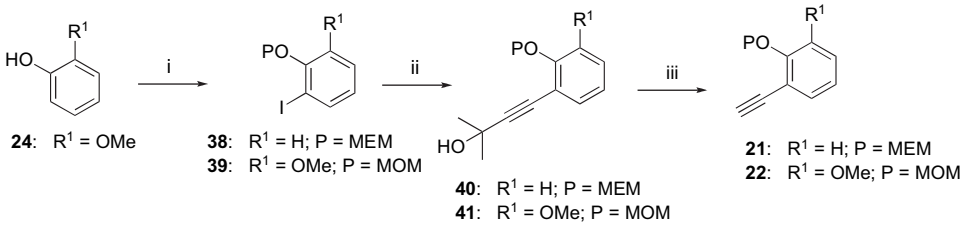
Acetylenes **21** and **22** were prepared (Scheme 3) via Sonogashira reaction of iodides **38** (prepared directly by MEM protection of 2-iodophenol) and **39** (prepared from 2-methoxyphenol **24** via MOM protection followed by ortholithiation and iodination) with 2-methyl-3-butyn-2-ol followed by pyrolysis of the resultant tertiary acetylenic alcohols **40** and **41** under basic conditions.

With both acetylenes **21**, **22** and aldehydes **18**–**20** in hand, the synthesis continued with the coupling of these two sub-units to construct the desired 6,6-spiroacetals **8**–**12** (Scheme 4). The coupling step involved generation of the acetylide by treatment of the appropriate acetylene **21** or **22** with butyllithium at −78 °C under nitrogen. After allowing time for the complete formation of the acetylide (40 min) the appropriate aldehyde **18**, **19** or **20** was added dropwise in tetrahydrofuran. After 1 h the reaction was allowed to warm to room temperature and stirred for a further 2 h. Aqueous workup followed by flash chromatography gave the desired propargyl alcohols **42**–**46** in good yield.

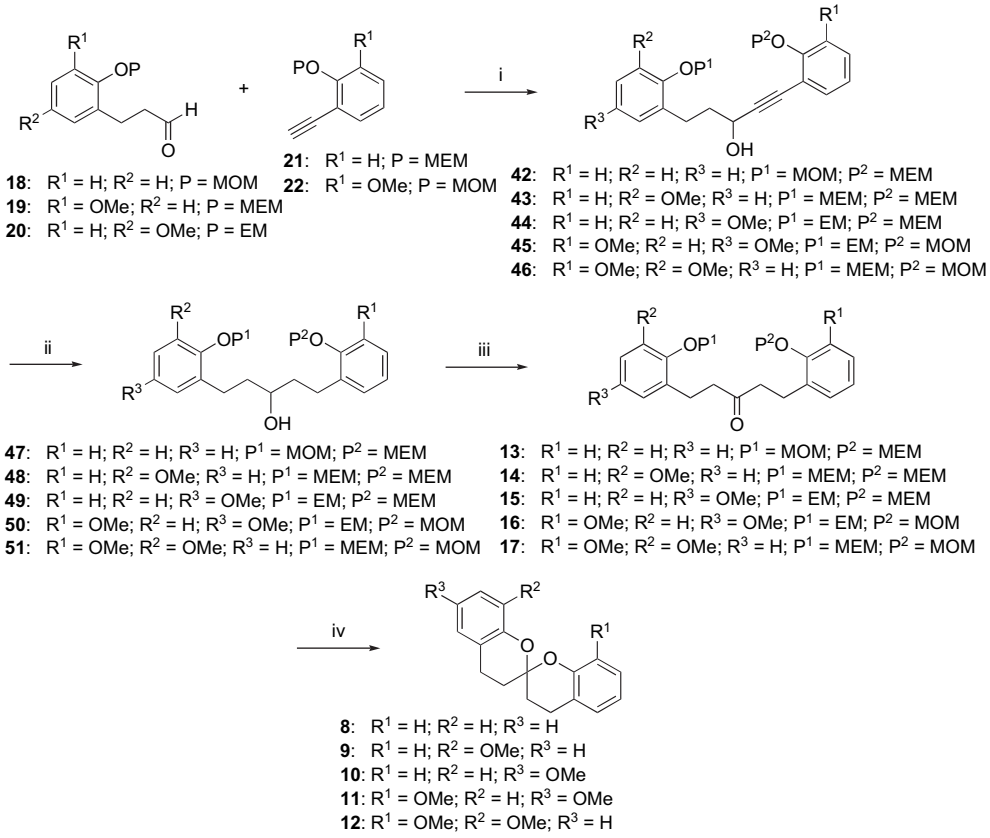
Hydrogenation of the alkyne was then effected by stirring the propargyl alcohols **42**–**46** in ethyl acetate with potassium carbonate over 10% palladium on carbon under hydrogen. The resulting secondary alcohols **47**–**51** were isolated in nearly quantitative yield after purification by flash chromatography. Oxidation of the secondary alcohols **47**–**51** using tetra-*n*-propylammonium perruthenate (TPAP), 4-methylmorpholine *N*-oxide (NMO) and 4 Å molecular sieves in dichloromethane provided the ketones **13**–**17** required for the final spirocyclisation step.

The final step in the synthesis of the aryl 6,6-spiroacetals **8**–**12** involved deprotection of the phenolic hydroxyl groups of the ketones **13**–**17** and subsequent Lewis acid catalysed cyclisation (Scheme 4). The ketones **13**–**17** were treated with trimethylsilyl bromide (10 equiv) in dichloromethane in the presence of 4 Å molecular sieves to effect both deprotection of the methoxyethoxymethyl, or equivalent group, and the cyclisation step.

The ^{1}H NMR spectra of the aryl 6,6-spiroacetals **8**–**12** were much simpler than those of the ketone precursors **13**–**17** due to the symmetrical, or almost, symmetrical nature of the products. The electronic differences induced by the presence of methoxy substituents on the aryl ring did not exhibit an effect on the central spiroacetal ring system. Additionally, the loss of the ether protecting groups led to cleaner NMR spectra. The most characteristic feature in the ^{13}C NMR spectra of the spiroacetals **8**–**12** was the presence of a characteristic quaternary spirocarbon at δ_C 96.2–96.4 ppm. In the ^{1}H NMR spectra four sets of doublets of doublets of doublets could be assigned to the diastereotopic protons of



Scheme 3. Reagents, conditions and yields: (i) MOMCl, $^{i}Pr_2EtN$, CH_2Cl_2, 0 °C then BuLi, THF, rt, 2 h then −45 °C, I_2, 1 h, **39**, 14%; (ii) PPh_3, $PdCl_2(PPh_3)_2$, 2-methyl-3-butyn-2-ol, Et_3N, CuI, **40**, 95%; **41**, 99%; (iii) NaOH, toluene, reflux, **21**, 86%; **22**, 72%.



Scheme 4. Reagents, conditions and yields: (i) ^{n}BuLi, THF, −78 °C to rt, **42**, 57%; **43**, 51%; **44**, 88%; **45**, 73%; **46**, 54%; (ii) 10% Pd/C, K_2CO_3, EtOAc, **47**, 71%; **48**, 77%; **49**, 70%; **50**, 99%; **51**, 83%; (iii) TPAP, NMO, 4 Å MS, CH_2Cl_2, **13**, 99%; **14**, 91%; **15**, 99%; **16**, 95%; **17**, 99%; (iv) TMSBr, CH_2Cl_2, −30 °C to rt, **8**, 97%; **9**, 96%; **10**, 99%; **11**, 96%; **12**, 96%.

the methylene groups in the spiroacetal ring system. The two methylene groups were distinguished using 2D spectroscopy (COSY). Long distance coupling between the aromatic protons of the outer aryl-rings with four protons in the inner spiroacetal rings allowed conclusive assignment of the benzylic CH_2 groups (Fig. 2).

An X-ray crystal structure was also obtained[17] for aryl spiroacetal **11**. The ORTEP diagram for spiroacetal **11** (Fig. 3) clearly shows that the spiroacetal rings adopt a flattened chair–chair arrangement with two anomeric effects stabilising the bis-axial conformation.

In summary five aryl 6,6-spiroacetals that are homologous to the aryl 5,6-spiroacetal ring system present in the telomerase inhibitor γ-rubromycin **3** have been prepared using trimethylsilyl bromide to effect cyclisation of a suitably protected diphenolic ketone precursor. The cyclisation precursors in turn were readily available via coupling of an aryl acetylene to an aryl aldehyde fragment. A Sonogashira reaction was used to prepare the acetylene precursors. The 6,6-spiroacetals thus prepared adopted a flattened chair–chair bis-axial conformation.

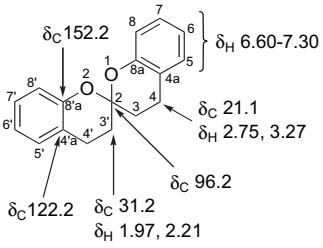


Figure 2. Characteristic ^{1}H and ^{13}C NMR chemical shifts for the parent 6,6-spiroacetal **8**.

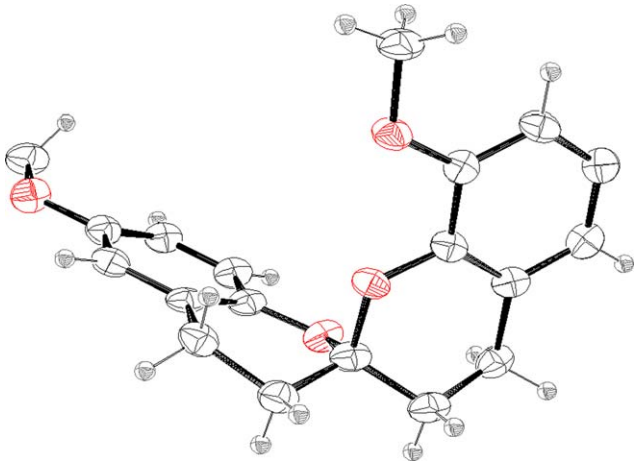


Figure 3. ORTEP diagram for 6,6-spiroacetal **11**.[17]

3. Experimental

3.1. General details

Dichloromethane, toluene and triethylamine were distilled from calcium hydride prior to use. Tetrahydrofuran was dried over sodium/benzophenone and distilled before use. Glassware was oven or flame-dried under an atmosphere of nitrogen. Reactions were carried out under an atmosphere of nitrogen unless otherwise specified. Infrared spectra (IR) were obtained using Perkin Elmer Spectrum 1000 Fourier Transform Infrared spectrometer from thin films between sodium chloride plates. Absorbtion peaks are expressed in wave numbers (cm^{-1}) and were measured between 450 cm^{-1} and 4000 cm^{-1}. The signal strengths are expressed by the abbreviations: s=strong, m=medium, w=weak, and br=broad. NMR spectra were recorded on a Bruker DRX300 spectrometer operating at 300 MHz for ^{1}H nuclei and 75 MHz for ^{13}C nuclei or on a Bruker DRX400 spectrophotometer operating at 400 MHz for ^{1}H nuclei and 100 MHz for ^{13}C nuclei. Chemical shifts are recorded as parts per million (ppm) downfield from tetramethylsilane (TMS) as the internal standard or relative to the ^{1}H in $CDCl_3$. The ^{13}C values were referenced to the residual chloroform peak at δ 77.0 ppm. ^{13}C shifts are reported as chemical shift and assignment. ^{1}H shifts are reported as chemical shift, relative integral, multiplicity, coupling constant and assignment. ^{1}H MNR data are reported as s (singlet); d (doublet); dd (doublet of doublets); dt (doublet of triplets); ddd (doublet of doublets of doublets); t (triplet); q (quartet); m (multiplet); br (broad). *J* values are given in Hertz. All assignments were made with the aid of DEPT 135, COSY and HSQC experiments where required. Low resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal accelerating voltage of 70 eV. High resolution mass spectra were recorded using a VG70-SE spectrometer operating at nominal resolution of 5000–10,000 as appropriate. Fragmentation was induced using desorptive electron impact (DEI^+), electron impact (EI) or fast atom bombardment (FAB^+). Fast atom bombardment (FAB) mass spectra were obtained using 3-nitrobenzyl alcohol as the matrix. Major and significant fragments are quoted in the form *x*(*y*), where *x* is the mass to charge ratio and *y* is the percentage abundance relative to the base peak. Purification by flash chromatography was performed using Merck silica gel 0.0063–0.10 mm with the solvent systems indicated. Thin layer chromatography (TLC) was run on silica precoated aluminium plates (Merck Kieselgel F_{254}). Compounds were visualised under UV fluorescence and by staining with vanillin in methanolic acid followed by heating. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

3.2. Standard procedures

3.2.1. Allylation of phenols. To a stirred solution of the appropriate phenol (5.0 g, 53 mmol) in acetone (30 mL) were added potassium carbonate (9.23 g, 159 mmol) and allyl bromide (4.58 mL, 54 mmol). The mixture was heated under reflux at 65 °C for 16 h, cooled to room temperature, filtered and the filtrate concentrated under reduced pressure. The residue was dissolved in dichloromethane (50 mL) and washed sequentially with 1 M aqueous sodium hydroxide (15 mL), water (15 mL) and brine (15 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.2. Claisen rearrangement of allyl ether. Neat allyl phenyl ether (475 mg, 3.5 mmol) was placed in an oven dried flask or a sealed tube and heated at 200 °C under a nitrogen atmosphere for 16 h. The reaction mixture changed from colourless oil to pale brown oil. The reaction mixture was allowed to cool and the thick oil was subjected to column chromatography using the specified solvent system.

3.2.3. Protection of allylated phenols as methoxymethyl, methoxyethoxymethyl or ethoxymethyl ethers. A stirred solution of the appropriate 2-allylphenol (344 mg, 2.56 mmol) in dry dichloromethane (5 mL) was cooled to 0 °C under nitrogen. Diisopropylethylamine (0.803 mL, 4.61 mmol) was added followed by methoxyethoxymethyl chloride (0.270 mL, 3.59 mmol) dropwise. The cooling bath was removed after 30 min and the mixture was warmed to room temperature over 12 h. Dichloromethane was removed in vacuo and the residue was taken up in diethyl ether (10 mL) and washed sequentially with water (10 mL), 10% aqueous sodium hydroxide (10 mL) and brine (10 mL). The organic layer was dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by column chromatography using the specified solvent system.

3.2.4. Hydroboration of protected allylphenol. Allylphenol (100 mg, 0.45 mmol) was dissolved in tetrahydrofuran (6 mL) and the solution was cooled to 0 °C. Borane–dimethyl sulfide complex (0.09 mL, 0.9 mmol) was added dropwise and the mixture was stirred at 0 °C for 5 h then warmed to room temperature and stirred overnight. The excess borane was quenched by the addition of methanol (0.5 mL). Sodium hydroxide (1 M, 0.5 mL) was added carefully followed by the dropwise addition of hydrogen peroxide (30%, 0.5 mL) and the resultant mixture stirred overnight. The mixture was extracted with diethyl ether (5 mL) and the combined organic extracts were dried over magnesium sulfate. The solvents were concentrated in vacuo and the resultant residue was purified by flash chromatography using the specified solvent system.

3.2.5. TPAP oxidation of the alcohol. To a mixture of the alcohol (294 mg, 1.5 mmol) in dichloromethane (5 mL) with 4 Å molecular sieves (300 mg) were added tetra-*n*-propylammonium perruthenate (30 mg, 0.075 mmol) and 4-methylmorpholine *N*-oxide (263 mg, 2.25 mmol) and the reaction was stirred at room temperature for 1 h. The mixture was filtered through a plug of flash silica and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.6. Sonogashira coupling. A mixture of the protected iodophenol (308 mg, 1.0 mmol), 2-methyl-3-butyn-2-ol (0.154 mL, 1.6 mmol), triphenylphosphine (5 mg, 0.02 mmol) and bis(triphenylphosphine)palladium(II) dichloride (7 mg, 0.01 mmol) in dry triethylamine (5 mL) was stirred under nitrogen at 80 °C for 15 min. Copper(I) iodide (4 mg, 0.002 mmol) was then added and the reaction was heated

overnight at 80 °C. The reaction mixture was filtered through a plug of Celite® and concentrated under reduced pressure. The resultant residue was purified by column chromatography using the specified solvent system.

3.2.7. Pyrolysis of the tertiary alcohol. A mixture of the alcohol (101 mg, 0.384 mmol) and solid sodium hydroxide (468 mg, 1.92 mmol) in dry toluene (10 mL) was heated under reflux for 3.5 h. The reaction was quenched by the addition of saturated ammonium chloride solution (4 mL) and extracted with diethyl ether (10 mL). The solvents were removed under reduced pressure and the resultant residue was purified by column chromatography using the specified solvent system.

3.2.8. Coupling of the acetylene with the aldehyde. *n*-Butyllithium (0.18 mL, 1.6 M in hexane, 0.29 mmol) was added dropwise to a stirred solution of the acetylene (75 mg, 0.31 mmol) in tetrahydrofuran (1 mL) at −78 °C under nitrogen. The solution was stirred at −78 °C for 40 min then a solution of the aldehyde (50 mg, 0.26 mmol) in tetrahydrofuran (0.5 mL) was added dropwise and the mixture was stirred for 1 h. The mixture was allowed to warm to room temperature and stirred for 2.5 h. Water (3 mL) was added and the mixture was extracted with ethyl acetate (3×2 mL). The combined organic extracts were washed with brine (1 mL), dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.9. Hydrogenation of acetylene. A mixture of the acetylene (80 mg, 0.17 mmol), 10% palladium on carbon (67 mg, 0.63 mmol) and potassium bicarbonate (86 mg, 0.63 mmol) in ethyl acetate (2 mL) was stirred under an atmosphere of hydrogen at room temperature for 2 h. The resulting mixture was filtered through a plug of Celite® and the filtrate was concentrated in vacuo. The resulting residue was purified by flash chromatography using the specified solvent system.

3.2.10. Oxidation of the secondary alcohol to a ketone. Tetra-*n*-propylammonium perruthenate (0.3 mg, 0.008 mmol) was added to a stirred mixture of the secondary alcohol (74 mg, 0.16 mmol), 4-methylmorpholine *N*-oxide (3 mg, 0.24 mmol) and 4 Å molecular sieves (45 mg) in dichloromethane (1 mL). The reaction was stirred at room temperature for 1.5 h then filtered through a plug of silica gel and the filtrate concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.2.11. Cyclisation of the ketone to a 6,6-spiroacetal. To a mixture of ketone (70 mg, 0.15 mmol), 4 Å molecular sieves (50 mg) in dichloromethane (1.5 mL) at −30 °C was added trimethylsilyl bromide (0.20 mL, 1.5 mmol) and the reaction was stirred under nitrogen for 1 h. The reaction was warmed to 0 °C stirred for 1 h, then poured into water (1 mL) and extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (1 mL), dried over magnesium sulfate and concentrated in vacuo. The resultant residue was purified by flash chromatography using the specified solvent system.

3.3. Spectroscopic data for individual compounds

3.3.1. Allyl phenyl ether (26). The allylation reaction was carried out according to the standard procedure using phenol **23** (5.0 g, 53 mmol), allyl bromide (4.58 mL, 54 mmol) and potassium carbonate (9.23 g, 159 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as eluent to give the title compound **26** (6.09 g, 86%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 4.52 (2H, d, *J* 5.5, $OCH_2CH{=}CH_2$), 5.28 (1H, dd, J_{gem} 1.6, *J* 7.8, $OCH_2CH{=}CH_AH_B$), 5.43 (1H, dd, J_{gem} 1.6, *J* 13.8, $OCH_2CH{=}CH_AH_B$), 6.06 (1H, m, $OCH_2CH{=}CH_2$), 7.3–6.9 (5H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 68.6 ($OCH_2CH{=}CH_2$), 117.5 ($OCH_2CH{=}CH_2$), 133.3 ($OCH_2CH{=}CH_2$), 114.7, 120.8, 129.4 (Ar-CH), 158.5 (q, Ar-C). The spectroscopic data were in agreement with the literature.[18]

3.3.2. 2-Allylphenol (29). The Claisen rearrangement reaction was carried out according to the standard procedure using allyl phenyl ether **26** (475 mg, 3.5 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the title compound **29** (338 mg, 72%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 3.42 (2H, d, *J* 6.7, $CH_2CH{=}CH_2$), 4.95 (1H, br s, O*H*), 5.17 (1H, m, $CH_2CH{=}CH_AH_B$), 5.18 (1H, t, *J* 1.5, $CH_2CH{=}CH_AH_B$), 6.03 (1H, m, $CH_2CH{=}CH_2$), 7.3–6.9 (4H, Ar-H); δ_C (75 MHz, $CDCl_3$) 35.0 ($CH_2CH{=}CH_2$), 116.3 ($CH_2CH{=}CH_2$), 115.7, 120.8 (Ar-CH), 125.2 (q, C2), 127.8, 136.2 (Ar-CH), 136.2 ($CH_2CH{=}CH_2$), 154.0 (q, C1). The spectroscopic data were in agreement with the literature.[19]

3.3.3. 1-Allyl-2-(methoxymethoxy)benzene (32). The protection step was carried out according to the standard procedure using 2-allylphenol **29** (344 mg, 2.56 mmol), diisopropylamine (0.803 mL, 4.61 mmol) and methoxymethyl chloride (0.270 mL, 3.59 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the title compound **32** (226 mg, 50%) as colourless oil. δ_H (400 MHz, $CDCl_3$) 3.41 (2H, d, *J* 6.2, $CH_2CH{=}CH_2$), 3.48 (3H, s, OCH_3), 5.02 (1H, m, $CH_2CH{=}CH_AH_B$), 5.07 (1H, m, $CH_2CH{=}CH_AH_B$), 5.20 (2H, s, OCH_2O), 5.98 (1H, m, $CH_2CH{=}CH_2$), 7.3–6.9 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 34.4 ($CH_2CH{=}CH_2$), 56.0 (OCH_3), 94.4 (OCH_2O), 115.4 ($CH_2CH{=}CH_2$), 137.0 ($CH_2CH{=}CH_2$), 115.4, 121.7, 127.3, 130.0 (Ar-CH), 137.0 (q, C2), 154.0 (q, C1). The spectroscopic data were in agreement with the literature.[20]

3.3.4. 3-(2-(Methoxymethoxy)phenyl)propan-1-ol (35). The hydroboration reaction was carried out according to the standard procedure using 1-allyl-2-(methoxymethoxy)-benzene **32** (100 mg, 0.45 mmol) and borane–dimethyl sulfide complex (0.09 mL, 0.9 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as eluent to give the *title compound* **35** (65 mg, 60%) as colourless oil. (Found: M^+, 196.1098, $C_{11}H_{16}O_3$ requires 196.1099); ν_{max} (film)/cm^{-1} 3368 (br, O–H), 2934 (s, ArC–H), 2358 (w, O–CH_2–O), 1233 (m, C–O), 1151 (w, C–OH); δ_H (400 MHz, $CDCl_3$) 1.68 (1H, br s, O*H*), 1.86 (2H, quintet, *J* 7.4, 6.2, $CH_2CH_2CH_2OH$), 2.75 (2H, t, *J* 7.4, $CH_2CH_2CH_2OH$), 3.50 (3H, s, OCH_3), 3.64 (2H, t, *J* 6.2, $CH_2CH_2CH_2OH$), 5.21 (2H, s, OCH_2O), 7.3–6.9

(4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.1 (CH_2, C-2), 33.0 (CH_2, C-3), 56.0 (OCH_3), 62.0 (CH_2OH), 94.6 (OCH_2O), 113.9, 121.8, 127.2, 130.2 (Ar-CH), 130.6 (q, C1′), 155.2 (q, C2′); *m/z* (EI, %) 196 (M^+, 4), 164 (15), 134 (71), 121 (7), 119 (12), 91 (11), 45 (100).

3.3.5. 3-(2-(Methoxymethoxy)phenyl)propanal (18). The oxidation was carried out according to the standard procedure using [3-(2-(methoxymethoxy)phenyl)]propan-1-ol (**35**) (294 mg, 1.5 mmol), tetra-*n*-propylammonium perruthenate (30 mg, 0.075 mmol), 4-methylmorpholine *N*-oxide (263 mg, 2.25 mmol) and 4 Å molecular sieves (500 mg). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **18** (148 mg, 51%) as a colourless oil. (Found: M^+, 194.0940, $C_{11}H_{14}O_3$ requires 194.0943); ν_{max} (film)/cm^{-1} 2932 (m, ArC–H), 2826 (m, CH_2–O–CH_2), 2724 (w, CHO), 1722 (s, C=O), 1492 (w, C–O–C), 1235 (w, C–O); δ_H (400 MHz, $CDCl_3$) 2.76 (2H, dt, *J* 7.8, 1.6, CH_2CHO), 2.98 (2H, t, *J* 7.8, ArCH_2), 3.50 (3H, s, OCH_3), 5.20 (2H, s, OCH_2O), 7.3–6.9 (4H, m, Ar-H), 9.83 (1H, t, *J* 1.6, C*H*O); δ_C (75 MHz, $CDCl_3$) 23.5 (*C*H_2CH$_2$CHO), 44.0 (*C*H_2CHO), 56.1 (OCH_3), 114.2 (OCH_2O), 114.0, 121.9, 127.2, 130.2 (Ar-CH), 129.2, (q, C1′), 155.1 (q, C2′), 202.3 (CHO); *m/z* (EI, %) 194 (M^+, 3), 162 (4), 132 (16), 121 (6), 91 (6), 77 (5), 45 (100).

3.3.6. 1-Iodo-2-((2-methoxyethoxy)methoxy)benzene (38). The protection step was carried out according to the standard procedure using 2-iodophenol (1.07 g, 4.9 mmol), diisopropylethylamine (1.65 mL, 9.4 mmol) and methoxyethoxymethyl chloride (0.81 mL, 7.2 mmol). The product was purified by column chromatography using hexane–ethyl acetate (85:15) as the eluent to give the *title compound* **38** (1.14 g, 75%) as a colourless oil. (Found: M^+, 307.9912, $C_{10}H_{13}IO_3$ requires 307.9909); ν_{max} (film)/cm^{-1} 2923 (s, ArC–H), 2879 (m, O–CH_2–O), 1472 (s, C–O–C), 1229 (s, C–O), 644 (w, C–I); δ_H (400 MHz, $CDCl_3$) 3.35 (3H, s, OCH_3), 3.57 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.87 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.36 (2H, s, OCH_2O), 6.65–7.80 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 58.9 (OCH_3), 68.1 (O*C*H$_2$CH$_2$OCH$_3$), 71.4 (OCH$_2$*C*H$_2$OCH$_3$), 87.1 (q, C-1), 93.9 (OCH_2O), 115.0, 123.7, 129.5, 139.4 (Ar-CH), 156.0 (q, C-2); *m/z* (EI, %) 308 (M^+, 6), 233 (5), 220 (5), 106 (6), 89 (99), 76 (7), 59 (100), 45 (6).

3.3.7. 4-[(2-Methoxyethoxy)methoxy)phenyl]-2-methylbut-3-yn-2-ol (40). The Sonogashira reaction was carried out according to the standard procedure using 1-iodo-2-((2-methoxyethoxy)methoxy) benzene (**38**) (308 mg, 1.0 mmol), 2-methyl-3-butyn-2-ol (0.154 mL, 1.6 mmol), triphenylphosphine (5 mg, 0.02 mmol), bis(triphenylphosphine)palladium(II) dichloride (7 mg, 0.01 mmol), triethylamine (5 mL) and copper(I) iodide (4 mg, 0.002 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **40** (247 mg, 95%) as a colourless oil. (Found: M^+, 264.1356, $C_{15}H_{20}O_4$ requires 264.1362); ν_{max} (film)/cm^{-1} 3423 (br, O–H), 2980 (s, ArC–H), 2930 (s, O–CH_2–O), 2228 (w, C=C), 1489 (s, C–O–C), 1449, 1372 (w, geminal CH_3); δ_H (400 MHz, $CDCl_3$) 1.63 (6H, 2×s, 2×CH_3), 3.81 (3H, s, OCH_3), 2.47 (1H, br s, O*H*), 3.59 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.91 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.32 (2H, s, OCH_2O), 6.90–7.40 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 31.0 (C(*C*H_3)$_2$), 59.0 (OCH_3), 65.6 (q, COH), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 78.3 (q, Ar–*C*≡C), 94.4 (OCH_2O), 97.9 (Ar–C=*C*), 113.7 (q, C1′), 115.8, 122.0, 129.6, 133.4, (Ar–CH), 157.7 (q, C2′); *m/z* (EI, %) 264 (M^+, 0.5), 158 (100), 143 (8), 131 (7), 115 (5), 89 (24), 59 (85), 43 (24).

3.3.8. 1-Ethynyl-2-((2-methoxyethoxy)methoxy)benzene (21). The reaction was carried out according to the standard procedure using 4-(2-((2-methoxyethoxy)-methoxy)-phenyl)-2-methylbut-3-yn-2-ol (**40**) (101 mg, 0.384 mmol) and sodium hydroxide (468 mg, 1.92 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **21** (68 mg, 86%) as a colourless oil. (Found: M^+, 206.0941, $C_{12}H_{14}O_3$ requires 206.0943); ν_{max} (film)/cm^{-1} 3235 (s, C≡C–H), 2970 (s, ArC–H), 2930 (m, O–CH_2–O), 2100 (w, C≡C), 1489 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 3.27 (1H, s, C≡C*H*), 3.37 (3H, s, OCH_3), 3.56 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.88 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 5.32 (2H, s, OCH_2O), 6.90–7.40 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 30.9 (C≡*C*H), 59.0 (OCH_3), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.5 (OCH$_2$*C*H$_2$OCH$_3$), 80.0 (q, Ar-*C*≡C), 81.0 (q, C1), 94.4 (OCH_2O), 115.0, 121.7, 130.2, 134.1, (Ar-CH), 158.3 (q, C2); *m/z* (EI, %) 206 (M^+, 3), 131 (15), 118 (5), 103 (4), 89 (70), 77 (8), 100 (85), 45 (5).

3.3.9. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]-pent-1-yn-3-ol (42). The coupling reaction was carried out according to the standard procedure using 3-(2-(methoxymethoxy)phenyl)propanal (**18**) (25 mg, 0.124 mmol), 1-ethynyl-2-((2-methoxyethoxy)-methoxy) benzene (**21**) (20 mg, 0.102 mmol) and *n*-butyllithium (0.064 mL, 0.122 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **42** (23 mg, 57%) as a colourless oil. (Found: M^+, 400.1874, $C_{23}H_{28}O_6$ requires 400.1886); ν_{max} (film)/cm^{-1} 3428 (br, O–H), 2925 (s, ArC–H), 2920 (m, O–CH_2–O), 1491 (s, C–O–C), 1078 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.10 (2H, q, *J* 7.8, 6.2, CH_2CH$_2$Ar), 2.41 (1H, br s, O*H*), 2.89 (2H, t, *J* 7.8, CH$_2$CH_2Ar), 3.31 (3H, s, CH$_2$CH$_2$OCH_3), 3.45 (3H, s, OCH$_2$OCH_3), 3.57 (2H, t, *J* 4.7, OCH_2CH$_2$OCH$_3$), 3.88 (2H, t, *J* 4.7, OCH$_2$CH_2OCH$_3$), 4.61 (1H, t, *J* 6.2, C*H*OH), 5.18 (2H, s, OCH_2OCH$_3$), 5.32 (2H, s, CH$_2$OCH_2O), 6.90–7.5 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.2 (CH_2, C-5), 38.0 (CH_2, C-4), 56.1 (OCH_3), 59.0 (OCH$_2$CH$_2$O*C*H$_3$), 62.5 (CHOH), 67.9 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 81.3 (q, Ar-*C*≡C), 94.1 (q, Ar-C≡*C*), 94.2 (O*C*H$_2$OCH$_2$), 94.5 (O*C*H$_2$OCH$_3$), 112.6 (q, C1′), 113.4 (q, C1″), 114.0, 115.5, 121.8, 121.9, 127.4, 129.8, 130.3, 133.5 (Ar-CH), 155.2 (q, C2″), 157.9 (q, C2′); *m/z* (EI, %) 400 (M^+, <0.5), 262 (20), 250 (18), 131 (19), 121 (15), 89 (44), 59 (100), 45 (65).

3.3.10. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[(2-(methoxymethoxy)phenyl]-pentan-3-ol (47). The hydrogenation was carried out according to the standard procedure using 1-[(2-methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)-phenyl]-pent-1-yn-3-ol (**42**) (7 mg, 0.0175 mmol), 10% palladium on carbon (7 mg, 0.0063 mmol) and potassium carbonate (9 mg, 0.063 mmol). The product

was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **42** (5 mg, 71%) as a colourless oil. (Found: $M^+(+NH_4)$, 422.2537, $C_{23}H_{32}O_6(+NH_4)$ requires 422.2543); ν_{max} (film)/cm^{-1} 3459 (br, O–H), 2928 (s, ArC–H), 1493 (s, C–O–C), 1078 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, m, C*H*$_2$CH$_2$Ar), 2.25 (1H, br s, O*H*), 2.75 (4H, m, CH$_2$C*H*$_2$Ar), 3.37 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.47 (3H, s, OCH$_2$OC*H*$_3$), 3.47 (1H, m, C*H*OH), 3.58 (2H, m, OC*H*$_2$CH$_2$OCH$_3$), 3.82 (2H, m, OCH$_2$C*H*$_2$OCH$_3$), 5.20 (2H, s, OC*H*$_2$OCH$_3$), 5.29 (2H, s, CH$_2$OC*H*$_2$O), 6.90–7.50 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.4 (CH$_2$Ar), 37.8 (*C*H$_2$CHOH), 56.1 (OCH$_2$O*C*H$_3$), 59.0 (OCH$_3$), 67.7 (O*C*H$_2$CH$_2$OCH$_3$), 70.4 (CHOH), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 93.6 (O*C*H$_2$OCH$_2$), 94.5 (O*C*H$_2$OCH$_3$), 114.0, 114.1, 121.9, 121.9, 127.1, 127.1, 130.1, 130.3 (Ar-CH), 131.1, (q, C1′ and *C*1″), 155.1, 155.1 (q, C2″ and C2′); *m*/*z* (DEI$^+$, %) 422 (M^+, 8), 405 (3), 329 (30), 314 (27), 297 (80), 284 (35), 267 (100), 107 (22).

3.3.11. 1-[((2-Methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]-pentan-3-one (13). The reaction was carried out according to the standard procedure using 1-[((2-methoxyethoxy)methoxy)phenyl]-5-[2-(methoxymethoxy)phenyl]pentan-3-ol (**47**) (5 mg, 0.0124 mmol), tetra-*n*-propylammonium perruthenate (0.2 mg, 0.0062 mmol), 4-methylmorpholine *N*-oxide (2 mg, 0.0186 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **13** (5 mg, >99%) as a colourless oil. (Found: $M^+(+NH_4)$, 420.2390, $C_{23}H_{30}O_6(+NH_4)$ requires 420.2386); ν_{max} (film)/cm^{-1} 2925 (s, ArC–H), 1714 (s, C=O), 1494 (m, C–O–C), 1079 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.70 (4H, m, C*H*$_2$CO), 2.89 (4H, m, CH$_2$C*H*$_2$Ar), 3.37 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.46 (3H, s, OCH$_2$OC*H*$_3$), 3.55 (2H, t, *J* 4.4, OC*H*$_2$CH$_2$OCH$_3$), 3.80 (2H, t, *J* 4.4, OCH$_2$C*H*$_2$OCH$_3$), 5.18 (2H, s, OC*H*$_2$OCH$_3$), 5.28 (2H, s, OC*H*$_2$OCH$_2$), 6.80–7.30 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 24.9 (CH$_2$*C*H$_2$Ar), 42.9 (*C*H$_2$CO), 56.0 (CH$_2$CH$_2$O*C*H$_3$), 59.0 (OCH$_3$), 67.7 (O*C*H$_2$CH$_2$OCH$_3$), 71.6 (OCH$_2$*C*H$_2$OCH$_3$), 93.4 (O*C*H$_2$OCH$_2$), 94.3 (O*C*H$_2$OCH$_3$), 113.9, 114.0, 121.7, 125.5, 127.4, 127.5 (Ar-CH), 129.9 (q, C1″ and C1′), 130.0, 130.1 (Ar-CH), 155.08, 155.14 (q, C2″ and C2′), 210.0 (CHO); *m*/*z* (DCI$^+$, %) 420 (68), 297 (44), 295 (25), 282 (28), 265 (100), 253 (62), 131 (24), 89 (14).

3.3.12. 3,4,3′,4′,-Tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (8). The reaction was carried out according to the standard procedure using 1-[((2-methoxyethoxy)-methoxy)-phenyl]-5-[2-(methoxymethoxy)phenyl]pentan-3-one (**13**) (15 mg, 0.0373 mmol), trimethylsilyl bromide (0.05 mL, 0.373 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **13** (9 mg, 97%) as a colourless solid, mp 63–65 °C. (Found: M^+, 252.1145, $C_{17}H_{16}O_2$ requires 252.1150); ν_{max} (film)/cm^{-1} 2925 (s, ArC–H), 1455 and 1488 (m, C–O–C), 1094 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.97 (2H, ddd, J_{gem} 13.0, $J_{3ax,4ax}$ 13.0, $J_{3ax,4eq}$ 5.9, 3 and 3′-H$_{ax}$), 2.21 (2H, ddd, J_{gem} 13.0, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H$_{eq}$), 2.75 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.9, $J_{4eq,3eq}$ 2.6, 4 and 4′-H$_{eq}$), 3.27 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.0, $J_{4ax,3eq}$ 5.9, 4 and 4′-H$_{ax}$), 6.60–7.30 (8H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.0 (CH$_2$, C-4 and C-4′), 31.2 (CH$_2$, C-3 and C-3′), 96.2 (q, C2), 117.1, 120.8, (Ar-CH), 122.2 (q, C4a and C4a′), 127.2, 129.0 (Ar-CH), 152.2 (q, C8a and C8a′); *m*/*z* (EI, %) 252 (M^+, 60), 158 (14), 145 (40), 131 (100), 107 (40), 77 (13), 57 (6), 43 (4).

3.3.13. 1-(Allyloxy)-2-methoxybenzene (27). The allylation reaction was carried out according to the standard procedure using 2-methoxyphenol (**24**) (5.0 g, 40 mmol), allyl bromide (4.87 mL, 40 mmol) and potassium carbonate (16.58 g, 120 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the title compound **27** (5.46 g, 83%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.89 (3H, s, OC*H*$_3$), 4.58 (2H, d, *J* 5.5, OC*H*$_2$CH=CH$_2$), 5.27 (1H, m, OCH$_2$CH=C*H*$_A$H$_B$), 5.40 (1H, m, OCH$_2$CH=CH$_A$*H*$_B$), 6.06 (1H, m, OCH$_2$C*H*=CH$_2$), 6.90–7.30 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.7 (OCH$_3$), 69.7 (O*C*H$_2$CH=CH$_2$), 111.7, 113.5 (Ar-CH), 117.7 (CH=*C*H$_2$), 120.6, 121.1 (Ar-CH), 133.3 (OCH$_2$*C*H=CH$_2$), 147.9 (q, C2), 149.4 (q, C1). The spectroscopic data were in agreement with the literature.[11]

3.3.14. 2-Allyl-6-methoxyphenol (30). The Claisen rearrangement was carried out according to the standard procedure using 1-(allyloxy)-2-methoxybenzene (**27**) (3.664 g, 22.3 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the title compound **30** (3.20 g, 87%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.40 (2H, m, C*H*$_2$CH=CH$_2$), 3.80 (3H, s, OC*H*$_3$), 4.65 (1H, br s, O*H*), 5.04 (1H, m, CH$_2$CH=C*H*$_A$H$_B$), 5.08 (1H, m, CH$_2$CH=CH$_A$*H*$_B$), 6.00 (1H, m, CH$_2$C*H*=CH$_2$), 6.60–6.80 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 33.6 (*C*H$_2$CH=CH$_2$), 55.6 (OCH$_3$), 108.5 (Ar-CH), 115.1 (CH$_2$CH=*C*H$_2$), 119.2, 122.0 (Ar-CH), 125.8 (q, C2), 136.5 (CH$_2$*C*H=CH$_2$), 143.2 (q, C1), 146.2 (q, C6).[11]

3.3.15. 1-Allyl-3-methoxy-2-((2-methoxyethoxy)methoxy)-benzene (33). The protection step was carried out according to the standard procedure using 2-allyl-6-methoxyphenol (**30**) (1.13 g, 7.9 mmol), diisopropylethylamine (2.48 mL, 14.70 mmol) and methoxyethoxymethyl chloride (0.90 mL, 7.9 mmol). The product was purified by column chromatography using hexane–ethyl acetate (70:30) as the eluent to give the *title compound* **33** (761 mg, 37%) as a colourless oil. ν_{max} (film)/cm^{-1} 3077 (w, CH=CH$_2$), 2934 (s, ArC–H), 1285 (w, C–O), 1150 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 3.33 (3H, s, CH$_2$CH$_2$OC*H*$_3$), 3.38 (2H, m, C*H*$_2$CH=CH$_2$), 3.54 (2H, m, OC*H*$_2$CH$_2$OCH$_3$), 3.89 (3H, s, OC*H*$_3$), 3.90 (2H, m, OCH$_2$C*H*$_2$OCH$_3$), 5.04 (1H, m, CH$_2$CH=C*H*$_A$H$_B$), 5.04 (1H, m, CH$_2$CH=CH$_A$*H*$_B$), 5.15 (2H, s, OC*H*$_2$O), 5.97 (1H, m, CH$_2$C*H*=CH$_2$), 6.70–7.00 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 33.8 (*C*H$_2$CH=CH$_2$), 55.1 (OCH$_3$), 58.5 (CH$_2$CH$_2$O*C*H$_3$), 68.6 (*C*H$_2$CH$_2$OCH$_3$), 71.3 (CH$_2$*C*H$_2$OCH$_3$), 97.3 (OCH$_2$O), 109.93 (Ar-CH), 115.2 (CH$_2$CH=*C*H$_2$), 121.5, 123.7 (Ar-CH), 133.7 (q, C1), 136.7 (CH$_2$*C*H=CH$_2$), 143.6 (q, C3), 151.8 (q, C2); *m*/*z* (EI, %) 163 (M^+, 5), 131 (25), 93 (52), 63 (100), 51 (9).

3.3.16. 3-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]propan-1-ol (36). The hydroboration reaction was

carried out according to the standard procedure using 1-allyl-3-methoxy-2-((2-methoxyethoxy)methoxy)benzene (**33**) (730 mg, 2.9 mmol) and borane–dimethyl sulfide complex (0.600 mL, 6.0 mmol). The product was purified by column chromatography using hexane–ethyl acetate (10:90) as the eluent to give the *title compound* **36** (430 mg, 55%) as a colourless oil. (Found: M^+, 270.1468, $C_{14}H_{22}O_5$ requires 270.1467); ν_{max} (film)/cm^{-1} 3431 (br, O–H), 2935 (s, ArC–H), 1264 (s, C–O), 1159 (w, C–OH); δ_H (400 MHz, $CDCl_3$) 1.86 (2H, m, $CH_2CH_2CH_2OH$), 2.60 (1H, br s, O*H*), 2.77 (2H, t, *J* 6.3, $CH_2CH_2CH_2OH$), 3.38 (3H, s, CH_2OCH_3), 3.59 (4H, m, CH_2OH and $OCH_2CH_2OCH_3$), 3.80 (3H, s, OCH_3), 3.94 (2H, t, *J* 5.1, $OCH_2CH_2OCH_3$), 5.17 (2H, s, OCH_2O), 6.75–7.00 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.1 (CH_2, C-2), 33.0 (CH_2, C-3), 55.5 (OCH_3), 58.9 ($CH_2CH_2OCH_3$), 61.7 (CH_2OH), 69.0 ($CH_2CH_2OCH_3$), 71.70 ($CH_2CH_2OCH_3$), 98.0 (OCH_2O), 109.9, 121.9, 124.2 (Ar-CH), 135.8 (q, C1′), 144.2 (q, C3′), 151.9 (q, C2′); *m*/*z* (EI, %) 270 (M^+, <0.5), 194 (20), 149 (5), 137 (5), 89 (21), 59 (100), 45 (4).

3.3.17. 3-[(3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]propanal (19). The oxidation was carried out according to the standard procedure using [3-(3-methoxy)-2-((2-methoxyethoxy)-methoxy)phenyl]propan-1-ol (**36**) (430 mg, 1.6 mmol), tetra-*n*-propylammonium perruthenate (3 mg, 0.08 mmol), 4-methylmorpholine *N*-oxide (200 mg, 2 mmol) and 4 Å molecular sieves (750 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **19** (301 mg, 70%) as a colourless oil. (Found: M^+, 268.1310, $C_{14}H_{20}O_5$ requires 268.1311); ν_{max} (film)/cm^{-1} 2932 (s, ArC–H), 2838 (m, CH_2–O–CH_2), 2724 (w, CHO), 1722 (s, C=O), 1476 (s, C–O–C), 1265 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.77 (2H, q, *J* 1.6, 7.0, CH_2CH_2CHO), 3.00 (2H, t, *J* 7.0, $ArCH_2$), 3.38 (3H, s, CH_2OCH_3), 3.57 (2H, t, *J* 6.3 $OCH_2CH_2OCH_3$), 3.81 (3H, s, OCH_3), 3.90 (2H, t, *J* 6.3, $OCH_2CH_2OCH_3$), 5.19 (2H, s, OCH_2O), 6.70–7.00 (3H, m, Ar-H), 9.81 (1H, t, *J* 1.6, C*H*O); δ_C (75 MHz, $CDCl_3$) 23.0 (CH_2, C-3), 44.3 (CH_2, C-2), 55.5 (OCH_3), 58.8 ($CH_2CH_2OCH_3$), 69.0 ($CH_2CH_2OCH_3$), 71.6 ($CH_2CH_2OCH_3$), 97.8 (OCH_2O), 110.5, 121.6, 124.2 (Ar-CH), 134.4 (q, C1′), 144.2 (q, C3′), 152.0 (q, C2′), 201.9 (CHO); *m*/*z* (EI, %) 268 (M^+, 6), 151 (4), 136 (5), 89 (64), 77 (4), 65 (3), 59 (100), 45 (4).

3.3.18. 5-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-1-([2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (43). The coupling reaction was carried out according to the standard procedure using 3-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**19**) (162 mg, 0.79 mmol), 1-ethynyl-2-((2-methoxyethoxy)methoxy)benzene (**21**) (165 mg, 0.654 mmol) and butyllithium (0.5 mL, 0.785 mmol). The product was purified by column chromatography using hexane–ethyl acetate (20:80) as the eluent to give the *title compound* **43** (152 mg, 51%) as a colourless oil. (Found: M^+, 400.1875, $C_{23}H_{28}O_6$ requires 400.1886); ν_{max} (film)/cm^{-1} 3435 (br, O–H), 2928 (m, ArC–H), 1474 (m, C–O–C), 1077 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.12 (2H, q, *J* 7.3, 5.9, CH_2CH_2Ar), 2.45 (1H, br s, O*H*), 2.96 (2H, t, *J* 7.3, CH_2CH_2Ar), 3.36, 3.54 (6H, each s, 2×$CH_2CH_2OCH_3$), 3.54 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.81 (3H, s, OCH_3), 3.88 (4H, m, 2×$OCH_2CH_2OCH_3$), 4.65 (1H, t, *J* 5.9, C*H*OH), 5.20 (2H, s, 2″-OCH_2OCH_2), 5.30 (2H, s, 2′-OCH_2OCH_2), 6.70–7.50 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 25.8 (CH_2, C-5), 38.7 (CH_2, C-4), 55.5 (OCH_3), 58.7 (2″-$OCH_2CH_2OCH_3$), 58.8 (CHOH), 62.3 (2′-$OCH_2CH_2OCH_3$), 67.7 (2′-$OCH_2CH_2OCH_3$), 68.9 (2″-$OCH_2CH_2OCH_3$), 71.4 (2′-$OCH_2CH_2OCH_3$), 71.7 (2″-$OCH_2CH_2OCH_3$), 80.7 (q, Ar-C≡C), 94.3 (q, Ar-C≡C), 94.0 (2′-OCH_2OCH_2), 98.0 (2″-OCH_2OCH_2), 110.1 (Ar-CH), 113.4 (q, C1″), 115.3, 121.7, 122.1, 124.1, 129.5, 133.4 (Ar-CH), 135.5 (q, C1′), 144.4 (q, C3′), 152.0 (q, C2′), 157.7 (q, C2″); *m*/*z* (EI, %) 400 (M^+, <0.5), 262 (25), 250 (21), 173 (5), 89 (45), 59 (100), 45 (65).

3.3.19. 1-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]-pentan-3-ol (48). The hydrogenation was carried out according to the standard procedure using 5-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]-pent-1-yn-3-ol (**43**) (116 mg, 0.253 mmol), 10% palladium on carbon (100 mg, 0.0912 mmol), potassium carbonate (126 mg, 0.912 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **48** (90 mg, 77%) as a colourless oil. (Found: M^+, 479.2648, $C_{26}H_{39}O_8$ requires 479.2645); ν_{max} (film)/cm^{-1} 3435 (br, O–H), 2928 (s, ArC–H), 1474 (m, C–O–C), 1077 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, quintet, *J* 7.6, 13.9, CH_2CH_2Ar), 2.79 (4H, m, CH_2CH_2Ar), 3.36, 3.37 (6H, each s, 2′- and 2″-$CH_2CH_2OCH_3$), 3.55 (5H, m, 2′- or 2″-$OCH_2CH_2OCH_3$ and C*H*OH), 3.80 (3H, s, OCH_3), 3.81 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 3.93 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 5.17 (2H, s, 2′-OCH_2OCH_2), 5.27 (2H, s, 2″-OCH_2OCH_2), 6.70–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.2, 26.4 (CH_2-Ar), 37.7, 38.2 (CH_2CHOH), 55.5 ($ArOCH_3$), 58.8, 58.9 ($OCH_2CH_2OCH_3$), 67.6, 69.0 ($OCH_2CH_2OCH_3$), 70.3 (CHOH), 71.4, 71.7 ($OCH_2CH_2OCH_3$), 93.5 (2″-OCH_2OCH_2), 98.0 (2′-OCH_2OCH_2), 109.9, 114.0, 121.7, 121.9, 124.1, 126.9, 130.0 (Ar-CH), 131.2 (q, C3″), 136.2 (q, C1″), 144.2 (q, C1′), 152.0 (q, C2′), 155.0 (q, C2″); *m*/*z* (FAB$^+$, %) 479 (M^+, 3), 402 (2), 372 (4), 219 (3), 165 (5), 154 (100), 136 (70), 89 (46).

3.3.20. 1-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-one (14). The oxidation was carried out according to the standard procedure using 1-[(3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]-5-[2-((2-methoxyethoxy)-methoxy)phenyl] pentan-3-ol (**48**) (90 mg, 0.195 mmol), tetra-*n*-propylammonium perruthenate (0.3 mg, 0.0097 mmol), 4-methylmorpholine *N*-oxide (3.4 mg, 0.29 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **14** (82 mg, 91%) as a colourless oil. (Found: M^+, 476.2406, $C_{26}H_{36}O_8$ requires 476.2410); ν_{max} (film)/cm^{-1} 2930 (s, ArC–H), 1712 (s, C=O), 1492 (s, C–O–C), 1078 (s, C–O); δ_H (400 MHz, $CDCl_3$) 2.70 (4H, t, *J* 8.1, CH_2CO), 2.91 (4H, m, CH_2Ar), 3.35 (6H, each s, 2×$CH_2CH_2OCH_3$), 3.55 (4H, m, 2×$OCH_2CH_2OCH_3$), 3.80 (3H, s, OCH_3), 3.82 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 3.93 (2H, m, 2′- or 2″-$OCH_2CH_2OCH_3$), 5.17 (2H, s, 2′-OCH_2OCH_2), 5.27 (2H, s, 2″-OCH_2OCH_2), 6.70–7.35 (7H, m, Ar-H); δ_C (75 MHz,

$CDCl_3$) 24.8, 24.9 (CH_2CH_2-Ar), 42.8, 43.2 (CH_2CH_2-Ar), 55.5 ($ArOCH_3$), 58.8, 58.9 ($OCH_2CH_2OCH_3$), 67.6, 69.0 ($OCH_2CH_2OCH_3$), 71.5, 71.6 ($OCH_2CH_2OCH_3$), 93.3 (2″-OCH_2OCH_2), 97.8 (2′-OCH_2OCH_2), 110.3, 113.9, 121.6, 121.8, 124.1, 127.3, 129.8 (Ar-CH), 129.8 (q, C1″), 135.2 (q, C1′), 144.2 (q, C3′), 152.0 (q, C2′), 155.0 (q, C2″), 209.6 (q, CO); *m/z* (FAB$^+$, %) 476 (M^+, 1), 400 (2), 325 (10), 295 (52), 282 (30), 154 (55), 89 (100), 77 (17).

3.3.21. 8-Methoxy-3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (9). The cyclisation was carried out according to the standard procedure using 1-[(3-methoxy)-2-((2-methoxyethoxy)-methoxy)phenyl]-5-[2-((2-methoxyethoxy)-methoxy)phenyl]pentan-3-one (**14**) (82 mg, 0.178 mmol), trimethylsilyl bromide (0.23 mL, 1.78 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **9** (48 mg, 96%) as a colourless solid, mp 125–126 °C. (Found: M^+, 282.1256, $C_{18}H_{18}O_3$ requires 282.1256); ν_{max} (film)/cm^{-1} 3054 (w, ArC–H), 1482, 1421 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.98 (2H, ddd, J_{gem} 13.3, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.7, 3 and 3′-H_{ax}), 2.31 (2H, ddd, J_{gem} 13.3, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.75 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.7, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4 and 4′-H_{ax}), 3.63 (3H, s, OCH_3), 6.60–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.0, 21.2 (CH_2CH_2Ar), 30.9, 31.3 (CH_2CH_2Ar), 56.5 (OCH_3), 96.3 (q, C2), 111.0, 117.0, 120.2, 121.3, 122.5 (Ar-H), 122.3, 123.1 (q, C4a and C4a′), 127.0, 128.9 (Ar-CH), 142.14 (q, C8), 148.6 (q, C8a), 152.2 (q, C8a′); *m/z* (EI, %) 282 (M^+, 80), 161 (28), 145 (42), 138 (50), 131 (100), 107 (25), 77 (14), 73 (22).

3.3.22. 1-(Allyloxy)-4-methoxybenzene (28). The allylation reaction was carried out according to the standard procedure using 4-methoxyphenol (**25**) (5.0 g, 40 mmol), allyl bromide (3.5 mL, 40 mmol) and potassium carbonate (11.0 g, 80 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the *title compound* **28** (6.38 g, 97%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.74 (3H, s, OCH_3), 4.56 (2H, d, *J* 5.1, $OCH_2CH{=}CH_2$), 5.41 (1H, dq, J_{gem} 1.5, *J* 10.6, $OCH_2CH{=}CH_AH_B$), 5.42 (1H, m, $OCH_2CH{=}CH_AH_B$), 6.10 (1H, m, $OCH_2CH{=}CH_2$), 6.80–6.95 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.5 (OCH_3), 69.3 ($OCH_2CH{=}CH_2$), 114.5, 115.6 (Ar-CH), 117.4 ($CH{=}CH_2$), 133.5 ($OCH_2CH{=}CH_2$), 152.6 (q, C1), 153.8 (q, C4). The spectroscopic data were in agreement with the literature.[21]

3.3.23. 2-Allyl-4-methoxyphenol (31). The Claisen rearrangement was carried out according to the standard procedure using 1-(allyloxy)-4-methoxybenzene (**28**) (6.37 g, 39 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **31** (6.37 g, >99%) as a colourless oil. δ_H (400 MHz, $CDCl_3$) 3.36 (2H, d, *J* 6.2, $CH_2CH{=}CH_2$), 3.74 (3H, s, OCH_3), 5.10 (1H, dq, J_{gem} 1.5, *J* 10.6, $CH_2CH{=}CH_AH_B$), 5.16 (1H, m, $CH_2CH{=}CH_AH_{2B}$), 5.20 (1H, br s, O*H*), 6.00 (1H, m, 6.2, $CH_2CH{=}CH_2$), 6.60–6.80 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 35.0 ($CH_2CH{=}CH_2$), 55.7 (OCH_3), 112.5, 115.9, 116.3 (Ar-CH), 116.7 ($CH_2CH{=}CH_2$), 126.7 (q, C2), 136.1 ($CH_2CH{=}CH_2$), 147.9 (q, C1), 153.5 (q, C4). The spectroscopic data were in agreement with the literature.[22]

3.3.24. 2-Allyl-1-(ethoxymethoxy)-4-methoxybenzene (34). The protection step was carried out according to the standard procedure using 2-allyl-4-methoxyphenol (**31**) (6.37 g, 39 mmol), diisopropylamine (12.2 mL, 70 mmol) and ethoxymethyl chloride (4.87 mL, 43 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **34** (6.41 g, 74%) as a colourless oil. (Found: M^+, 222.1255, $C_{13}H_{18}O_3$ requires 222.1256); ν_{max} (film)/cm^{-1} 3077 (w, $CH{=}CH_2$), 2934 (s, ArC–H), 1285 (w, C–O), 1150 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 3.37 (2H, d, *J* 6.7, $CH_2CH{=}CH_2$), 3.71 (2H, q, *J* 7.0, OCH_2CH_3), 3.74 (OCH_3), 5.03 (1H, m, $CH_2CH{=}CH_AH_B$), 5.07 (1H, m, $CH_2CH{=}CH_AH_B$), 5.15 (2H, s, OCH_2O), 5.98 (1H, m, $CH_2CH{=}CH_2$), 6.60–7.10 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (OCH_2CH_3), 34.4 ($CH_2CH{=}CH_2$), 55.5 (OCH_3), 64.1 (OCH_2CH_3), 94.1 (OCH_2O), 115.8 ($CH_2CH{=}CH_2$), 111.6, 115.4, 115.7 (Ar-CH), 132.7 ($CH_2CH{=}CH_2$), 136.7 (q, C2), 149.2 (q, C1), 154.4 (q, C4); *m/z* (EI, %) 222 (M^+, 65), 192 (22), 163 (36), 149 (31), 103 (11), 77 (10), 59 (100), 41 (10).

3.3.25. 3-[2-(Ethoxymethoxy)-5-methoxyphenyl]propan-1-ol (37). The hydroboration reaction was carried out according to the standard procedure using 2-allyl-1-(ethoxymethoxy)-4-methoxybenzene (**34**) (3.0 g, 13.5 mmol) and borane–dimethyl sulfide complex (2.7 mL, 27 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **37** (2.28 g, 70%) as a colourless oil. (Found: M^+, 240.1362, $C_{13}H_{20}O_4$ requires 240.1362); ν_{max} (film)/cm^{-1} 3411 (br, O–H), 2936 (s, ArC–H), 2834 (m, O–CH_2–O), 1278 (w, C–O), 1151 (m, C–OH); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 1.84 (2H, quintet, *J* 6.2, 7.7, $CH_2CH_2CH_2OH$), 2.60 (1H, br s, O*H*), 2.70 (2H, t, *J* 7.7, $CH_2CH_2CH_2OH$), 3.70 (2H, t, *J* 6.2, CH_2OH), 3.71 (OCH_2CH_3), 3.80 (3H, s, OCH_3), 5.13 (2H, s, OCH_2O), 6.60–7.10 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.0 (OCH_2CH_3), 26.1 (CH_2, C2), 32.9 (CH_2, C3), 55.4 (OCH_3), 61.6 (CH_2OH), 64.2 (OCH_2CH_3), 94.0 (OCH_2O), 111.3, 115.5, 115.9 (Ar-CH), 132.6 (q, C1′), 149.3 (q, C2′), 154.3 (q, C5′); *m/z* (EI, %) 240 (M^+, 10), 194 (10), 164 (100), 149 (25), 137 (16), 77 (9), 59 (35), 41 (10).

3.3.26. 3-[2-(Ethoxymethoxy)-5-methoxyphenyl]propanal (20). The oxidation was carried out according to the standard procedure using 3-[2-(ethoxymethoxy)-5-methoxyphenyl]propan-1-ol (**37**) (1.28 g, 5.3 mmol), tetra-*n*-propylammonium perruthenate (100 mg, 0.267 mmol), 4-methylmorpholine *N*-oxide (900 mg, 8.0 mmol) and 4 Å molecular sieves (1 g). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **20** (506 mg, 40%) as a colourless oil. (Found: M^+, 238.1206, $C_{13}H_{18}O_4$ requires 238.1205); ν_{max} (film)/cm^{-1} 2975 (s, ArC–H), 2834 (m, CH_2–O–CH_2), 2724 (w, CHO), 1725 (s, C=O), 1504 (m, C–O–C), 1280 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.0, OCH_2CH_3), 2.72 (2H, dt, *J* 1.5, 7.6, CH_2CH_2CHO), 2.92 (2H, t, *J* 7.6, $ArCH_2$), 3.67 (2H, q,

J 7.0, OCH_2CH_3), 3.73 (3H, s, OCH_3), 5.17 (2H, s, OCH_2O), 6.70–7.00 (3H, m, Ar-H), 9.80 (1H, t, *J* 1.5, C*H*O); δ_C (75 MHz, $CDCl_3$) 15.0 (OCH_2CH_3), 23.5 (CH_2, C-3), 43.9 (CH_2, C-2), 55.4 (OCH_3), 64.1 (OCH_2CH_3), 93.7 (OCH_2O), 111.7, 115.2, 115.8 (Ar-CH), 130.5 (q, C1′), 149.3 (q, C2′), 154.2 (q, C5′), 202.0 (CHO); *m*/*z* (EI, %) 238 (M^+, 43), 208 (30), 180 (14), 151 (17), 136 (24), 77 (7), 59 (100), 41 (6).

3.3.27. 5-[2-(Ethoxymethoxy)-5-methoxyphenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (44). The coupling reaction was carried out according to the standard procedure using 3-[2-(ethoxymethoxy)-5-methoxyphenyl]propanal (**20**) (40 mg, 0.17 mmol), 1-ethynyl-2-((2-methoxyethoxy)methoxy)benzene (**21**) (42 mg, 0.20 mmol) and *n*-butyllithium (0.13 mL, 0.20 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **44** (75 mg, 88%) as a colourless oil. (Found: M^+, 444.2146, $C_{25}H_{32}O_7$ requires 444.2148); ν_{max} (film)/cm^{-1} 3428 (br, O–H), 2930 (m, ArC–H), 1495 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, m, OCH_2CH_3), 2.11 (2H, m, CH_2COH), 2.65 (1H, br s, O*H*), 2.87 (2H, m, CH_2CH_2Ar), 3.34 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 3.75 (2H, q, *J* 7.4, OCH_2CH_3), 3.75 (3H, s, OCH_3), 3.88 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 4.61 (1H, t, *J* 6.7, C*H*OH), 5.18 (2H, s, $OCH_2OCH_2CH_3$), 5.32 (2H, s, OCH_2OCH_2), 6.60–7.50 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.3 (CH_2, C-5), 38.0 (CH_2, C-4), 55.5 (OCH_3), 58.9 (CH_2CH_3), 60.3 (CHOH), 62.3 ($OCH_2CH_2OCH_3$), 64.17 (2×OCH_2O), 67.8 ($OCH_2CH_2OCH_3$), 71.5 ($OCH_2CH_2OCH_3$), 81.2 (q, Ar-C≡*C*), 94.1 (q, Ar-*C*≡C), 111.4 (Ar-CH), 113.4 (q, C1′), 115.4, 115.6, 116.2, 121.8, 129.7 (Ar-CH), 131.8 (q, C1″), 133.5 (Ar-CH), 149.5 (q, C5″), 154.4 (q, C2′), 157.8 (q, C2″); *m*/*z* (EI, %) 444 (M^+, 1), 292 (20), 277 (8), 222 (29), 180 (25), 89 (27), 59 (100), 45 (4).

3.3.28. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-ol (49). The hydrogenation was carried out according to the standard procedure using 5-[2-(ethoxymethoxy)-5-methoxyphenyl]-1-[2-((2-methoxyethoxy)methoxy)phenyl]pent-1-yn-3-ol (**44**) (60 mg, 0.14 mmol), 10% palladium on carbon (51 mg, 0.049 mmol) and potassium carbonate (70 mg, 0.49 mmol). The product was purified by column chromatography using hexane–ethyl acetate (80:20) as the eluent to give the *title compound* **49** (48 mg, 70%) as a colourless oil. (Found: M^+, 448.2461, $C_{25}H_{36}O_7$ requires 448.2461); ν_{max} (film)/cm^{-1} 3584 (br, O–H), 2929 (s, ArC–H), 1495 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.24 (3H, t, *J* 7.0, OCH_2CH_3), 1.75 (2H, q, *J* 7.8, CH_2Ar), 2.73 (3H, m, CH_2COH and CHO*H*), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, m, $OCH_2CH_2OCH_3$), 3.55 (1H, m, C*H*OH), 3.75 (2H, m, CH_2CH_3), 3.75 (3H, s, OCH_3), 3.82 (2H, t, *J* 4.4, $OCH_2CH_2OCH_3$), 5.16 (2H, s, $OCH_2OCH_2CH_3$), 5.29 (2H, s, OCH_2OCH_2), 6.60–7.30 (7H, m, Ar–H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.3, 26.4 (CH_2Ar), 37.8, 37.8 (CH_2CHOH), 55.5 (OCH_3), 58.9 (CH_2CH_3), 62.3 ($OCH_2CH_2OCH_3$), 67.7 ($OCH_2CH_2OCH_3$), 70.1 (CHOH), 71.6 ($OCH_2CH_2OCH_3$), 93.6, 94.2 (2×OCH_2O), 111.3, 114.1, 115.7, 115.9, 121.8, 127.1, 130.1 (Ar–CH), 131.1 (q, C1′), 132.6 (q, C1″), 149.4 (q, C5″), 154.5 (q, C2′), 155.1 (q, C2″); *m*/*z* (EI, %) 448 (M^+, <0.5), 402 (14), 372 (25), 296 (30), 284 (16), 137 (25), 89 (45), 59 (100).

3.3.29. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-one (15). The oxidation was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]pentan-3-ol (**49**) (43 mg, 0.096 mmol), tetra-*n*-propylammonium perruthenate (0.2 mg, 0.0048 mmol), 4-methylmorpholine *N*-oxide (17 mg, 0.14 mmol) and 4 Å molecular sieves (100 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **15** (43 mg, >99%) as a colourless oil. (Found: M^+, 446.2303, $C_{25}H_{34}O_7$ requires 446.2305); ν_{max} (film)/cm^{-1} 2931 (s, ArC–H), 1713 (s, C=O), 1495 (s, C–O–C), 1083 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.1, OCH_2CH_3), 2.69 (2H, t, *J* 8.2, CH_2CH_2Ar), 2.87 (2H, m, CH_2CH_2Ar), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.55 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 3.73 (3H, s, OCH_3), 3.75 (2H, q, *J* 7.1, CH_2CH_3), 3.80 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 5.15 (2H, s, $OCH_2OCH_2CH_3$), 5.28 (2H, s, OCH_2OCH_2), 6.60–7.20 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 24.9, 25.0 (CH_2Ar), 42.9, 42.9 (CH_2CO), 55.5 (OCH_3), 59.0 ($OCH_2CH_2OCH_3$), 64.1 (CH_2CH_3), 67.7 ($OCH_2CH_2OCH_3$), 71.6 ($OCH_2CH_2OCH_3$), 93.4, 93.9 (2×OCH_2O), 111.6, 113.9, 115.5, 115.9, 121.7, 127.4, 129.9 (Ar-CH), 130.0 (q, C1′), 131.44 (q, C1″), 149.4 (q, C5″), 154.3 (q, C2′), 155.1 (q, C2″), 209.9 (q, CO); *m*/*z* (EI, %) 446 (M^+, 4), 400 (5), 294 (5), 282 (51), 161 (13), 107 (10), 89 (32), 59 (100).

3.3.30. 6-Methoxy-3,4,3′,4′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (10). The cyclisation was carried out according to the standard procedure using 1-([2-(ethoxymethoxy-5-methoxyphenyl]-5-[2-((2-methoxyethoxy)methoxy)phenyl]-pentan-3-one (**15**) (40 mg, 0.09 mmol), trimethylsilyl bromide (0.12 mL, 0.9 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **10** (25 mg, >99%) as a colourless solid, mp 87.5–89.0 °C. (Found: M^+, 282.1252, $C_{18}H_{18}O_3$ requires 282.1256); ν_{max} (film)/cm^{-1} 2958 (w, ArC–H), 1488 and 1455 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.95 (2H, ddd, J_{gem} 13.2, $J_{3ax,4ax}$ 13.2, $J_{3ax,4eq}$ 5.6, 3 and 3′-H_{ax}), 2.19 (2H, ddd, J_{gem} 13.2, $J_{3eq,4ax}$ 6.0, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.72 (2H, ddd, J_{gem} 16.5, $J_{4eq,3ax}$ 5.6, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.5, $J_{4ax,3ax}$ 13.2, $J_{4ax,3eq}$ 6.0, 4 and 4′-H_{ax}), 3.74 (3H, s, OCH_3), 6.60–7.30 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.3, 22.0 (CH_2CH_2Ar), 31.1, 31.1 (CH_2CH_2Ar), 55.6 (OCH_3), 96.2 (q, C2), 113.1, 113.6, 117.1, 117.6, 120.7 (Ar-CH), 122.2, 122.7 (q, C4a and C4a′), 127.1, 129.0 (Ar-CH), 146.2 (q, C8 and C8′), 152.2 (q, C8a), 153.7 (q, C8a′); *m*/*z* (EI, %) 282 (M^+, 100), 175 (21), 161 (60), 145 (42), 131 (38), 107 (23), 77 (11), 73 (20).

3.3.31. 1-Iodo-3-methoxy-2-(methoxymethoxy)benzene (39). The protection step was carried out according to the standard procedure using 1-methoxyphenol (**24**) (0.996 g, 8.03 mmol), diisopropylethylamine (2.52 mL, 14.4 mmol) and methoxymethyl chloride (0.92 mL, 8.03 mmol). The product was purified by column chromatography using hexane–ethyl acetate (90:10) as the eluent to give the MOM

ether[23] (1.19 g, 88%) as a colourless oil that was used directly in the iodination step; δ_H (400 MHz, $CDCl_3$) 3.50 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.21 (2H, s, OCH_2O), 6.84–7.15 (4H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.6 (OCH_3), 56.0 (OCH_3), 95.4 (OCH_2O), 111.7, 116.5, 120.8, 122.4 (Ar-CH), 146.5 (q, C-1), 149.8 (q, C-2). To a solution of the MOM ether (1.00 g, 5.93 mmol) in tetrahydrofuran (5 mL) cooled to −15 °C under nitrogen was added *n*-butyllithium (4.08 mL, 6.53 mmol) dropwise with stirring. The reaction mixture was allowed to warm to room temperature over 2 h then cooled to −45 °C and a solution of iodine was (0.825 g, 6.53 mmol) in tetrahydrofuran (1 mL) added dropwise over 1 h. The cooling bath was removed and the solution was warmed to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was taken up with diethyl ether (10 mL) and then washed with 20% sodium thiosulfate (5 mL) and aqueous saturated sodium bicarbonate (5 mL). The organic extract was dried over magnesium sulfate and concentrated under reduced pressure. The resultant residue was purified by flash chromatography using hexane–ethyl acetate (90:10) as eluent to give the *title compound* **39** (0.236 g, 14%) as a colourless oil. (Found: M^+, 293.9755, $C_9H_{11}IO_3$ requires 293.9753); ν_{max} (film)/cm^{-1} 2938 (w, ArC–H), 1569 (C–O), 1580 (O–C–O), 1290 (C–O); δ_H (400 MHz, $CDCl_3$) 3.67 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 5.16 (2H, s, OCH_2O), 6.75–7.37 (3H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 55.9 (OCH_3), 58.3 (OCH_3), 92.6 (q, C1), 98.7 (OCH_2O), 112.8, 125.9, 131.0 (Ar-CH), 145.9 (q, C2), 152.4 (q, C3). *m/z* (EI, %) 294 (M^+, 20), 264 (30), 249 (7), 167 (21), 107 (6), 94 (4), 51 (7), 45 (100).

3.3.32. 4-[(3-Methoxy)-2-(methoxymethoxy)phenyl]-2-methylbut-3-yn-2-ol (41). The Sonogashira reaction was carried out according to the standard procedure using 1-iodo-3-methoxy-2-[(methoxymethoxy)]benzene (**39**) (200 mg, 0.68 mmol), 2-methyl-3-butyn-2-ol (0.106 mL, 1.09 mmol), triphenylphosphine (4 mg, 0.014 mmol), bis(triphenylphosphine)palladium(II) dichloride (5 mg, 0.0068 mmol), triethylamine (5 mL) and copper(I) iodide (2 mg, 0.0013 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **41** (170 mg, >99%) as a colourless oil. (Found: M^+, 250.1208, $C_{14}H_{18}O_4$ requires 250.1205); ν_{max} (film)/cm^{-1} 3689 (br, OH), 3053 (Ar-CH), 2305 (C≡C), 1469 (OCH_2O), 1265, 1208, 1160 (CO); δ_H (400 MHz, $CDCl_3$) 1.60 (6H, each s, 2×CH_3), 2.88 (1H, br s, O*H*), 3.65 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.22 (2H, s, OCH_2O), 6.84–7.00 (3H, m, Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 31.0, 31.4 (C(*C*H_3)$_2$), 55.9 (OCH_3), 57.5 (OCH_3), 65.6 (q, C-2), 84.0 (q, Ar-C≡*C*), 98.0 (q, Ar-*C*≡C-3), 98.5 (OCH_2O), 112.8, 115.4 (Ar-CH), 117.8 (q, C1′), 124.0 (Ar-CH), 146.8 (q, C3′), 152.4 (q, Ar-C2′). *m/z* (EI, %) 250 (M^+, 2), 188 (100), 175 (5), 173 (7), 160 (14), 145 (14), 131 (15), 115 (7), 45 (49), 43 (29).

3.3.33. 1-Ethynyl-3-methoxy-2-(methoxymethoxy)benzene (22). The reaction was carried out according to the standard procedure using 4-[(3-methoxy-2-(methoxymethoxy)phenyl]-2-methylbut-3-yn-2-ol (**41**) (198 mg, 0.79 mmol) and sodium hydroxide (158 mg, 3.96 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **22** (109 mg, 72%) as a colourless oil. (Found: M^+, 192.0797, $C_{11}H_{12}O_3$ requires 192.0780); ν_{max} (film)/cm^{-1} 3075 (Ar-CH), 2268 (C≡C), 1469 (OCH_2O), 1265, 1208, 1160 (CO); δ_H (400 MHz, $CDCl_3$) 3.25 (1H, s, C≡C*H*), 3.64 (3H, s, OCH_2OCH_3), 3.84 (3H, s, OCH_3), 5.24 (2H, s, OCH_2OCH$_3$), 6.90–7.10 (3H, m, Ar-C*H*); δ_C (75 MHz, $CDCl_3$) 55.9 (OCH_3), 57.5 (OCH_2OCH_3), 80.1 (C≡*C*H), 81.1 (q, *C*≡CH), 98.5 (OCH_2O), 113.4 (Ar-CH), 117.3 (q, *C*-1), 124.1, 125.7 (Ar-CH), 147.6 (q, C-3′), 152.4 (q, C-2′). *m/z* (EI, %) 192 (M^+, 5), 191 (6), 162 (30), 161 (22), 147 (6), 131 (11), 119 (8), 91 (7), 76 (7), 45 (100).

3.3.34. 5-[2-(Ethoxymethoxy)-5-methoxyphenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (45). The coupling reaction was carried out according to the standard procedure using 3-[5-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**20**) (75 mg, 0.31 mmol), 1-ethynyl-3-methoxy-2-(methoxymethoxy)benzene (**22**) (50 mg, 0.26 mmol) and *n*-butyllithium (0.18 mL, 0.29 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **45** (87 mg, 73%) as a colourless oil. (Found: M^+, 430.1985, $C_{24}H_{30}O_7$ requires 430.1992); ν_{max} (film)/cm^{-1} 3435 (br, O–H); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, m, CH_2CH_3), 2.07 (2H, quintet, *J* 6.6, 8.6, CH_2CH$_2$Ar), 2.70 (1H, br s, O*H*), 2.84 (2H, m, CH_2CH_2Ar), 3.63 (2H, m, OCH_2CH$_3$), 3.71 (3H, s, OCH_2OCH_3), 3.73 (3H, s, 5″-OCH_3), 3.83 (3H, s, 3′-OCH_3), 4.60 (1H, t, *J* 6.6, C*H*OH), 5.17 (2H, s, OCH_2OCH$_2$), 5.22 (2H, s, OCH_2OCH$_3$), 6.60–7.30 (7H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 26.2 (CH_2, C-5), 37.9 (CH_2, C-4), 55.5, 55.8 (2×OCH_3), 57.4 (OCH_2OCH_3), 62.3 (CHOH), 64.2 (OCH_2CH_3), 81.3 (q, Ar-*C*≡C), 94.0 (OCH_2OCH_2), 94.1 (q, Ar-C≡*C*), 98.5 (OCH_2OCH_3), 117.8 (q, C1′), 111.6, 112.9, 115.6, 116.0, 124.0, 125.2 (Ar-CH), 131.6 (q, C1″), 147.0 (q, C3′), 149.5 (q, C5″), 152.5 (q, C2′), 154.4 (q, C2″); *m/z* (EI, %) 430 (M^+, 4), 322 (46), 310 (35), 180 (55), 161 (52), 151 (44), 59 (64), 45 (100).

3.3.35. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-ol (50). The hydrogenation was carried out according to the standard procedure using 5-[2-(ethoxymethoxy)-5-methoxyphenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (**45**) (80 mg, 0.17 mmol), 10% palladium on carbon (67 mg, 0.063 mmol) and potassium carbonate (86 mg, 0.63 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **50** (80 mg, 99%) as a colourless oil. (Found: M^+, 434.2309, $C_{24}H_{34}O_7$ requires 434.2305); ν_{max} (film)/cm^{-1} 3584 (br, O–H), 2933 (s, ArC–H), 1499 (m, C–O–C), 1080 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, t, *J* 7.1, CH_2CH_3), 1.74 (4H, m, CH_2CH$_2$Ar), 2.70 (1H, br s, O*H*), 2.70 (4H, m, CH_2Ar), 2.80 (1H, m, C*H*OH), 3.70 (2H, q, *J* 7.1, OCH_2CH$_3$), 3.72 (3H, s, OCH_2OCH_3), 3.72 (3H, s, 5′-OCH_3), 3.81 (3H, s, 3″-OCH_3), 5.09 (2H, s, OCH_2OCH$_2$), 5.15 (2H, s, OCH_2OCH$_3$), 6.60–7.10 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.0 (CH_2CH_3), 26.1, 26.5 (CH_2Ar), 37.8, 38.2 (*C*H_2CHOH), 55.4, 55.5 (2×OCH_3), 57.5 (OCH_2OCH_3), 64.1 (OCH_2CH_3), 69.9 (CHOH), 94.0 (OCH_2OCH_2), 99.0 (OCH_2OCH_3), 109.9, 111.3, 115.5,

115.7, 121.9, 124.2 (Ar-CH), 132.6 (q, C″), 136.1 (q, C1″), 144.1 (q, C3″), 149.3 (q, C5′), 152.0 (q, C2″), 154.3 (q, C2′); *m/z* (DEI, %) 434 (M^+, 1), 388 (38), 314 (50), 189 (46), 177 (43), 137 (100), 59 (44), 45 (95).

3.3.36. 1-[2-(Ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (16). The oxidation was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-ol (**50**) (74 mg, 0.16 mmol), tetra-*n*-propylammonium perruthenate (0.3 mg, 0.008 mmol), 4-methylmorpholine *N*-oxide (3 mg, 0.24 mmol) and 4 Å molecular sieves (20 mg). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **16** (74 mg, 95%) as a colourless oil. (Found: M^+, 432.2148, $C_{24}H_{32}O_7$ requires 432.2148); ν_{max} (film)/cm^{-1} 2931 (s, ArC–H), 1713 (s, C=O), 1495 (s, C–O–C), 1160 (m, C–O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, t, *J* 7.0, CH_2CH_3), 2.72 (4H, m, CH_2CO), 2.86, 2.93 (4H, m, CH_2CH_2Ar), 3.54 (3H, s, OCH_2OCH_3), 3.70 (2H, q, *J* 7.0, OCH_2CH_3), 3.71 (3H, s, 5′-OCH_3), 3.82 (3H, s, 3″-OCH_3), 5.08 (2H, s, OCH_2OCH_2), 5.15 (2H, s, OCH_2OCH_3), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 15.1 (CH_2CH_3), 24.7, 25.0 (CH_2CH_2Ar), 42.9, 43.4 (CH_2CO), 55.5, 55.6 (2×OCH_3), 57.4 (OCH_2OCH_3), 64.1 (OCH_2CH_3), 93.8 (OCH_2OCH_2), 98.9 (OCH_2OCH_3), 110.4, 111.7, 115.4, 115.8, 121.9, 124.2 (Ar-CH), 131.4 (q, C1′), 135.3 (q, C1″), 144.3 (q, C3″), 149.4 (q, C5′), 152.1 (q, C2″), 154.3 (q, C2′), 209.7 (q, CO); *m/z* (EI, %) 432 (M^+, 0.5), 386 (38), 312 (50), 187 (46), 175 (43), 137 (100), 59 (44), 45 (95).

3.3.37. 6,8′-Dimethoxy-3,4,3′,4′,-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (11). The cyclisation reaction was carried out according to the standard procedure using 1-[2-(ethoxymethoxy)-5-methoxyphenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (**16**) (70 mg, 0.15 mmol), trimethylsilyl bromide (0.20 mL, 1.5 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **11** (45 mg, 96%) as a colourless solid, mp 146–147 °C. (Found: M^+, 312.1358, $C_{19}H_{20}O_4$ requires 312.1362); ν_{max} (film)/cm^{-1} 2931 (m, ArC–H), 1482 and 1421 (w, C–O–C); δ_H (400 MHz, $CDCl_3$) 1.98 (2H, ddd, J_{gem} 13.1, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.7, 3 and 3′-H_{ax}), 2.19 (2H, ddd, J_{gem} 13.1, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3 and 3′-H_{eq}), 2.90 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.7, $J_{4eq,3eq}$ 2.6, 4 and 4′-H_{eq}), 3.30 (2H, ddd, J_{gem} 16.3, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4 and 4′-H_{ax}), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 20.9, 21.5 (CH_2CH_2Ar), 30.8, 31.2 (CH_2CH_2Ar), 55.6 (6-OCH_3), 56.5 (8′-OCH_3), 96.2 (q, C2), 111.0, 113.0, 113.6, 117.5, 120.2, 121.3 (Ar-CH), 122.8 (q, C4a), 123.2 (q, C4′a), 142.2 (q, C8′a,), 146.2 (q, C8a), 148.6 (q, C8 and C8′), 153.6 (q, C6); *m/z* (EI, %) 312 (M^+, 80), 188 (6), 176 (55), 174 (32), 161 (100), 137 (40), 91 (6), 77 (10).

3.3.38. 5-[(3-Methoxy)-2-((2-methoxyethoxy)methoxy)-phenyl]-1-[3-methoxy-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (46). The coupling reaction was carried out according to the standard procedure using 3-[(3-methoxy)-2-((2-methoxyethoxy)methoxy)phenyl]propanal (**19**) (50 mg, 0.21 mmol), 1-ethynyl-3-methoxy-2-(methoxymethoxy)-benzene (**22**) (40 mg, 0.21 mmol) and *n*-butyllithium (0.14 mL, 0.23 mmol). The product was purified by column chromatography using hexane–ethyl acetate (60:40) as the eluent to give the *title compound* **46** (52 mg, 54%) as a colourless oil. (Found: M^+, 460.2102, $C_{25}H_{32}O_8$ requires 460.2097); ν_{max} (film)/cm^{-1} 3426 (br, O–H), 2934 (s, ArC–H), 1471 (s, C–O–C), 1076 (m, C–O); δ_H (400 MHz, $CDCl_3$) 2.11 (2H, m, CH_2CH_2Ar), 2.92 (2H, m, CH_2CH_2Ar), 2.94, (1H, br s, O*H*), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.47 (2H, t, *J* 4.5, $OCH_2CH_2OCH_3$), 3.58 (3H, s, OCH_2OCH_3), 3.81, 3.83 (2×OCH_3), 3.92 (2H, m, $OCH_2CH_2OCH_3$), 4.60 (1H, t, *J* 6.0, C*H*OH), 5.19 (2H, s, OCH_2OCH_3), 5.21 (2H, s, CH_2OCH_2O), 6.70–7.10 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 25.9 (CH_2, C-5), 38.7 (CH_2, C-4), 55.6, 55.8 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 58.9 (OCH_2OCH_3), 62.3 (CHOH), 69.0 ($OCH_2CH_2OCH_3$), 71.8 ($OCH_2CH_2OCH_3$), 81.0 (q, Ar-C≡C), 94.4 (q, Ar-C≡C), 98.1 (OCH_2OCH_2), 98.5 (OCH_2OCH_3), 110.2, 112.8, (Ar-CH), 117.9 (q, C1′), 122.1, 124.0, 124.2, 125.3 (Ar-CH), 135.4 (q, C1″), 144.5, 147.0 (q, C3′ and C5″), 152.0, 152.5 (q, C2″ and C2′); *m/z* (EI, %) 460 (M^+, <0.5), 322 (14), 310 (31), 174 (20), 161 (23), 89 (25), 59 (100), 45 (50).

3.3.39. 1-[3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[(3-methoxy)-2-(methoxymethoxy)phenyl]-pentan-3-ol (51). The hydrogenation was carried out according to the standard procedure using 5-[3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl]-1-[(3-methoxy)-2-(methoxymethoxy)phenyl]pent-1-yn-3-ol (**46**) (52 mg, 0.11 mmol), 10% palladium on carbon (43 mg, 0.041 mmol) and potassium carbonate (56 mg, 0.41 mmol). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **51** (43 mg, 83%) as a colourless oil. (Found: M^+, 465.2502, $C_{25}H_{37}O_8$ requires 465.2489); ν_{max} (film)/cm^{-1} 3469 (br, O–H), 2932 (s, ArC–H), 1474 (m, C–O–C), 1072 (w, C–O); δ_H (400 MHz, $CDCl_3$) 1.76 (4H, m, CH_2CO), 2.80 (4H, m, CH_2Ar), 2.80 (1H, m, C*H*OH), 3.37 (3H, s, $CH_2CH_2OCH_3$), 3.57 (3H, s, OCH_2OCH_3), 3.57 (2H, m, $OCH_2CH_2OCH_3$), 3.81, 3.82 (6H, s, 2×OCH_3), 3.93 (2H, m, $OCH_2CH_2OCH_3$), 5.08 (2H, s, OCH_2OCH_3), 5.16 (2H, s, OCH_2OCH_2), 6.70–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 26.3, 26.3 (CH_2Ar), 38.2, 38.3 (CH_2CHOH), 55.6, 55.6 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 59.0 (OCH_2OCH_3), 69.0 ($OCH_2CH_2OCH_3$), 70.1 (CHOH), 71.8 ($OCH_2CH_2OCH_3$), 98.0 (OCH_2OCH_2), 99.0 (OCH_2OCH_3), 109.9, 110.0, 122.0, 122.0, 124.2, 124.2 (Ar-CH), 136.3, 136.3 (q, C1″ and C1′), 144.2, 144.2 (q, C3′ and C5″), 151.0, 152.0 (q, C2″ and C2′); *m/z* (FAB$^+$, %) 465 (M^+, <0.5), 307 (20), 289 (14), 154 (100), 136 (68), 107 (22), 89 (21), 77 (20).

3.3.40. 1-[3-Methoxy-2-((2-methoxyethoxy)methoxy)-phenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (17). The oxidation was carried out according to the standard procedure using 1-[3-methoxy-2-((2-methoxyethoxy)methoxy)phenyl)]-5-[(3-methoxy)-2-(methoxymethoxy)phenyl)pentan-3-ol (**51**) (43 mg, 0.09 mmol), tetra-*n*-propylammonium perruthenate (0.01 mg, 0.005 mmol), 4-methylmorpholine *N*-oxide (0.1 mg, 0.01 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate

(50:50) as the eluent to give the *title compound* **17** (43 mg, >99%) as a colourless oil. (Found: $M^+(+NH_4)$, 480.2594, $C_{25}H_{38}NO_8$ requires 480.2597); ν_{max} (film)/cm^{-1} 2936 (s, ArC–H), 1712 (s, CO), 1476 (s, C–O–C), 1073 (s, C–O); δ_H (400 MHz, $CDCl_3$) 2.73 (4H, m, CH_2CO), 2.95 (4H, m, CH_2CH_2Ar), 3.36 (3H, s, $CH_2CH_2OCH_3$), 3.56 (3H, s, OCH_2OCH_3), 3.56 (2H, t, *J* 4.7, $OCH_2CH_2O CH_3$), 3.81, 3.82 (6H, s, 2×OCH_3), 3.89 (2H, t, *J* 4.7, $OCH_2CH_2OCH_3$), 5.08 (2H, s, OCH_2OCH_3), 5.17 (2H, s, CH_2OCH_2O), 6.70–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 24.6, 24.7 (CH_2CH_2Ar), 43.3, 43.3 (CH_2CO), 55.6, 55.6 (OCH_3), 57.4 ($OCH_2CH_2OCH_3$), 58.9 (OCH_2OCH_3), 69.0 ($OCH_2CH_2OCH_3$), 71.7 ($OCH_2CH_2OCH_3$), 97.8 (OCH_2OCH_2), 98.9 (OCH_2OCH_3), 110.3, 110.4, 121.8, 121.85, 124.1, 124.13 (Ar-CH), 135.2, 135.2 (q, C1″ and C1′), 144.2, 144.3 (q, C3′ and C5″), 152.1, 152.1 (q, C2″ and C2′), 209.6 (CO); *m/z* (DEI, %) 462 (M^+, <0.5), 324 (14), 312 (71), 161 (55), 137 (30), 89 (28), 59 (100), 45 (62).

3.3.41. 8,8′-Dimethoxy-3,4,4′,3′-tetrahydro-2,2′-spirobis(2*H*-1-benzopyran) (12). The reaction was carried out according to the standard procedure using 1-[3-methoxy-2-((2-methoxyethoxy)-methoxy)phenyl]-5-[3-methoxy-2-(methoxymethoxy)phenyl]pentan-3-one (**17**) (39 mg, 0.08 mmol), trimethylsilyl bromide (0.11 mL, 0.84 mmol) and 4 Å molecular sieves (50 mg). The product was purified by column chromatography using hexane–ethyl acetate (50:50) as the eluent to give the *title compound* **12** (25 mg, 96%) as a colourless solid, mp 195–196 °C. (Found: M^+, 312.1358, $C_{19}H_{20}O_4$ requires 312.1358); ν_{max} (film)/cm^{-1} 2934 (w, ArC–H), 1478 and 1440 (m, C–O–C); δ_H (400 MHz, $CDCl_3$) 2.00 (2H, ddd, J_{gem} 13.1, $J_{3ax,4ax}$ 13.1, $J_{3ax,4eq}$ 5.8, 3-H_{ax}), 2.32 (2H, ddd, J_{gem} 13.1, $J_{3eq,4ax}$ 5.9, $J_{3eq,4eq}$ 2.6, 3-H_{eq}), 2.76 (2H, ddd, J_{gem} 16.2, $J_{4eq,3ax}$ 5.8, $J_{4eq,3eq}$ 2.6, 4-H_{eq}), 3.35 (2H, ddd, J_{gem} 16.2, $J_{4ax,3ax}$ 13.1, $J_{4ax,3eq}$ 5.9, 4-H_{ax}), 3.66 (6H, s, 2×OCH_3), 6.60–7.30 (6H, m, Ar-H); δ_C (75 MHz, $CDCl_3$) 21.1 (CH_2CH_2Ar), 31.1 (CH_2CH_2Ar), 56.4 (2×OCH_3), 96.4 (q, C2), 110.9, 120.2, 121.3 (Ar-CH), 123.3 (q, C4a and C4a′), 142.14 (q, C8 and C8′), 148.5 (q, C8a and C8a′); *m/z* (EI, %) 312 (M^+, 75), 295 (5), 188 (12), 175 (44), 161 (100), 137 (44), 115 (3), 77 (8).

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Regiospecific and enantioselective synthesis of methylated metabolites of tea catechins

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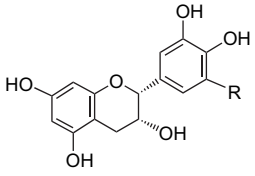
Abstract—The regiospecific and enantioselective syntheses of various methylated regioisomers of *epi*catechin gallate (EGC) and *epi*gallocatechin gallate (EGCG) have been achieved.

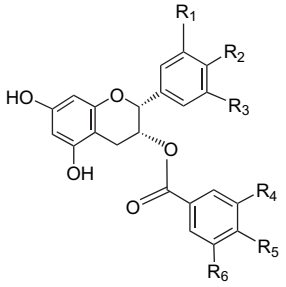
1. Introduction

Tea, produced from the plant *Camellia sinensis*, has been consumed by humans for thousands of years. It is one of the most popular beverages worldwide, second to water. Tea catechins, which are polyphenols, constitute about 30–40% of the water-soluble compounds in brewed green tea. The major tea catechins are: (−)-*epi*catechin (**1**, EC), (−)-*epi*gallocatechin (**2**, EGC), (−)-*epi*catechin gallate (**3**, ECG), and (−)-*epi*gallocatechin gallate (**4**, EGCG).[1] Of these, EGCG is by far the most abundant and has been reported to have various biological activities, which may account for the beneficial effects attributed to green tea.[2,3]

Recently, the metabolic transformations of tea catechins have been investigated. Catechins were found to be substrates of human catechol-*O*-methyltransferase (COMT). In humans, 4′-*O*-methyl-EGC[4] and 4′,4″-di-*O*-methyl-EGCG (**12**)[5] were detected after green tea and catechin consumption. In rats, 4′-*O*-methyl-EGCG (**11**), 4″-*O*-methyl-EGCG (**9**), 3′-*O*-methyl-EGCG, 3″-*O*-methyl-EGCG (**8**), and 4′,4″-dimethyl-EGCG (**12**) were found to be the biliary metabolites of EGCG.[6] Indeed, some of these methylated catechins have been found as minor components in tea infusions.[7] Methylated EGCG has been shown to inhibit type I allergic reactions in mice.[7a,8]



1: R=H, EC
2: R=OH, EGC



3: R_1=H, R_2=R_3=R_4=R_5=R_6=OH; ECG
4: R_1=R_2=R_3=R_4=R_5=R_6=OH; EGCG
5: R_3=H, R_1=R_2=R_4=R_5=OH, R_6=OMe
6: R_3=H, R_1=R_2=R_4=R_6=OH, R_5=OMe
7: R_3=H, R_1=R_2=R_4=OH, R_5=R_6=OMe
8: R_1=R_2=R_3=R_4=R_5=OH, R_6=OMe
9: R_1=R_2=R_3=R_4=R_6=OH, R_5=OMe
10: R_1=R_2=R_3=R_4=OH, R_5=R_6=OMe
11: R_1=R_3=R_4=R_5=R_6=OH, R_2=OMe
12: R_1=R_3=R_4=R_6=OH, R_2=R_5=OMe
13: R_1=R_3=R_4=OH, R_2=R_5=R_6=OMe

Biomethylation of catechins may play a significant role in affecting the biological effects of tea. Recently, it has been reported that among women who carried at least one low activity *COMT* allele, tea drinkers showed a significantly reduced risk of breast cancer compared with nontea drinkers. In contrast, risk of breast cancer did not differ between tea drinkers and nontea drinkers among those who were homozygous for the high activity *COMT* allele.[9] These data suggest that methylation of catechins may reduce the cancer protecting activities of tea polyphenols. EGCG is known to inhibit *COMT*[10] as well as DNA methyltransferase.[11]

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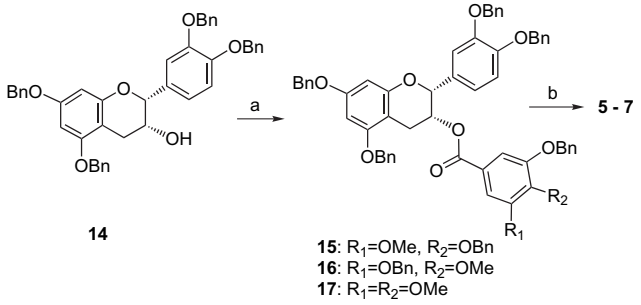
Because of our interest in the synthesis of EGCG[12] and its role as proteasome inhibitors in cancer protection,[13] we became interested in the synthesis of various methylated metabolites of catechins. Previously, (−)-EGCG had been methylated in a nonregiospecific manner to give a mixture of 4″-methyl-EGCG (**9**), 4′,4″-dimethyl-EGCG (**12**), and 4′,3″,4″-trimethyl-EGCG (**13**).[5] Herein, we report a regiospecific and enantioselective synthesis of the various methylated ECG and EGCG (**5**–**13**).

2. Results and discussion

2.1. Syntheses of compounds 5–7

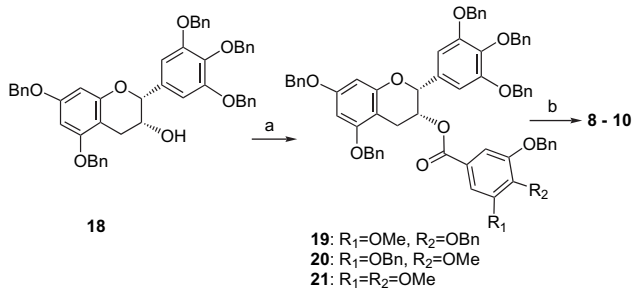
Previously, we had reported on the enantioselective synthesis of the benzylated *epi*catechin **14** [(−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3,4-bis(benzyloxy)phenyl]-chroman-3-ol].[12b] The same compound **14** can be obtained by the direct benzylation of (−)-*epi*catechin isolated from nature.[14] Acylation of **14** with 3,4-bis(benzyloxy)-5-methoxybenzoyl chloride, 3,5-bis(benzyloxy)-4-methoxybenzoyl chloride or 3-benzyloxy-4,5-dimethoxybenzoyl chloride gave the protected esters **15**–**17**, respectively. Hydrogenolysis of **15**–**17** afforded compounds **5**–**7** in good yields (Scheme 1). The synthetic compounds **5** and **6** have optical rotations and spectroscopic data similar to those reported for the natural products.[7]



Scheme 1. (a) Acid chloride/DMAP in CH_2Cl_2, rt; (b) H_2/Pd(OH)$_2$/MeOH/THF.

2.2. Syntheses of compounds 8–10

Compounds **8**–**10** were prepared from the perbenzylated *epi*-gallocatechin **18**[12a] according to the same acylation and hydrogenolysis sequence (Scheme 2). Compound **8** showed the same optical rotation and spectroscopic data as the natural compound.[6] Compound **9** had been previously synthesized,



Scheme 2. (a) Acid chloride/DMAP in CH_2Cl_2, rt; (b) H_2/Pd(OH)$_2$/MeOH/THF.

but only characterized by its ^{1}H NMR spectrum.[5] With both compounds **8** and **9** at hand, we have assigned their regiochemistry unambiguously by the synthesis.

2.3. Syntheses of compounds 11–13

In order to obtain the methylated compounds **11**–**13**, a total synthesis starting from a properly protected B-ring precursor is used (Scheme 3). 3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (**22**) was converted to the cinnamyl alcohol **24** via a Wittig–Horner reaction followed by DIBAL reduction. Friedel–Craft alkylation of 3,5-dibenzyloxyphenol (**25**) with **24** gave the alkylation product **26**. Compound **26** was first protected as the *tert*-butyldimethylsilyl ether and then dihydroxylated with the Sharpless asymmetric dihydroxylation protocol followed by desilylation to give the optically active diol **27**. The (+)-(1*S*,2*S*)-diol **27** was obtained from AD-mix α in agreement with our previous observation that similar enantioselectivity was obtained in EGCG synthesis.[12a] Cyclization of **27** under the orthoformate/acidic conditions followed by base hydrolysis gave the protected flavan-3-ol **28**. The trans stereochemistry of **28** was evident from its ^{1}H NMR spectrum. Compound **28** was then oxidized by Dess–Martin periodinane to the corresponding ketone **29**. Reduction of the carbonyl function in **29** with L-Selectride at −78 °C gave exclusively the cis-substituted compound **30**. The stereochemistry of **30** was also evident from its ^{1}H NMR where the coupling of H-2 and H-3 hydrogens is distinctly different from that of compound **28**. Esterification of **30** with 3,4-bis(benzyloxy)-5-methoxybenzoyl chloride, 3,5-bis(benzyloxy)-4-methoxybenzoyl chloride or 3-benzyloxy-4,5-dimethoxybenzoyl chloride gave the protected esters **31**–**33**, respectively. Hydrogenolysis of **31**–**33** afforded the methylated compounds **11**–**13**. The spectroscopic data of compounds **11**–**13** are in agreement with those reported previously for the metabolites.[5,6]

The structure–activity relationships (SARs) of these methylated metabolites of tea catechins were also examined as a function of inhibition of a purified 20S proteasome. We found that addition of a methyl group to the B- and/or D-ring led to diminished proteasome-inhibitory activity in vitro and that as the number of methyl groups increased on these catechin molecules, their effectiveness as proteasome inhibitors decreased.[15]

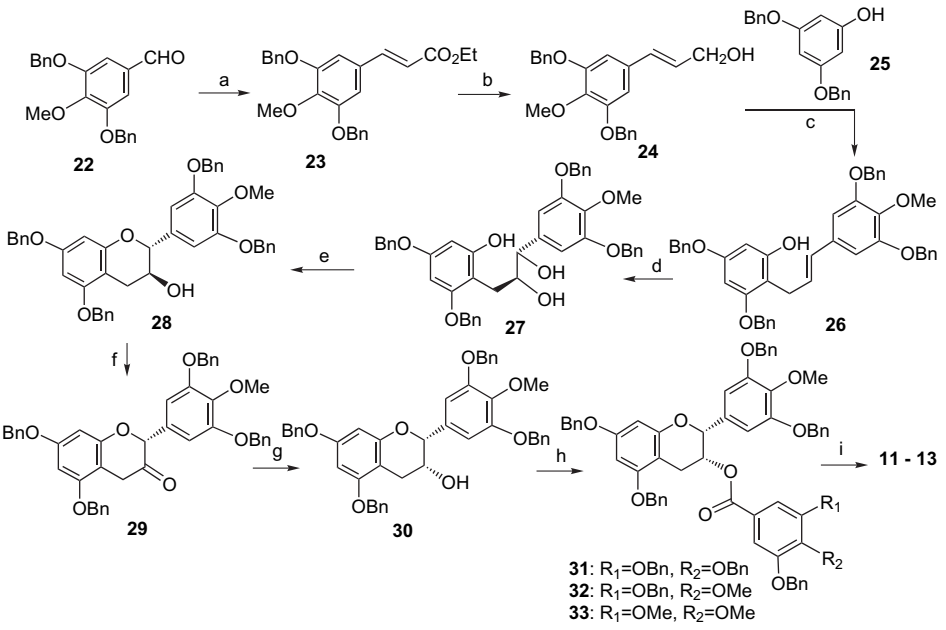
3. Conclusion

We have synthesized nine different methylated catechins, which are metabolites or potential metabolites of tea catechins in biomethylation. The synthesis is regiospecific and enantioselective. These compounds will allow us to evaluate the role of biomethylation in affecting the biological effects of tea consumption.

4. Experimental

4.1. General

The starting materials and reagents, purchased commercially, were used without further purification. Literature



Scheme 3. (a) Triethyl phosphonoacetate/NaH/THF, 0 °C–rt; (b) DIBAL/THF, −78 °C–rt; (c) $H_2SO_4/SiO_2/CH_2Cl_2$, rt; (d) (i) TBSCl/imidazole/DMF, rt; (ii) AD-mix α/$CH_3SO_2NH_2/H_2O$/*t*-BuOH/CH_2Cl_2, 0 °C; (iii) TBAF/THF, rt; (e) (i) $CH(OEt)_3$/PPTS/CH_2Cl_2, 60 °C; (ii) K_2CO_3/MeOH/DME, rt; (f) Dess–Martin periodinane/CH_2Cl_2, rt; (g) L-Selectride/THF, −78 °C; (h) acid chloride/DMAP/CH_2Cl_2, rt; (i) H_2/Pd(OH)$_2$/MeOH/THF.

procedures were used for the preparation of 3,5-bis(benzyloxy)phenol,[16] 3,4,5-tris(benzyloxy)benzoic acid,[9] silica gel supported H_2SO_4,[12a] and 3,5-bis(benzyloxy)-4-methoxybenzaldehyde.[17]

Anhydrous THF was distilled under nitrogen from sodium benzophenone ketyl. Anhydrous methylene chloride was distilled under nitrogen from CaH_2. Anhydrous DMF was distilled under vacuum from CaH_2. Reaction flasks were flame-dried under a stream of N_2. All moisture-sensitive reactions were conducted under a nitrogen atmosphere. Flash chromatography was carried out using silica gel 60 (70–230 mesh). The melting points were uncorrected. ^1H and ^{13}C NMR (400 MHz) spectra were measured with TMS as internal standard when $CDCl_3$ and acetone-d_6 were used as solvent. High-resolution electrospray ionization (ESI) mass spectra were recorded using a QTOF-2 Micromass spectrometer.

4.2. Ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (23)

3,5-Bis(benzyloxy)-4-methoxybenzaldehyde (**22**, 3.48 g, 10.0 mmol) was dissolved in dry THF (100 mL) under a nitrogen atmosphere and cooled in an ice bath. To this solution triethyl phosphonoacetate (3.3 g, 15.0 mmol) was added. Sodium hydride (0.48 g, 60% dispersion in mineral oil, 12.0 mmol) was then added in five batches. The mixture was allowed to be stirred at rt for 2 h. Saturated aqueous $NaHCO_3$ solution was added. The organic phase was separated, and the aqueous layer was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$), and evaporated to afford a solid. The solid was washed with hexane to remove the mineral oil to yield ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (3.76 g, 90.0% yield): mp 80–82 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (A of AB, J=15.9 Hz, 1H), 7.42–7.25 (m, 10H), 6.77 (s, 2H), 6.26 (B of AB, J=15.9 Hz, 1H), 5.07 (s, 4H), 4.21 (q, J=7.1 Hz, 2H), 3.89 (s, 3H), 1.29 (t, J=7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 166.6, 152.4, 144.2, 141.2, 136.5, 129.5, 128.3, 127.7, 127.0, 117.2, 107.5, 70.8, 60.7, 60.2, 14.1; HRMS (ESI): calcd for $C_{26}H_{26}O_5Na$ (M+Na) 441.1678, found 441.1697.

4.3. (*E*)-3,5-Bis(benzyloxy)-4-methoxycinnamyl alcohol (24)

To a solution of ethyl-(*E*)-3,5-bis(benzyloxy)-4-methoxycinnamate (**23**, 5.0 g, 11.9 mmol) in dry THF (100 mL) at −78 °C under a nitrogen atmosphere, DIBAL (18 mL, 1 M solution in hexane, 18.0 mmol) was added dropwise. The mixture was stirred at −78 °C for 1 h and then at rt for another 1 h. The mixture was cooled to 0 °C and poured into a stirred mixture of hexane (150 mL) and saturated aqueous Na_2SO_4 solution (5 mL). The resulting mixture was stirred until a large quantity of solid was formed. The mixture was filtered, and the solid was thoroughly washed with EtOAc. The organic solutions were combined and dried ($MgSO_4$). The residue after evaporation of the solvent was washed again with hexane, and the solid was collected and recrystallized in EtOAc and hexane to afford (*E*)-3,5-bis-(benzyloxy)-4-methoxycinnamyl alcohol (4.1 g, 91% yield): mp 99–101 °C; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.27 (m, 10H), 6.62 (s, 2H), 6.39 (A of AB, J=15.8 Hz, 1H), 6.13 (B of ABt, J=15.8, 5.6 Hz, 1H), 5.08 (s, 4H), 4.21 (d, J=5.6 Hz, 2H), 3.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 152.4, 139.1, 136.9, 132.2, 130.5, 128.4, 128.0, 127.7, 127.1, 106.1, 71.0, 63.3, 60.9; HRMS (ESI): calcd for $C_{24}H_{24}O_4Na$ (M+Na) 399.1572, found 399.1554.

4.4. (*E*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3,5-bis(benzyloxy)-4-methoxyphenyl]propene (26)

At rt under a N_2 atmosphere, 25% H_2SO_4/SiO_2 (1.6 g, 4 mmol) was added in one batch to a stirred mixture of

3,5-bis(benzyloxy)phenol (3.06 g, 10 mmol) and (*E*)-3,4-bis(benzyloxy)cinnamyl alcohol (3.76 g, 10 mmol) in dry CH_2Cl_2 (100 mL). The resulting mixture was stirred at rt overnight. After filtration and evaporation, the residue was purified by column chromatography on silica gel (benzene) to afford the desired compound as white solid (3.0 g, 45.1% yield): mp 96–98 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.27 (m, 20H), 6.59 (s, 2H), 6.32 (A of AB, J=15.8 Hz, 1H), 6.26 (d, J=2.0 Hz, 1H), 6.16 (d, J=2.0, 1H), 6.16–6.12 (B of ABt, m, 1H), 5.29 (br s, 1H), 5.07 (s, 4H), 5.01 (s, 2H), 4.96 (s, 2H), 3.85 (s, 3H), 3.54 (d, J=6.2 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 157.9, 155.5, 152.5, 138.6, 137.1, 137.0, 136.8, 133.1, 129.9, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.5, 127.4, 127.2, 127.1, 106.9, 105.8, 95.0, 93.4, 71.0, 70.2, 70.0, 60.9, 26.2; HRMS (ESI): calcd for $C_{44}H_{40}O_6Na$ (M+Na) 687.2723, found 687.2697.

4.5. (+)-(1*S*,2*S*)-3-[2,4-Bis(benzyloxy)-6-hydroxyphenyl]-1-[3′,4′-bis(benzyloxy)-4′-methoxyphenyl]propane-1,2-diol ((+)-27)

The propene **26** (3.0 g, 4.5 mmol) was dissolved in dry DMF (30 mL), and to this solution imidazole (1.0 g, 14.7 mmol) and TBSCl (1.1 g, 7.2 mmol) were added successively. The resulting mixture was stirred at rt overnight, and then saturated Na_2CO_3 solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 6/1 v/v) to afford [3,5-bis(benzyloxy)]-2-[3′-[3″,5″-bis(benzyloxy)-4″-methoxyphenyl]allyl]phenoxy-*tert*-butyldimethylsilane (3.1 g). This material was used in the next step without further purification.

AD-mix α (12.8 g) and methanesulfonamide (0.85 g) were dissolved in a solvent mixture of *t*-BuOH (60 mL) and H_2O (60 mL). The resulting mixture was stirred at rt for 5 mm, then the mixture was cooled to 0 °C, and a solution of [3,5-bis(benzyloxy)-2-[3′-[3″,5″-bis(benzyloxy)-4″-methoxyphenyl]allyl]phenoxy-*tert*-butyldimethylsilane (3.1 g) in dichloromethane (60 mL) was added. After the mixture had been stirred overnight, a total of four batches of AD-mix α (6.4 g each) and methanesulfonamide (0.43 g each) were added in 24 h intervals. After another 24 h of stirring at 0 °C, TLC showed that the reaction was completed. Then a 10% aqueous $Na_2S_2O_3$ solution was added to quench the reaction. The mixture was extracted with EtOAc. The organic phases were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 4/1 v/v). The product was redissolved in THF (30 mL) and then TBAF (10 mL, 1 M in THF) was added. The resulting mixture was stirred at rt for 4 h, and saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc and the organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (5% EtOAc/CH_3Cl) and then recrystallized in EtOAc to give a white solid (2.2 g, 69.7% yield): mp 125–127 °C; $[\alpha]_D$ +7.0 (*c* 3, CH_3Cl); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.14 (m, 20H), 6.57 (s, 2H), 6.26 (d, J=2.1 Hz, 1H), 6.21 (d, J=2.1 Hz, 1H), 4.97 (s, 2H), 4.96 (s, 2H), 4.93 (s, 2H), 4.87 (s, 2H), 4.39 (d, J=5.6 Hz, 1H), 3.90–3.85 (m, 1H), 3.81 (s, 3H), 2.89 (A of AB, J=14.6, 3.6 Hz, 1H), 2.73 (B of AB, J=14.6, 8.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.9, 157.7, 157.1, 152.2, 138.6, 136.8, 136.7, 136.1, 128.5, 128.4, 128.3, 127.8, 127.7, 127.6, 127.5, 127.2, 127.0, 126.9, 126.4, 105.1, 95.7, 93.3, 76.4, 70.8, 69.9, 60.7, 26.6; HRMS (ESI): calcd for $C_{44}H_{42}O_8Na$ (M+Na) 721.2777, found 721.2759.

4.6. (+)-(2*R*,3*S*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-ol ((+)-28)

To a suspension of compound (+)-**27** (3.0 g, 4.3 mmol) in 1,2-dichloroethane (50 mL) was added triethyl orthoformate (2 mL), followed by PPTS (500 mg, 2.0 mmol). The mixture was stirred at rt for 20 min and the solid was dissolved. The mixture was heated to 50 °C for 5 h until TLC showed the reaction had been completed. After evaporation of the solvent, the residue was redissolved in DME (30 mL) and MeOH (30 mL), K_2CO_3 (600 mg) was added, and the mixture was stirred at rt overnight. The solvent was evaporated, and the residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1/3 v/v) to afford the desired product as white solid (2.1 g, 71.8% yield): mp 123–125 °C; $[\alpha]_D$ +5.5 (*c* 7.0, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.41–7.23 (m, 20H), 6.67 (s, 2H), 6.26 (s, 1H), 6.20 (s, 1H), 5.05 (s, 2H), 5.04 (s, 2H), 4.97 (s, 2H), 4.95 (s, 2H), 4.54 (d, J=8.1 Hz, 1H), 3.90–3.86 (m, 1H), 3.85 (s, 3H), 3.05 (A of ABq, J=16.4, 5.4 Hz, 1H), 2.61 (B of ABq, J=16.4, 8.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 157.6, 155.0, 152.4, 139.2, 136.7, 133.2, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 106.5, 102.1, 94.2, 93.7, 81.6, 70.8, 69.9, 69.7, 67.8, 60.7, 27.4; HRMS (ESI): calcd for $C_{44}H_{40}O_7Na$ (M+Na) 703.2672, found 703.2684.

4.7. (+)-(2*R*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-one ((+)-29)

Dess–Martin periodinane (19.7 mL, 15% g/mL in CH_2Cl_2, 4.6 mmol) was added in one batch to a stirred solution of (+)-**28** (2.1 g, 3.1 mmol) in CH_2Cl_2 (30 mL) under a N_2 atmosphere. The mixture was stirred at rt for about 2 h till TLC showed the absence of starting material. Subsequently, saturated $NaHCO_3$ solution (40 mL) and 10% aqueous $Na_2S_2O_3$ solution (40 mL) were added to quench the reaction. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (benzene) and then recrystallized in $CHCl_3$ and ether to afford the desired compound (1.8 g, 85.7%): mp 149–151 °C; $[\alpha]_D$ +20.2 (*c* 7, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.23 (m, 20H), 6.63 (s, 2H), 6.35 (d, J=0.6 Hz, 1H), 6.33 (d, J=0.6 Hz, 1H), 5.18 (s, 1H), 5.03 (s, 2H), 5.02 (s, 2H), 4.98 (s, 2H), 4.97 (s, 2H), 3.84 (s, 3H), 3.58–3.35 (AB, J=21.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 204.4, 159.3, 156.9, 154.1, 152.5, 139.3, 136.7, 136.4, 136.2, 130.0, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.3, 127.2, 127.0, 106.0, 101.6, 95.5, 94.8, 82.8, 70.8, 70.0, 69.9, 60.7, 33.3; HRMS (ESI): calcd for $C_{44}H_{39}O_7$ (M+H) 679.2696, found 679.2700.

4.8. (−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-ol ((−)-30)

Under a N_2 atmosphere, the ketone (+)-**29** (1.8 g, 2.6 mmol) was dissolved in dry THF (30 mL), and the solution was cooled to −78 °C. Then L-Selectride (4.0 mL, 1 M solution in THF, 4.0 mmol) was added dropwise. The resulting solution was stirred at −78 °C overnight. When TLC showed the reaction was completed, saturated aqueous $NaHCO_3$ solution (30 mL) was added to quench the reaction. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic phases were dried ($MgSO_4$) and evaporated. The residue was purified by flash chromatography on silica gel (EtOAc/hexane, 1/3 v/v) and then recrystallized with EtOAc and *n*-hexane to afford the desired product (1.6 g, 88.8%) as a white solid: mp 107–109 °C; $[\alpha]_D$ −21.2 (*c* 4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.43–7.26 (m, 20H), 6.76 (s, 2H), 6.26 (s, 2H), 5.11 (s, 4H), 4.98 (s, 4H), 4.81 (s, 1H), 4.13 (br s, 1H), 3.88 (s, 3H), 2.96 (A of AB, *J*=17.1 Hz, 1H), 2.87 (B of ABq, *J*=17.1, 3.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 158.6, 158.1, 155.0, 152.5, 139.1, 136.9, 136.8, 136.7, 133.5, 128.4, 128.3, 128.2, 127.8, 127.7, 127.4, 127.3, 127.2, 127.0, 126.9, 106.0, 100.8, 94.5, 93.9, 78.3, 70.9, 69.9, 69.7, 66.1, 60.7, 27.9; HRMS (ESI): calcd for $C_{44}H_{40}O_7Na$ (M+Na) 703.2672, found 703.2659.

4.9. (−)-(2*R*,3*R*)-5,7-Bis(benzyloxy)-2-[3,4-bis(benzyloxy)-phenyl]chroman-3-yl-3,4-dibenzyloxy-5-methoxybenzoate ((−)-15)

Under a N_2 atmosphere, a solution of 3,4-dibenzyloxy-5-methoxybenzoic acid (246 mg, 0.67 mmol) was refluxed with oxalyl (1 mL) in dry CH_2Cl_2 (10 mL) and one drop of DMF for 3 h. The excess oxally chloride and solvent were removed by distillation and the residue was dried under vacuum for 3 h and dissolved in CH_2Cl_2 (2 mL). This solution was added dropwise to a solution of (−)-**14** (220 mg, 0.34 mmol)[12b] and DMAP (75 mg, 0.62 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred at rt overnight, then saturated aqueous $NaHCO_3$ solution was added. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The organic phases were combined, dried ($MgSO_4$), and evaporated. The residue was purified by flash chromatography on silica gel (*n*-hexane/EtOAc, 3/1 v/v) to afford the desired compound (300 mg, 88.9% yield). Recrystallization in $CHCl_3$ and ether gave a white powder: mp 129–131 °C; $[\alpha]_D$ −37.5 (*c* 2.5, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.26 (m, 30H), 7.22 (s, 1H), 7.16 (s, 1H), 6.88 (AB, *J*=8.2 Hz, 2H), 6.34 (s, 1H), 6.30 (s, 1H), 5.60 (br s, 1H), 5.08 (s, 4H), 5.01 (s, 6H), 4.97 (s, 2H), 4.77 (AB, *J*=11.7 Hz, 2H), 3.76 (s, 3H), 3.08 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.9, 158.6, 157.8, 155.5, 153.2, 151.9, 148.7, 141.7, 137.2, 136.9, 136.8, 136.7, 136.6, 136.3, 130.9, 128.4, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.2, 127.0, 124.9, 119.8, 114.4, 113.5, 108.6, 107.1, 100.7, 94.4, 77.3, 74.8, 71.1, 70.9, 70.7, 69.9, 69.7, 56.0, 25.8; HRMS (ESI): calcd for $C_{65}H_{56}O_{10}Na$ (M+Na) 1019.3771, found 1019.3782.

4.10. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′-bis-(benzyloxy)phenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (16)

Following the procedure for the preparation of **15**, the esterification of (−)-**14** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **16** (86% yield): mp 126–128 °C; $[\alpha]_D$ −76.5 (*c* 3.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.21 (m, 31H), 7.00 (d, *J*=1.8 Hz, 1H), 6.86 (A of ABq, *J*=8.3, 1.6 Hz, 1H), 6.81 (B of AB, *J*=8.3 Hz, 1H), 6.37 (d, *J*=2.0 Hz, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 5.60 (br s, 1H), 5.10–4.98 (m, 12H), 4.61 (AB, *J*=11.6 Hz, 2H), 3.83 (s, 3H), 3.12 (A of ABq, *J*=17.7, 4.4 Hz, 1H), 3.05 (B of AB, *J*=17.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.8, 158.7, 157.9, 155.6, 151.9, 148.9, 148.8, 143.5, 137.1, 136.9, 136.7, 136.4, 130.9, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 124.6, 119.9, 114.6, 113.5, 109.1, 100.8, 94.5, 93.8, 77.6, 77.2, 71.1, 71.0, 70.9, 70.1, 69.9, 68.4, 60.8, 26.1; HRMS (ESI): calcd for $C_{65}H_{57}O_{10}$ (M+H) 997.3952, found 997.3923.

4.11. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′-bis-(benzyloxy)phenyl]chroman3-yl-3″-benzyloxy-4″, 5″-dimethoxybenzoate (17)

Following the procedure for the preparation of **15**, the esterification of (−)-**14** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **17** (83% yield): mp 72–74 °C; $[\alpha]_D$ −72.0 (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 25H), 7.16 (s, 1H), 7.06 (s, 1H), 6.88 (AB, *J*=8.3 Hz, 2H), 6.36 (s, 1H), 6.31 (s, 1H), 5.61 (br s, 1H), 5.08–5.00 (m, 10H), 4.75 (AB, *J*=11.6 Hz, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.09 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 165.0, 158.8, 157.9, 155.6, 153.0, 151.6, 148.9, 148.8, 142.8, 137.1, 136.9, 136.8, 136.4, 131.0, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.4, 127.3, 127.1, 124.8, 120.0, 114.6, 113.6, 108.8, 107.1, 100.8, 94.5, 93.8, 77.5, 71.2, 71.1, 70.8, 70.1, 69.9, 68.6, 60.8, 56.1, 26.0; HRMS (ESI): calcd for $C_{59}H_{53}O_{10}$ (M+H) 921.3639, found 921.3677.

4.12. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris-(benzyloxy)phenyl]chroman-3-yl-3″,4″-bis(benzyloxy)-5″-methoxybenzoate (19)

Following the procedure for the preparation of **15**, the esterification of (−)-**18**[12a] with 3,4-dibenzyloxy-5-methoxybenzoic acid gave the product **19** (82% yield): mp 120–121 °C; $[\alpha]_D$ −41.7 (*c* 2.3, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.40–7.25 (m, 35H), 7.20 (s, 2H), 6.75 (s, 2H), 6.37 (s, 1H), 6.32 (s, 1H), 5.65 (br s, 1H), 5.03–4.96 (m, 9H), 4.90 (s, 2H), 4.78 (AB, *J*=11.5 Hz, 4H), 3.74 (s, 3H), 3.09 (br s, 2H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.8, 158.7, 157.8, 155.5, 153.3, 152.7, 152.0, 141.9, 138.3, 137.6, 137.3, 136.8, 136.7, 136.6, 136.2, 133.2, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 124.9, 108.7, 107.3, 106.4, 100.8, 94.5, 93.8, 77.7, 75.0, 74.8, 71.1, 70.9, 70.0, 69.9, 68.3, 56.1, 26.0; HRMS (ESI): calcd for $C_{72}H_{62}O_{11}Na$ (M+Na) 1125.4190, found 1125.4204.

4.13. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris(benzyloxy)phenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (20)

Following the procedure for the preparation of **15**, the esterification of (−)-**18** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **20** (87% yield): mp 49–51 °C; $[\alpha]_D$ −54.7 (*c* 2.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): δ 7.39–7.20 (m, 37H), 6.70 (s, 2H), 6.40 (s, 1H), 6.34 (s, 1H), 5.65 (br s, 1H), 5.04–4.94 (m, 11H), 4.67 (AB, *J*=11.5 Hz, 4H), 3.77 (s, 3H), 3.11 (A of ABq, *J*=17.6, 4.2 Hz, 1H), 3.04 (B of AB, *J*=17.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ 164.6, 158.8, 158.0, 155.6, 152.8, 152.0, 151.9, 147.1, 143.6, 138.3, 137.7, 136.8, 136.7, 136.3, 133.1, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2, 124.6, 109.1, 106.6, 100.9, 77.9, 77.2, 75.0, 71.0, 70.9, 70.1, 69.9, 68.1, 60.8, 26.2; HRMS (ESI): calcd for $C_{72}H_{63}O_{11}$ (M+H) 1103.4370, found 1103.4425.

4.14. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,4′,5′-tris(benzyloxy)phenyl]chroman-3-yl-3″-benzyloxy-4″,5″-dimethoxybenzoate (21)

Following the procedure for the preparation of **15**, the esterification of (−)-**18** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **21** (82% yield): mp 57–59 °C; $[\alpha]_D$ −52.5 (*c* 2.5, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.41–7.21 (m, 32H), 6.74 (s, 2H), 6.38 (d, *J*=2.0 Hz, 1H), 6.32 (d, *J*=2.0 Hz, 1H), 5.65 (br s, 1H), 5.06–4.93 (m, 9H), 4.76 (AB, *J*=11.5 Hz, 4H), 3.76 (s, 6H), 3.10–3.09 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.8, 158.8, 158.0, 155.6, 153.1, 152.8, 151.7, 143.0, 138.4, 137.7, 136.8, 136.7, 136.3, 133.2, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.4, 127.2, 124.8, 108.9, 107.2, 106.7, 100.9, 94.6, 93.9, 77.8, 75.1, 71.3, 71.2, 70.9, 70.1, 69.9, 68.3, 60.8, 56.2, 26.1; HRMS (ESI): calcd for $C_{65}H_{59}O_{11}$ (M+H) 1027.4057, found 1027.4100.

4.15. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″,4″,5″-tris(benzyloxy)benzoate (31)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3,4,5-tris(benzyloxy)benzoic acid gave the product **31** (88% yield): mp 57–59 °C; $[\alpha]_D$ −54.2 (*c* 5.0, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.23 (m, 37H), 6.70 (s, 2H), 6.38 (d, *J*=1.6 Hz, 1H), 6.33 (d, *J*=1.6 Hz, 1H), 5.64 (br s, 1H), 5.02–4.99 (m, 9H), 4.91 (s, 2H), 4.74 (AB, *J*=11.7 Hz, 4H), 3.80 (s, 3H), 3.08 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.7, 158.7, 157.9, 155.5, 152.5, 152.2, 142.6, 139.4, 137.3, 136.8, 136.6, 136.3, 132.9, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.8, 127.7, 127.3, 127.2, 127.1, 124.8, 109.0, 106.7, 100.8, 94.5, 93.9, 77.8, 74.9, 71.0, 70.9, 70.0, 69.8, 60.7, 26.1; HRMS (ESI): calcd for $C_{72}H_{62}O_{11}Na$ (M+Na) 1125.4190, found 1125.4181.

4.16. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″,5″-bis(benzyloxy)-4″-methoxybenzoate (32)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3,5-dibenzyloxy-4-methoxybenzoic acid gave the product **32** (85% yield): mp 65–67 °C; $[\alpha]_D$ −49.8 (*c* 2.7, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.21 (m, 32H), 6.68 (s, 2H), 6.38 (s, 1H), 6.34 (s, 1H), 5.63 (br s, 1H), 5.04–4.98 (m, 9H), 4.70 (AB, *J*=11.7 Hz, 4H), 3.79 (s, 3H), 3.77 (s, 3H), 3.08–3.05 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.5, 158.7, 157.9, 155.5, 152.4, 151.8, 143.5, 139.3, 136.8, 136.6, 136.2, 132.8, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.3, 127.1, 127.0, 124.5, 109.0, 106.6, 100.8, 94.5, 93.8, 77.8, 70.9, 70.8, 70.0, 69.8, 68.0, 60.7, 26.1; HRMS (ESI): calcd for $C_{66}H_{59}O_{11}$ (M+H) 1027.4057, found 1027.4054.

4.17. (−)-(2*R*,3*R*)-*cis*-5,7-Bis(benzyloxy)-2-[3′,5′-bis(benzyloxy)-4′-methoxyphenyl]chroman-3-yl-3″-benzyloxy-4″,5″-dimethoxybenzoate (33)

Following the procedure for the preparation of **15**, the esterification of (−)-**30** with 3-benzyloxy-4,5-dimethoxybenzoic acid gave the product **33** (86% yield): mp 51–53 °C; $[\alpha]_D$ −47.1 (*c* 3.5, $CHCl_3$); ^1H NMR ($CHCl_3$, 400 MHz): δ 7.38–7.21 (m, 26H), 7.17 (s, 1H), 6.72 (s, 2H), 6.35 (s, 1H), 6.32 (s, 1H), 5.63 (br s, 1H), 5.05–5.01 (m, 7H), 4.79 (AB, *J*=11.6 Hz, 4H), 3.81 (s, 3H), 3.77 (s, 3H), 3.76 (s, 3H), 3.08 (m, 2H); ^{13}C NMR ($CHCl_3$, 400 MHz): δ 164.7, 158.7, 157.8, 155.4, 153.0, 152.4, 151.6, 142.9, 139.4, 136.8, 136.6, 136.2, 132.9, 128.5, 128.4, 128.3, 127.9, 127.8, 127.7, 127.6, 127.3, 127.1, 127.0, 124.7, 108.8, 107.1, 106.7, 100.7, 94.4, 93.8, 77.6, 71.0, 70.8, 70.0, 69.8, 68.2, 60.7, 60.6, 56.1, 26.0; HRMS (ESI): calcd for $C_{60}H_{55}O_{11}$ (M+H) 951.3744, found 951.3757.

4.18. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″,4″-dihydroxy-5″-methoxybenzoate (5)

Under a H_2 atmosphere, $Pd(OH)_2/C$ (20%, 200 mg) was added to a solution of **15** (280 mg, 0.28 mmol) in a solvent mixture of THF/MeOH (1/1 v/v, 25 mL). The resulting reaction mixture was stirred at rt under H_2 for 6 h, TLC showed that the reaction was completed. The reaction mixture was filtered to remove the catalyst. The filtrate was evaporated, and the residue was rapidly purified by flash chromatography on silica gel (10% MeOH/CH_2Cl_2, then 20% MeOH/CH_2Cl_2) to afford **5** (100 mg, 80% yield): mp 248–250 °C (decomposed); $[\alpha]_D$ −167 (*c* 1, EtOH), lit. 168 (*c* 1, EtOH);[18] ^1H NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 7.22 (d, *J*=1.7 Hz, 1H), 7.18 (d, *J*=1.8 Hz, 1H), 7.11 (d, *J*=1.7 Hz, 1H), 7.02 (A of ABq, *J*=8.2, 1.8 Hz, 1H), 6.90 (B of AB, *J*=8.2 Hz, 1H), 6.14 (AB, *J*=2.0 Hz, 2H), 5.54 (br s, 1H), 5.22 (br s, 1H), 3.90 (s, 3H), 3.16 (A of ABq, *J*=17.3, 4.1 Hz, 1H), 3.04 (B of AB, *J*=17.3 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 166.9, 157.3, 157.2, 156.7, 148.6, 145.5, 145.3, 145.2, 140.1, 131.0, 120.9, 118.9, 115.9, 114.8, 111.6, 105.9, 98.7, 96.4, 95.5, 77.8, 70.3, 56.6, 26.3; HRMS (ESI): calcd for $C_{23}H_{20}O_{10}Na$ (M+Na) 479.0954, found 479.0960.

4.19. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (6)

Following the preparation procedure for **5**, the hydrogenolysis of **16** afforded **6** (88% yield): mp 248–250 °C

(decomposed); $[\alpha]_D$ −161.3 (*c* 4.0, Me_2CO), lit. 160.1 (*c* 1.1, Me_2CO);[18] ^1H NMR (acetone-d_6, 400 MHz): δ 7.25 (d, *J*=1.8 Hz, 1H), 7.17 (s, 2H), 7.07 (A of ABq, *J*=8.2, 1.8 Hz, 1H), 6.95 (B of AB, *J*=8.2 Hz, 1H), 6.24 (d, *J*=2.2 Hz, 1H), 6.22 (d, *J*=2.2 Hz, 1H), 5.73 (br s, 1H), 5.31 (br s, 1H), 3.98 (s, 3H), 3.23 (A of ABq, *J*=17.4, 4.5 Hz, 1H), 3.11 (B of ABq, *J*=17.4, 1.8 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.5, 155.4, 155.1, 154.7, 148.8, 143.2, 143.1, 138.1, 129.0, 124.1, 116.8, 113.4, 112.5, 107.6, 96.6, 94.2, 93.5, 75.6, 67.5, 58.3, 24.2; HRMS (ESI): calcd for $C_{23}H_{20}O_{10}Na$ (M+Na) 479.0954, found 479.0965.

4.20. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′-dihydroxyphenyl)-chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (7)

Following the preparation procedure for **5**, the hydrogenolysis of **17** afforded **7** (86% yield): mp 239–241 °C (decomposed); $[\alpha]_D$ −135.9 (*c* 4.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.25 (AB, *J*=1.9 Hz, 2H), 7.18 (d, *J*=1.9 Hz, 1H), 7.07 (A of ABq, *J*=8.2, 1.9 Hz, 1H), 6.94 (B of AB, *J*=8.2 Hz, 1H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.70–5.68 (m, 1H), 5.34 (br s, 1H), 3.98 (s, 3H), 3.93 (s, 3H), 3.23 (A of ABq, *J*=17.5, 4.4 Hz, 1H), 3.15 (B of ABq, *J*=17.5, 2.3 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.6, 156.6, 156.2, 155.7, 152.5, 149.8, 144.4, 144.2, 140.2, 130.1, 125.1, 117.7, 114.4, 113.5, 110.0, 104.6, 97.5, 95.2, 94.4, 76.6, 68.9, 55.0, 25.1; HRMS (ESI): calcd for $C_{24}H_{22}O_{10}Na$ (M+Na) 493.1111, found 493.1107.

4.21. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″,4″-dihydroxy-5″-methoxybenzoate (8)

Following the preparation procedure for **5**, the hydrogenolysis of **19** afforded **8** (83% yield): mp 221–223 °C (decomposed); $[\alpha]_D$ −160 (*c* 1, EtOH), lit. 162 (*c* 1, EtOH);[18] ^1H NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 7.17 (d, *J*=1.9 Hz, 1H), 7.07 (d, *J*=1.9 Hz, 1H), 6.71 (s, 2H), 6.09 (AB, *J*=2.2 Hz, 2H), 5.47 (br s, 1H), 5.10 (br s, 1H), 3.85 (s, 3H), 3.07 (A of ABq, *J*=17.4, 4.3 Hz, 1H), 3.01 (B of AB, *J*=17.4 Hz, 1H); ^{13}C NMR (acetone-d_6/D_2O, 3/1 v/v, 400 MHz): δ 167.0, 157.3, 157.2, 156.6, 148.6, 146.2, 145.5, 140.1, 133.0, 130.6, 121.0, 111.6, 106.5, 106.0, 98.7, 96.4, 95.5, 77.8, 70.5, 56.6, 26.3; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0920.

4.22. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (9)

Following the preparation procedure for **5**, the hydrogenolysis of **20** afforded **9** (89% yield): mp 226–228 °C (decomposed); $[\alpha]_D$ −158.9 (*c* 1, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.14 (s, 2H), 6.78 (s, 2H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.72 (br s, 1H), 5.23 (br s, 1H), 3.97 (s, 3H), 3.20 (A of ABq, *J*=17.3, 4.6 Hz, 1H), 3.07 (B of AB, *J*=17.4, 2.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.5, 156.5, 156.1, 155.7, 149.8, 144.9, 139.1, 131.8, 129.3, 125.1, 108.6, 105.3, 97.6, 95.1, 94.5, 76.6, 68.3, 59.2, 25.2; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0914.

4.23. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,4′,5′-trihydroxyphenyl)chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (10)

Following the preparation procedure for **5**, the hydrogenolysis of **21** afforded **10** (83% yield): mp 229–231 °C (decomposed); $[\alpha]_D$ −128.3 (*c* 1.5, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.24 (d, *J*=1.9 Hz, 1H), 7.18 (d, *J*=1.9 Hz, 1H), 6.81 (s, 2H), 6.20 (s, 1H), 6.19 (s, 1H), 5.69 (br s, 1H), 5.27 (br s, 1H), 3.99 (s, 3H), 3.93 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.2 Hz, 1H), 3.12 (B of ABq, *J*=17.4, 2.2 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.5, 155.0, 154.9, 154.7, 154.0, 151.1, 148.3, 143.5, 138.8, 130.2, 127.9, 127.8, 123.6, 108.6, 103.6, 103.1, 95.7, 93.6, 92.7, 75.1, 67.8, 58.0, 53.6, 23.6; HRMS (ESI): calcd for $C_{24}H_{22}O_{11}Na$ (M+Na) 509.1060, found 509.1069.

4.24. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″,4″,5″-trihydroxybenzoate (11)

Following the preparation procedure for **5**, the hydrogenolysis of **31** afforded **11** (90% yield): mp 219–221 °C (decomposed); $[\alpha]_D$ −128.4 (*c* 2.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.18 (s, 2H), 6.79 (s, 2H), 6.20 (AB, *J*=2.2 Hz, 2H), 5.72 (br s, 1H), 5.24 (br s, 1H), 3.89 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.4 Hz, 1H), 3.07 (B of ABq, *J*=17.4, 2.0 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 164.5, 156.2, 155.9, 155.4, 149.4, 144.4, 137.3, 134.1, 133.8, 120.2, 108.4, 105.4, 97.5, 95.0, 94.3, 76.4, 67.6, 59.0, 25.1; HRMS (ESI): calcd for $C_{23}H_{20}O_{11}Na$ (M+Na) 495.0903, found 495.0924.

4.25. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″,5″-dihydroxy-4″-methoxybenzoate (12)

Following the preparation procedure for **5**, the hydrogenolysis of **32** afforded **12** (90% yield): mp 228–230 °C (decomposed); $[\alpha]_D$ −131.1 (*c* 2.0, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.15 (s, 2H), 6.80 (s, 2H), 6.21 (AB, *J*=2.2 Hz, 2H), 5.75 (br s, 1H), 5.26 (br s, 1H), 3.96 (s, 3H), 3.89 (s, 3H), 3.19 (A of ABq, *J*=17.4, 4.4 Hz, 1H), 3.11 (AB, *J*=17.4, 1.8 Hz, 1H); ^{13}C NMR(acetone-d_6, 400 MHz): δ 164.1, 156.1, 155.8, 155.2, 149.4, 149.3, 138.8, 134.0, 133.7, 124.7, 108.2, 105.1, 97.2, 94.9, 94.1, 76.1, 67.9, 58.9, 24.9; HRMS (ESI): calcd for $C_{24}H_{22}O_{11}Na$ (M+Na) 509.1060, found 509.1046.

4.26. (−)-(2*R*,3*R*)-5,7-Dihydroxy-2-(3′,5′-dihydroxy-4′-methoxyphenyl)chroman-3-yl-3″-hydroxy-4″,5″-dimethoxybenzoate (13)

Following the preparation procedure for **5**, the hydrogenolysis of **33** afforded **13** (89% yield): mp 199–201 °C (decomposed); $[\alpha]_D$ −139.0 (*c* 1.2, Me_2CO); ^1H NMR (acetone-d_6, 400 MHz): δ 7.24 (d, *J*=1.9 Hz, 1H), 7.17 (d, *J*=1.9 Hz, 1H), 6.82 (s, 2H), 6.18 (AB, *J*=2.2 Hz, 2H), 5.65 (br s, 1H), 5.26 (br s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.88 (s, 3H), 3.17 (A of ABq, *J*=17.4, 4.3 Hz, 1H), 3.14 (B of ABq, *J*=17.4, 2.5 Hz, 1H); ^{13}C NMR (acetone-d_6, 400 MHz): δ 163.9, 155.7, 155.3, 154.5. 151.7, 148.9, 139.3, 133.4, 133.3, 124.2, 109.1, 104.4, 103.6, 96.3, 94.2,

93.3, 75.5, 68.1, 58.6, 58.5, 58.4, 58.3, 54.2, 54.1, 24.1; HRMS (ESI): calcd for $C_{25}H_{24}O_{11}Na$ (M+Na) 523.1216, found 523.1203.

Acknowledgements

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Structural studies and binding properties of pendant diazacoronands—precursors to macrocyclic compounds of planar chirality

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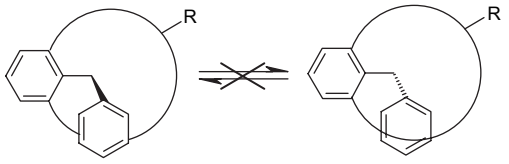
Abstract—Structural studies of pendant diazacoronands having an *N*-benzoyl, *N*-acetyl, *O*-benzyl or *O*-benzoyl side arm were performed by means of X-ray and temperature-dependent ^{1}H NMR experiments. The energies of macroring flipping process were determined for three pendant diazacoronands. The complexation properties of pendant diazacoronands toward the alkali metal cations (Na^+, K^+, and Rb^+) were estimated by ESI-MS experiments.

1. Introduction

The design and synthesis of macrocyclic compounds are closely related to the supramolecular chemistry and host–guest interactions.[1] However, up to now, no special effort has been made to prepare receptors of planar chirality.[2] Among the known macrocyclic compounds of planar chirality, most of them are based on a [2.2]paracyclophane framework having small, rigid macroring structure.[3] For these reasons, they cannot be efficient receptors for supramolecular applications. Hitherto, only several examples of such chiral compounds having a larger macroring have been published.[4] This is probably caused by the difficult preparation sequence requiring non-commercially available substrates. In addition, contrary to the [2.2]paracyclophane derivatives, the chiral compounds having larger macroring are conformationally flexible, thus their structural analysis and determination of energy barrier of deformation are indispensable to the design and synthesis of stable atropoisomers.[5]

Recently, our attention has been focused on the synthesis of diazacoronands of planar chirality, as potential receptors for supramolecular applications.[6] To the existence of such atropoisomers, two independent requirements are indispensable: (1) the presence of a large pendant arm, which is located on only one side of the macroring and cannot easily jump through it; (2) the presence of a non-symmetric moiety in the molecule (Scheme 1).



Scheme 1. The source of planar chirality in the pendant macrocyclic compounds.

The intraannular arm is an essential part of the presented planar–chiral system. Its size strongly affects the stability of such enantiomers and additionally it could modify the binding properties of the macrocyclic compounds. Therefore, the synthesis of efficient and stable macrocyclic receptors of planar chirality requires initial structural studies for simpler, non-chiral pendant diazacoronands. Additionally, knowledge of the influence of the type of intraannular group on the binding properties makes it possible to design appropriate chiral receptors.

In this contribution, we would like to present the conformational analysis of pendant diazacoronands investigated by variable temperature ^{1}H NMR spectroscopy and X-ray analysis. The binding properties of pendant diazacoronands toward alkali metal cations (Na^+, K^+, and Rb^+) were estimated by the electrospray ionization mass spectrometry (ESI-MS) experiments.

Keywords: Binding properties; Diazacoronands; ESI-MS; Supramolecular chemistry.
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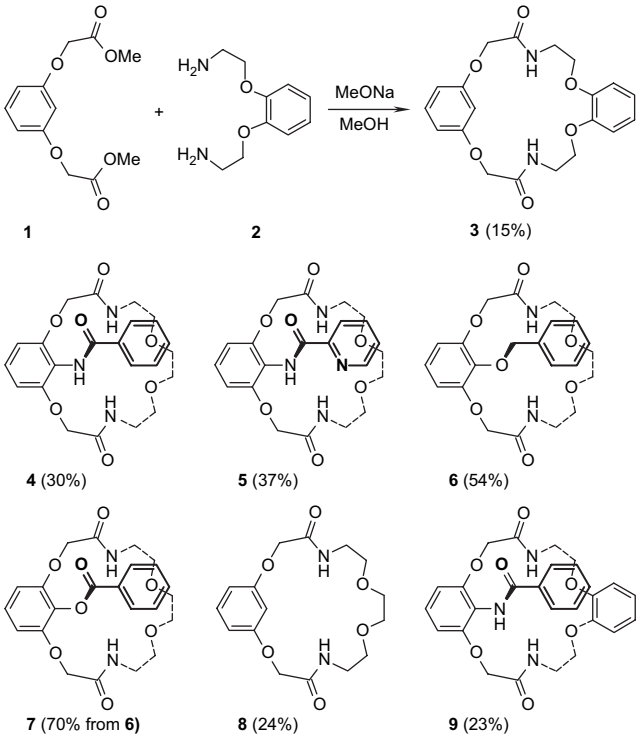
2. Results and discussion

2.1. Synthesis

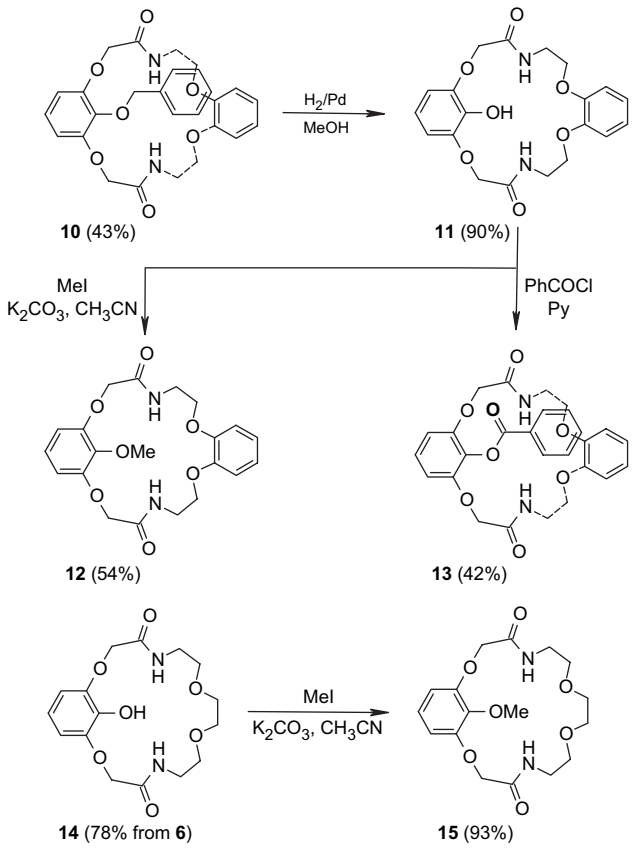
For the preparation of the title compounds, the double-amidation reaction was applied. In this reaction, originally introduced by Tabushi,[7] and developed in our laboratory,[8] dimethyl α,ω-dicarboxylates react with a primary α,ω-diamine in the presence of MeO^- under non-high dilution conditions. For example, diazacoronand **3** was prepared via the reaction of the appropriate diester **1**[9] with diamine **2**[10] in moderate yield (15%). To assess the influence of pendant arm on binding properties, two types of diazacoronands were compared, namely (1) those having a pendant arm, i.e., **4**–**7**,[11] **9**,[6a] **10**,[12] **13**, and (2) their analogs, compounds **3** and **8**,[13] unsubstituted at the intraannular position (Scheme 2).



Scheme 2. Pendant diazacoronands **4**–**7**, **9** and their unsubstituted analogs **3** and **8**.

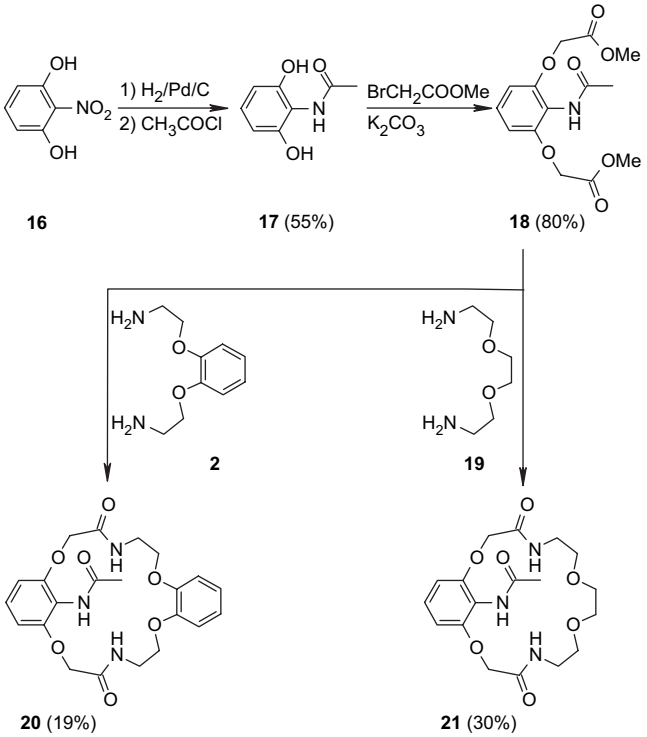
An advantage of compounds **6** and **10** is their chemical versatility resulting from the presence of the *O*-benzyl group. Starting from diazacoronand **10**, the intraannular function was easily removed by hydrogenation to form the hydroxy derivative **11** in good yield (90%). Compound **11** could be modified in various ways, including alkylation and acylation, and it was easily transformed into the *O*-methyl derivative **12** as well as into the *O*-benzoyl compound **13**, in satisfactory yields of 80% and 42%, respectively (Scheme 3). The alkylation of phenol **14**[11] was performed analogously and the reference *O*-methyl compound **15**[14] was isolated in good yield.

The syntheses of the reference compounds having the less sterically demanding *N*-acetyl intraannular group, were performed via the reaction sequence shown in Scheme 4. Starting from 2-nitroresorcinol **16**, after catalytic reduction and acylation of the resulting amino group, we obtained compound **17**, which in turn was elongated by means of



Scheme 3. Modifications of macrocyclic phenols **11** and **14**.

methyl bromoacetate. Diester **18** was then examined in macrocyclization reactions with the diamino-ethers **2**[10] and **19** to afford macrocyclic compounds **20** and **21**, respectively



Scheme 4. The synthesis of *N*-acetyl diazacoronands **20** and **21**.

(Scheme 4). Interestingly, the isolated yields of these compounds are comparable to the yields of *N*-benzoyl derivatives **4** and **9**, although the *N*-acetyl side arm is sterically less demanding. Furthermore, the compounds with no intraannular group (**3** and **8**) were synthesized in even lower yields (15% and 24%, respectively). This proves that the intraannular group plays an important role in the macrocyclization step.

2.2. Structural analysis

2.2.1. Structural analysis of *N*-substituted compounds. Diazacoronands **4**, **5**, and **9** having N-type side arm readily crystallized from methanolic solutions in a vapor diffusive system (*n*-pentane or diethyl ether). X-ray analysis of **4** displayed the presence of two types of hydrogen bonds:

(1) intramolecular between the oxygen atom of the benzamide group and the amide function (Fig. 1A);
(2) intermolecular between the proton of the benzamide group and the oxygen atom from the other molecule (Fig. 1B).

In addition, the macroring adopts a U-shaped arrangement with the intraannular function turned away from the macroring.

The solid-state analysis of compound **5** reveals analogous intra- and intermolecular hydrogen bonds. The pendant arm is turned out of the macroring as well. The characteristic crystal packing, observed also for compound **4**, is a 'molecular zipper'. Two chains of molecules of **5** make sides of the 'zipper', which are linked together by intermolecular π–π interactions of the pyridine moieties (Fig. 2).

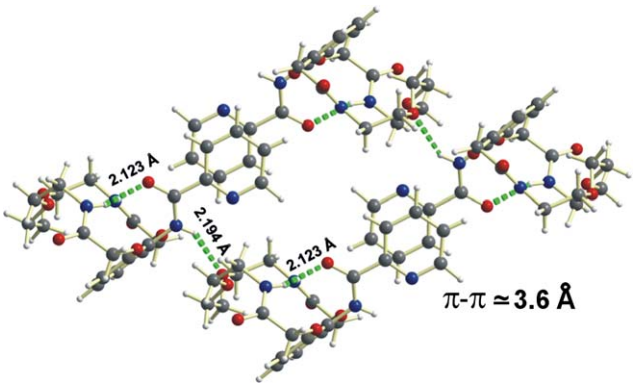


Figure 2. X-ray analysis of **5** reveals a 'molecular zipper'.

Structural analysis of compound **9** reveals a similar shape to the aliphatic analogs **4** and **5**; however, two intramolecular hydrogen bonds are observed (Fig. 3A). Additionally, the benzamide function participates in the intermolecular interactions, forming a network of hydrogen bonds with the methanol molecules (Fig. 3B).

2.2.2. ^{1}H NMR studies of *N*-substituted compounds. The conformational studies of pendant diazacoronands in solution were performed by means of ^{1}H NMR spectroscopy. The temperature-dependent experiment was designed to establish the transition state free energy at the coalescence temperature ($\Delta G_c^{\#}$), which represents the energy barrier of a macroring flipping process. According to the structural studies of compounds **4**, **5**, and **9** in the solid state, the length of the intraannular group is greater than the diameter of the macroring, thus the pendant arm cannot easily jump through it. Therefore, diazacoronands **4**, **5**, and **9** should exhibit a satisfactory structural stability also in solution. In fact, at room

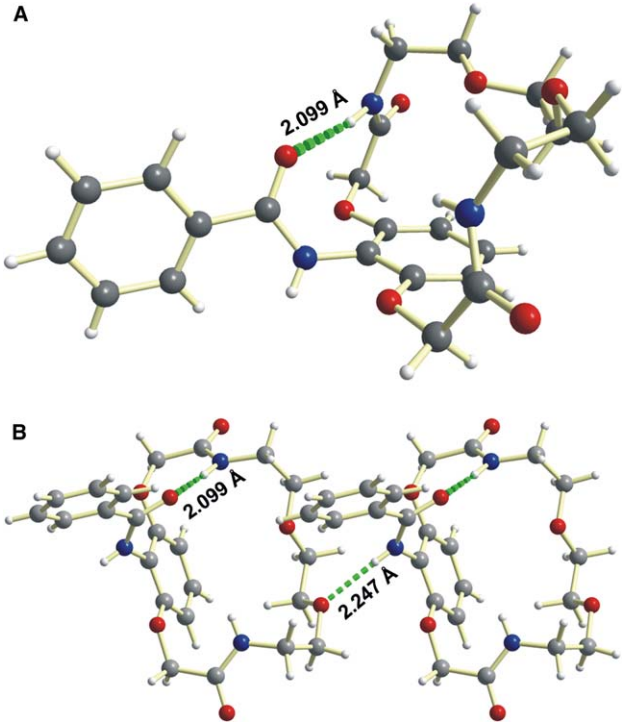


Figure 1. X-ray analysis of compound **4**. (A) Intramolecular hydrogen bond and (B) intermolecular hydrogen bond.

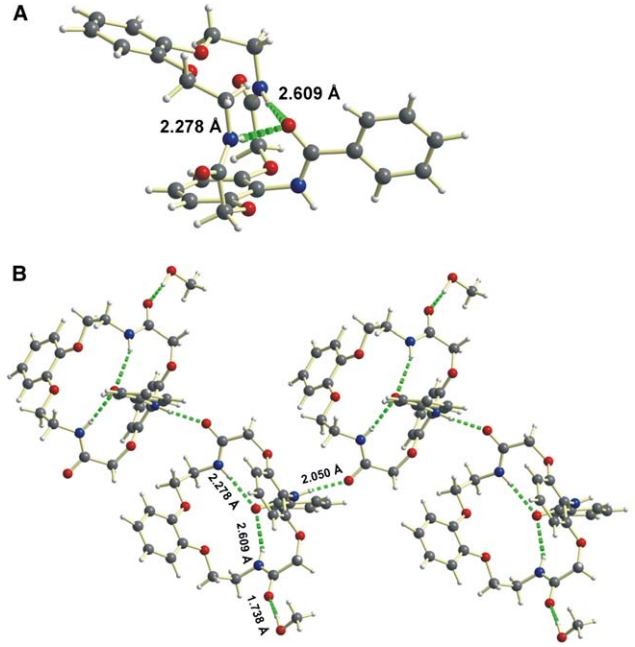


Figure 3. X-ray analysis of compound **9**. (A) Intramolecular hydrogen bonds and (B) a network of hydrogen bonds.

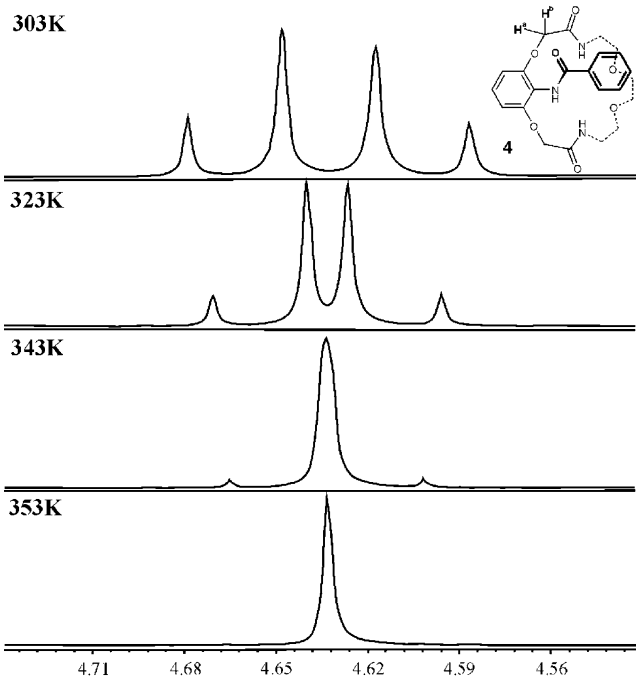


Figure 4. The temperature-dependent ^{1}H NMR spectrum of isolated CH_aH_b protons of compound **4** in DMSO-d_6.

temperature, the protons H^a, H^b of the isolated methylene group appear as an AB quartet and they are diastereotopic. The ^{1}H NMR experiment for compound **4** at various temperatures revealed coalescence of the AB-type signal at 353 K (Fig. 4).

To establish the influence of the pyridine moiety on the structural stability, an analogous experiment was carried out for compound **5** and the conformational stability was determined to be higher than that of compound **4**. The AB-type signal coalesces only at 390 K.

To verify the influence of the size of the intraannular function on the conformational stability, an analogous ^{1}H NMR experiment was carried out for the reference *N*-acetyl compound **21**. Surprisingly, the AB-type signal coalesces at 373 K, even higher than that of the *N*-benzoyl derivative **4**. This suggests that the size of the side arm has a minor influence on the conformational stability of *N*-substituted diazacoronands.

The ^{1}H NMR experiments for compounds **9** and **20** have shown that the widths of the AB-type signals at 373 K are close to these widths at room temperature. Due to limitation of the NMR apparatus, we could not establish $\Delta G_c^{\#}$ for them, but, from the viewpoint of this work, we could assume that if the signal of the methylene group did not coalesce at 373 K, then the pendant diazacoronand possessed conformational stability sufficient for the further purposes. Our assumption was also supported by our earlier results where enantiomers of a non-symmetrical diazacoronand based on the framework of compound **9** retained their enantiomeric purity for at least six months at room temperature and even extended boiling of solutions in acetonitrile (24 h) did not lead to any racemization.[6a]

The free energy of activation for the macroring flipping process ($\Delta G_c^{\#}$) was determined by Eyring[15] equations using the experimentally found coalescence temperature T_c.

$$k_c = \pi/2^{1/2}\left(\Delta\nu^2 + 6J^2\right)^{1/2} \quad (1)$$

$$\Delta G_c^{\#} = 2.303RT_c\left(10.32 + \log T_c - \log k_c\right) \quad (2)$$

where k_c is a rate constant, $\Delta\nu$ is the shift difference at low temperature and J is a coupling constant. According to Eq. 2, the values of $\Delta G_c^{\#}$ were calculated and amounted to 73.0 kJ/mol for **4**, 80.2 kJ/mol for **5**, and 77.1 kJ/mol for **21** (Table 1).

To find the reason for the significantly higher structural stability of diazacoronands with an additional benzene ring (**9** and **20**), NOESY experiment was carried out for compound **9** (Fig. 5). Strong cross peaks were observed between aliphatic and aromatic protons close to the macroring (A and B in Fig. 5). These findings indicate that the macroring system is not planar, and it probably adopts a U-shaped conformation. The absence of any cross peak between the *N*-benzoyl group (dotted line) and the macrocycle protons suggests that the intraannular function is located out of the macrocyclic cavity. This assumption is additionally supported by the fact that chemical shift related to intraannular NH proton is concentration dependent. This implies involvement of amide NH's in the intermolecular hydrogen bonding. The result of the NOESY experiment agrees well with the result of the X-ray analysis for the solid state and gives no explanation of the higher conformational stability of compound **9** over compound **4**.

Considering the similar structural results for diazacoronands **4** and **9**, and because the *N*-benzoyl function is turned away from the macrocyclic cavity, we proposed the following route of the macroring flipping process in compound **4** (Fig. 6).

According to our suggestions, not the intraannular group but the hydrogen atom at *para* position jumps through the macroring plane. Due to high flexibility of the macroring in compound **4**, the *N*-benzoyl side arm can easily rotate and cross the plane defined by macroring. In the case of compound **9**, which bears an additional benzene ring, the macroring is more rigid and such deformation is more energy demanding. This assumption is additionally supported by the fact that the reference diazacoronands **20** and **21** with smaller *N*-acetyl intraannular function possess comparable conformational stability as *N*-benzoyl derivatives **4** and **9**. Surprisingly, according to these findings, the flexibility of the macroring rather than the size of the intraannular group seems to have the major influence on the conformational stability of such diazacoronands. Therefore, the further synthesis of

Table 1. Thermodynamic parameters determined for diazacoronands **4**, **5**, and **21**

	T_c [K]	$\Delta\nu$ [Hz]	J [Hz]	k_c [Hz]	$\Delta G_c^{\#}$ [kJ/mol]
4	353	35.0	16.1	116.7	73.0
5	390	55.0	16.0	150.0	80.2
21	373	39.4	16.1	123.8	77.1

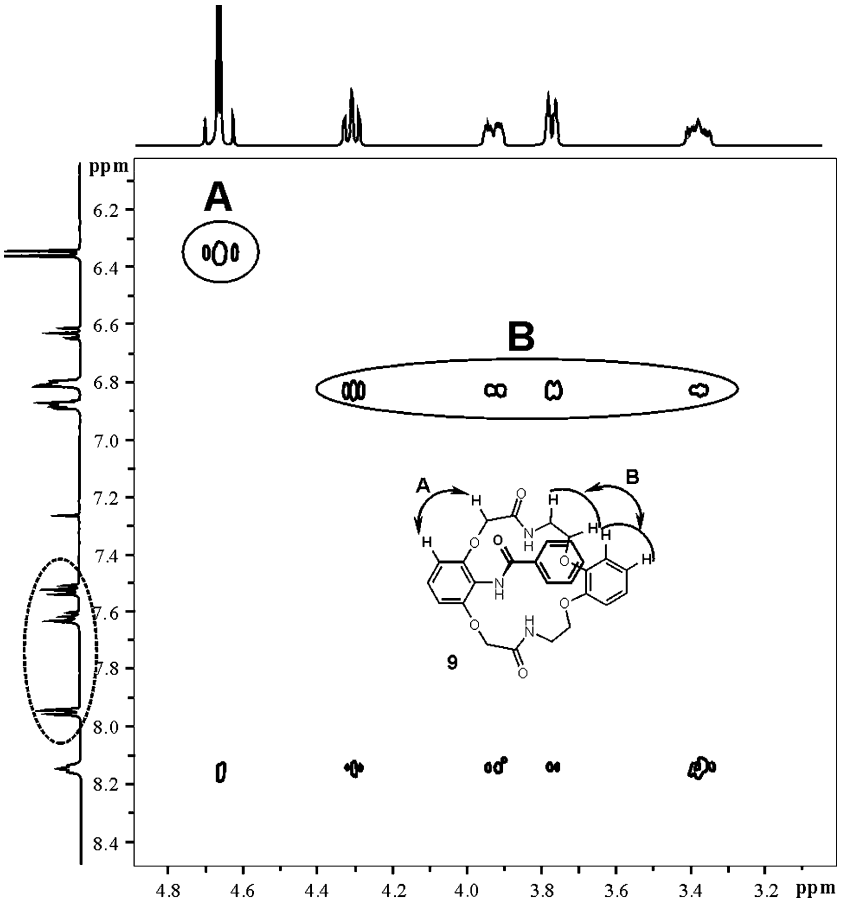


Figure 5. 2D ^{1}H NMR NOESY spectrum of compound **9**; signals from *N*-benzoyl group (dotted line).

a stable, chiral compound with *N*-benzoyl side arm requires the presence of a rigid macroring structure.

2.2.3. Structural analysis of *O*-substituted compounds. Attempts to obtain suitable single crystals of *O*-substituted compounds were unsuccessful, thus the structural studies of these compounds were carried out only in solution. The temperature-dependent ^{1}H NMR experiments carried out for the *O*-substituted compounds **6**, **7**, **10**, and **13** have shown stabilities significantly higher than for the *N*-substituted diazacoronands. The diastereotopic protons of *O*-benzyl derivative **6** do not coalesce at 373 K. Furthermore, the width of the AB-type signals is almost independent of the temperature (Fig. 7).

Comparable ^{1}H NMR results were observed for the derivative **7** as well as for **10** and **13** with an additional benzene ring. ^{1}H NMR spectra for the reference compounds **12** and **15**[14] with an *O*-methyl side arm, the smallest of the possible *O*-substituents, do not reveal a typical AB-type signal. These findings show that the structures of the *O*-substituted derivatives are completely different from the *N*-substituted diazacoronands **4**, **5**, **21**, **9**, and **20**. To support our proposal, a NOESY experiment was carried out for compound **6**, and revealed cross peaks between protons of the benzyl function and the macroring (Fig. 8, A and B). This suggested that the intraannular group was oriented inwards the macroring, which was additionally proved for compound **10**.[12] The

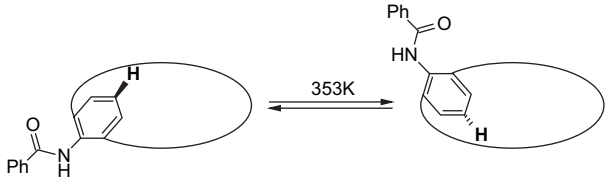


Figure 6. Proposed way of macroring flipping process in compound **4**.

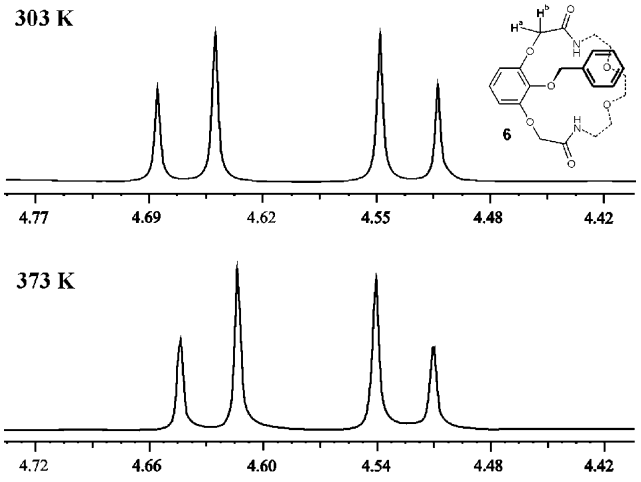


Figure 7. The temperature-dependent ^{1}H NMR spectrum of isolated CH_aH_b protons of compound **6** in DMSO-d_6.

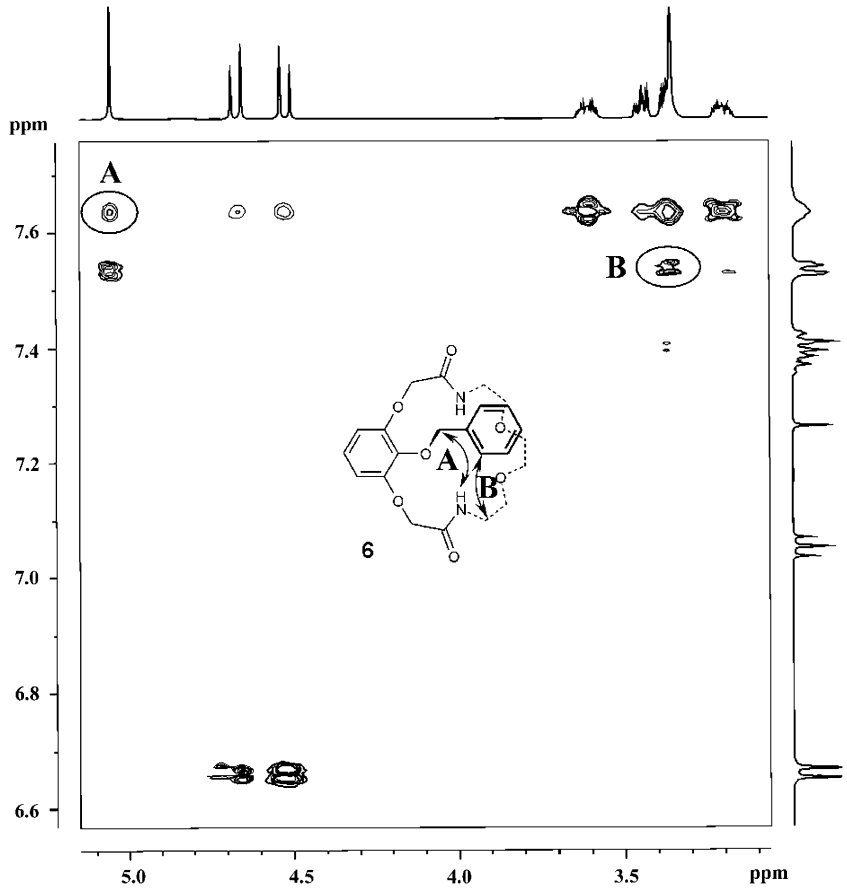


Figure 8. 2D ^{1}H NMR NOESY spectrum of compound **6**.

flipping process is significantly more energy demanding than in the case of the aliphatic *N*-benzoyl derivative **4**. Therefore, in the case of compound **6**, the size and structure of the *O*-benzyl group ensure sufficient conformational stability.

According to the presented results, the type of the intraannular group strongly affects the structural stability of pendant diazacoronands. In the case of compounds **4**, **5**, and **21**, the coalescence temperatures and $\Delta G_c^{\#}$ were measurable. The rest of the presented diazacoronands **6**, **7**, **9**, **10**, **13**, and **20** have significantly higher conformational stability, thus we assume that they are sufficiently stable for our further purposes. The *O*-substituted compounds have higher stability than the *N*-substituted derivatives **4**, **5**, and **21**. Surprisingly, in the case of the latter group of compounds, rigidity of the macroring, and not the size of intraannular function has the main effect on the conformational stability. The *O*-substituted diazacoronands **6** and **7**, although having an aliphatic macroring, reveal a substantial structural stability and the signal from diastereotopic protons do not coalesce at 373 K. Summing up, further synthesis of stable macrocycles of planar chirality requires the presence of additional benzene ring in the case of *N*-substituted derivatives. On the contrary, chiral *O*-substituted diazacoronands can possess an aliphatic macroring.

2.3. Binding properties (ESI-MS)

To estimate the influence of the intraannular group on the binding properties of pendant diazacoronands, ESI-MS was used. Although complexation experiments are typically carried out by means of NMR, potentiometry, extraction or UV–vis techniques, these conventional methods are more time-consuming and require up to 1000 times more analyte than ESI-MS. Up to now, several studies have evaluated the use of ESI-MS for the applications involving non-covalent host–guest interactions,[16] and revealed that this approach is suitable for quick, initial characterization of the considered host.

Our investigations focused on checking competition between two ligands toward one alkali metal cation. It is well known from the ESI-MS technique that the response factor depends on the solvation energy of the given ions. In order to perform a quantitative analysis of the results, one should introduce the corresponding coefficients for correlation of the different ligand response factors. Such a procedure is possible but quite tedious and unnecessary from the viewpoint of this work. For our purposes, it is reasonable to assume that the peak intensity ratios higher than 4:1 are indicative for the stronger complexing properties of one out of the two complexing ligands. To verify how structural changes of diazacoronands affect their binding properties, three ESI-MS experiments were carried out.

(1) *Effect of the intraannular group*: Table 2 shows six pairs consisting of the pendant diazacoronands and the unsubstituted reference compounds **3** and **8**. The peak ratio is the highest in the case of derivatives **4** and **6** (entries 1 and 2). No differences were observed for the pair **7/8**

Table 2. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
1	**4**	**8**	2.5	3.4	5.7
2	**6**	**8**	2.6	4.2	7.6
3	**7**	**8**	1.0	1.3	2.0
4	**9**	**3**	0.7	0.3	0.2
5	**10**	**3**	1.0	0.8	0.71
6	**13**	**3**	0.3	0.1	0.1

The values given in the table are averages of three measurements reproducible within ±10%.

(entry 3). Similar experiments carried out for diazacoronands **9**, **10**, and **13** possessing additional benzene ring revealed surprisingly weaker affinity to alkali metal cations than compound **3** (entries 4–6).

(2) *Effect of the rigidity of the macroring*: In order to thoroughly explore the effect of rigidity of the macroring, four further experiments were carried out. Each diazacoronand with aliphatic macroring was subjected to ESI-MS investigation with an appropriate compound possessing additional benzene ring (Table 3).

In all of the examined pairs, the aliphatic diazacoronands are better receptors for cations than their aromatic analogs. This is probably caused by the higher rigidity of the macroring structure in compounds **3**, **9**, **10**, and **13**, which prevents their geometry from adapting to the guest molecule. In the case of compound **13**, the highest ratio of signal intensities was observed and amounted to 34.2 (entry 10).

(3) *Comparison of the type of intraannular groups*: To determine which pendant arm modifies the binding properties best, direct comparison of two pendant diazacoronands was carried out (Table 4). The best receptors are compounds **4** and **5** with *N*-substituted side arm and only slightly weaker ligand is the derivative **6** possessing the *O*-benzyl function (entries 11 and 12). On the contrary, the weakest receptors are compounds **7** and **12** with *O*-benzoyl side arm (entries 13–15).

As expected, derivative **5** with a pyridine moiety is a slightly more efficient host than its benzene analog **4**. An apparent experiment showing another advantage of diazacoronad **5** over **4** consists in inducing color changes of Cu^{2+} solutions (Fig. 9). Several typical copper salts were used to exclude

Table 3. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
7	**8**	**3**	7.0	6.6	4.7
8	**4**	**9**	15.9	15.2	24.8
9	**6**	**10**	10.1	7.6	8.6
10	**7**	**13**	23.1	31.1	34.2

The values given in the table are averages of three measurements reproducible within ±10%.

Table 4. The ratio of signal intensities (ESI-MS spectra) for two ligands and one alkali metal cation

Entry	Ligands		Signal intensities ratio in ESI-MS spectra $[L1+M^+]/[L2+M^+]$		
	L1	L2	Na^+	K^+	Rb^+
11	**5**	**4**	2.7	3.5	4.3
12	**4**	**6**	2.7	3.0	2.3
13	**4**	**7**	9.1	7.1	6.4
14	**9**	**13**	4.8	4.5	3.9
15	**10**	**13**	8.8	12.5	19.4

The values given in the table are averages of three measurements reproducible within ±10%.

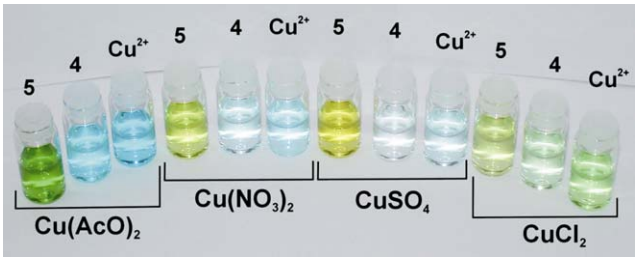


Figure 9. Color changes of Cu^{2+} solution induced by the addition of compounds **4** or **5**. Cu^{2+}=free salt; **4**=**4**+Cu^{2+}; **5**=**5**+Cu^{2+}.

the influence of counterions on color changes. Typically, an appropriate diazacoronand (2 mg in 1 ml of MeOH) was added to an appropriate copper salt solution (ca. 3 mg in 1 ml of MeOH).

Color changes were observed only in the case of compound **5**, although its mixture with $CuCl_2$ gave a slight difference. The derivative **4**, although structurally very similar to **5**, did not give any visible results. This simple experiment demonstrated that a minor change in the structure of diazacoronands can result in different and interesting binding properties.

3. Conclusions

In this paper, we presented the structural studies and initial binding properties of pendant diazacoronands. Here, the intraannular group plays a double role: (1) it ensures a sufficient conformational stability, indispensable in the case of further synthesis of stable atropoisomers and (2) it is an extra binding side, slightly modifying the complexation properties of the macrocyclic receptors. The structural studies performed by means of the X-ray analysis and the variable temperature ^1H NMR experiments show that the *O*-substituted compounds exhibit higher conformational stability than the *N*-substituted analogs. On the contrary, initial binding experiments (ESI-MS) show that the *N*-substituted diazacoronands are slightly better receptors than the *O*-substituted diazacoronands. The main advantage of the presented system is a diversity of intraannular groups, which can be introduced into the diazacoronand framework, and the possibility of almost unlimited modifications. Application of the above-presented synthetic approach to preparation of macrocycles with planar chirality as well as their use in asymmetric synthesis is in progress.

4. Experimental

4.1. General methods

Melting points were determined using a Boëtius M HMK hot-stage apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker AM 500 or Varian BB 200 spectrometer. Chemical shifts are reported as δ values relative to TMS peak defined at δ=0.00. The mass spectral analysis was performed by the ESI-TOF technique on a Mariner mass spectrometer from PerSeptive Biosystem. Column chromatography was performed on silica gel (Kieselgel-60, 200–400 mesh).

4.1.1. 2,8,15,21-Tetraoxa-5,18-diazatricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (3). *Procedure A*: An appropriate diester (39 mmol) was dissolved in dry MeOH (300 ml) and added to diamino-ether **2** or **19** (39 mmol) in dry MeOH (100 ml). Then, a solution of MeONa (5.4 g, 100 mmol) in dry MeOH (100 ml) was added to the mixture. The mixture was left at ambient temperature for a period of 2–7 days (TLC monitored). Subsequently, the solvent was evaporated and the residue was purified by column chromatography (silica gel; AcOEt/MeOH, 9:1 or $CHCl_3$/MeOH, 95:5 in the case of **20** and **21**, respectively) to give the desired product. Yield (15%), crystallization in a vapor diffusive system (MeOH/$CHCl_3$, 2:3/Et_2O) gives white crystals, mp 224.3–225.4 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.93 (br t, 2H, CONH); 7.19 (t, 1H, J=8.2, ArH); 7.02–6.98 (m, 2H, ArH); 6.93–6.88 (m, 2H, ArH); 6.58 (dd, 2H, J^1=8.2, J^2=2.3, ArH); 6.47 (t, 1H, J=2.3, ArH); 4.51 (s, 4H, OCH_2CO); 4.07 (br t, 4H, CH_2O); 3.52 (br q, 4H, CH_2N), ^{13}C NMR 125 MHz (DMSO): δ=167.8 (CONH), 158.7, 148.1, 130.1, 121.3, 114.3, 107.8, 101.1, 67.1, 66.8, 38.2, ESI HRMS (MeOH) m/z calcd for $C_{20}H_{22}N_2O_6Na$ [M+Na]$^+$: 409.1370; found: 409.1394. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.34; H, 5.45; N, 7.27. Found: C, 62.32; H, 5.63; N, 7.22%.

4.1.2. 26-Hydroxy-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (11). A mixture of compound **10** (3 g, 6.1 mmol) and Pd/C (0.5 g, 10%) in MeOH (200 ml) was stirred overnight under an atmosphere of hydrogen (balloon pressure) at rt. The reaction mixture was filtered through Celite and the resulting solution was evaporated. Crystallization from MeOH (120 ml) gave light purple crystals (2.2 g, 90%), mp 168.9–171.4 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.74 (br s, 1H, OH); 8.30 (br t, 2H, CONH); 6.95–6.91 (m, 2H, ArH); 6.88–6.84 (m, 2H, ArH); 6.81–6.78 (m, 2H, ArH); 6.75–6.71 (m, 1H, ArH); 4.58 (s, 4H, OCH_2CO); 4.01 (t, 4H, J=4.9); 3.55 (q, 4H, J=4.9, CH_2N); ^{13}C NMR 125 MHz (DMSO): δ=168.6 (CONH), 148.0, 147.6, 137.8, 121.0, 119.3, 113.5, 111.3, 70.5, 67.1, 38.3, ESI HRMS (MeOH) m/z calcd for $C_{20}H_{22}N_2O_7Na$ [M+Na]$^+$: 425.1319; found: 425.1304. Anal. Calcd for $C_{20}H_{22}N_2O_7$: C, 59.70; H, 5.51; N, 6.96. Found: C, 59.57; H, 5.77; N, 6.91%.

4.1.3. 26-Methoxy-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaene-4,19-dione (12). *Procedure B*: To phenol **11** (1 g, 2.5 mmol) dissolved in MeCN (150 ml), 5 equiv of MeI (0.5 ml, 12.5 mmol) and 3 equiv of anhydrous K_2CO_3 (1 g, 7.5 mmol) were added. The reaction mixture was stirred at rt for 12 h. Next, a second portion of MeI (0.5 ml, 12.5 mmol) was added and the reaction was carried out for the subsequent 12 h. After filtration, the solvent was evaporated and the residue was crystallized in a vapor diffusive system (MeOH/$CHCl_3$, 1:1/n-pentane), to give white crystals (0.56 g, 54%), mp 239.8–241.0 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.94 (br t, 2H, CONH); 7.07–6.99 (m, 3H, ArH); 6.91–6.87 (m, 4H, ArH); 4.63 (s, 4H, OCH_2CO); 4.07 (br t, 4H, CH_2O); 3.72 (s, 3H, OMe); 3.60 (br q, 4H, CH_2N). ^{13}C NMR 125 MHz (DMSO): δ=167.9 (CONH), 152.4, 147.8, 140.2, 124.9, 121.0, 112.9, 112.1, 70.8, 67.4, 61.5, 38.2, ESI HRMS (MeOH) m/z calcd for $C_{21}H_{24}N_2O_7Na$ [M+Na]$^+$: 439.1476; found: 439.1480. Anal. Calcd for $C_{21}H_{24}N_2O_7$: C, 60.57; H, 5.76; N, 6.73. Found: C, 60.60; H, 5.93; N, 6.74%.

4.1.4. Benzoic acid 4,19-dioxo-2,8,15,21-tetraoxa-5,18-diaza-tricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaen-26-yl ester (13). To phenol **11** (1g, 2.5 mmol) dissolved in pyridine (10 ml) and cooled (0 °C), benzoyl chloride (0.34 ml, 3.0 mmol) was added dropwise. The reaction mixture was stirred overnight at rt and subsequently acidified with 1 M aq HCl. After extraction with AcOEt (3×100 ml), the organic layers were combined, dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel; AcOEt) to give the desired product (42%, 0.53 g). Crystallization in a vapor diffusive system (MeOH/Et_2O) gave white needles, mp 203.4–204.6 °C. ^{1}H NMR 500 MHz ($CDCl_3$): δ=8.22 (br d, 2H, CONH); 7.66 (t, 1H, J=7.5, ArH); 7.48 (t, 2H, J=7.5, ArH); 7.10 (br s, 2H, ArH); 6.91–6.78 (m, 5H, ArH); 6.53 (d, 2H, J=7.5, ArH); 4.69 (d_{AB}, 2H, J=16.5, OCH_2CO); 4.64 (d_{AB}, 2H, J=16.5, OCH_2CO); 4.20–4.14 (m, 2H, CH_2O); 3.90–3.83 (m, 4H, CH_2O+CH_2N); 3.46–3.40 (m, 2H, CH_2N); ^{13}C NMR 125 MHz ($CDCl_3$): δ= 168.2 (CONH), 150.1, 148.0, 134.3, 130.6, 128.8, 128.2, 127.1, 120.8, 111.8, 66.8, 65.8, 39.1, ESI HRMS (MeOH) m/z calcd for $C_{27}H_{26}N_2O_8Na$ [M+Na]$^+$: 529.1581; found: 529.1552. Anal. Calcd for $C_{27}H_{26}N_2O_8$: C, 64.03; H, 5.17; N, 5.53. Found: C, 63.81; H, 5.34; N, 5.42%.

4.1.5. 22-Methoxy-2,8,11,17-tetraoxa-5,14-diaza-bicyclo-[16.3.1]docosa-1(21),18(22),19-triene-4,15-dione (15). *Procedure B*: (93%), mp 108.2–109.9 °C, lit.[14] mp 109–111 °C. ^{1}H NMR 500 MHz (DMSO): δ=7.59 (br t, 2H, CONH); 7.03 (t, 1H, J=8.4, ArH); 6.79 (d, 2H, J=8.4, ArH); 4.58 (s, 4H, OCH_2CO); 3.85 (s, 3H, OMe); 3.47–3.42 (m, 8H, CH_2O); 3.33–3.28 (m, 4H, CH_2N), ^{13}C NMR 125 MHz (DMSO): δ=167.8 (CONH), 151.9, 139.5, 124.3, 110.3, 70.1, 69.6, 68.9, 61.2, 38.7, ESI HRMS (MeOH) m/z calcd for $C_{17}H_{24}N_2O_7Na$ [M+Na]$^+$: 391.1476; found: 391.1471.

4.1.6. *N*-(2,6-Dihydroxyphenyl)acetamide (17). A mixture of compound **16** (10 g, 64 mmol) and Pd/C (1 g, 10%) in MeOH (200 ml) was stirred at rt under an atmosphere of hydrogen (balloon pressure) for 2 days. The catalyst was filtered off on Celite. Then, the solution was cooled to −20 °C and acetyl chloride was added dropwise. The reaction mixture was stirred at −20 °C→rt overnight. After evaporation of the solvent, the residue was crystallized from EtOH to give gray crystals (5.9 g, 55% overall yield), mp 95.5–97.1 °C.

^{1}H NMR 200 MHz ($CDCl_3$): δ=7.53 (br s, 1H, NHCOMe); 6.94 (t, 1H, J=8.3, ArH); 6.49 (d, 2H, J=8.3, ArH); 2.30 (s, 3H, Me), ^{13}C NMR 50 MHz ($CDCl_3$): δ=168.1 (NHCO), 147.8, 129.8, 124.8, 120.9, 25.6, ESI HRMS (MeOH) m/z calcd for $C_8H_9NO_3Na$ $[M+Na]^+$: 190.1556; found: 190.1563. Anal. Calcd for $C_8H_9NO_3$: C, 57.48; H, 5.43; N, 8.38. Found: C, 57.68; H, 5.54; N, 8.26%.

4.1.7. Methyl [2-(acetylamino)-3-(2-methoxy-2-oxoethoxy)phenoxy]acetate (18). To a mixture of **17** (10 g, 149 mmol), and anhydrous K_2CO_3 (40 g, 290 mmol) in anhydrous 2-butanone (300 ml), methyl bromoacetate (26 ml, 290 mmol) was added. The reaction mixture was stirred at 80 °C for 2 days under an argon atmosphere. After cooling the suspension to room temperature, the insoluble inorganic salts were removed by filtration. Then, the solvent was evaporated and the residue was purified by column chromatography (silica gel; AcOEt) to give the desired product (14.9 g, 80%), mp 92.6–93.4 °C. ^{1}H NMR 500 MHz ($CDCl_3$): δ=7.33 (br s, 1H, NHCO); 7.12 (t, 1H, J=8.3, ArH); 6.55 (d, 2H, J=8.3, ArH); 4.67 (s, 4H, OCH_2CO); 3.77 (s, 6H, OMe); 2.18 (br s, 3H, COMe), ^{13}C NMR 125 MHz ($CDCl_3$): δ=169.5 (CO); 168.8 (NHCO); 154.2, 127.5, 117.6, 108.3, 66.9, 52.2, 23.3, ESI HRMS (MeOH) m/z calcd for $C_{14}H_{17}NO_7Na$ $[M+Na]^+$: 334.2839; found: 334.2845. Anal. Calcd for $C_{14}H_{17}NO_7$: C, 54.02; H, 5.50; N, 4.50. Found: C, 54.15; H, 5.44; N, 4.55%.

4.1.8. *N*-(4,19-Dioxo-2,8,15,21-tetraoxa-5,18-diazatricyclo[20.3.1.0^{9,14}]hexacosa-1(25),9(14),10,12,22(26),23-hexaen-26-yl)-acetamide (20). *Procedure A*: (19%) Crystallization in a vapor diffusive system (MeOH/*n*-pentane) gives white needles, mp 221.3–221.9 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.44 (s, 1H, NHCO); 7.54 (br t, 2H, CONH); 6.95 (t, 1H, J=8.5, ArH); 6.82 (s, 4H, ArH); 6.57 (d, 2H, J=8.5, ArH); 4.74 (d_{AB}, 2H, J=16.3, OCH_2CO); 4.66 (d_{AB}, 2H, J=16.3, OCH_2CO); 3.87–3.80 (m, 2H, CH_2O); 3.75–3.63 (m, 4H, CH_2O+CH_2N); 3.13–3.05 (m, 2H, CH_2N); 2.09 (s, 3H, COMe), ^{13}C NMR 125 MHz (DMSO): δ=169.9 (NHCO), 168.1 (CONH), 153.2, 148.3, 127.7, 121.0, 114.9, 113.9, 105.0, 67.0, 66.4, 38.5, 22.6, ESI HRMS (MeOH) m/z calcd for $C_{22}H_{25}N_3O_7Na$ $[M+Na]^+$: 466.1585; found: 466.1562. Anal. Calcd for $C_{22}H_{25}N_3O_7$: C, 59.59; H, 5.64; N, 9.48. Found: C, 59.68; H, 5.73; N, 9.43%.

4.1.9. *N*-(4,15-Dioxo-2,8,11,17-tetraoxa-5,14-diaza-bicyclo[16.3.1]docosa-1(21),18(22),19-trien-22-yl)-acetamide (21). *Procedure A*: (30%) Crystallization in a vapor diffusive system (MeOH/*n*-pentane), gives white needles, mp 174.3–174.6 °C. ^{1}H NMR 500 MHz (DMSO): δ=9.39 (s, 1H, NHCO); 7.72 (br q, 2H, CONH); 7.15 (t, 1H, J=8.5, ArH); 6.58 (d, 2H, J=8.5, ArH); 4.67 (d_{AB}, 2H, J=16.1, OCH_2CO); 4.58 (d_{AB}, 2H, J=16.1, OCH_2CO); 3.56–3.48 (m, 2H, CH_2O); 3.41–3.35 (m, 2H, CH_2O); 3.25–3.19 (m, 2H, CH_2O); 3.11–3.04 (m, 2H, CH_2O); 2.96–2.81 (m, 4H, CH_2N); 2.10 (s, 3H, COMe), ^{13}C NMR 125 MHz (DMSO): δ=169.0 (NHCO), 167.8 (CONH), 153.1, 127.3, 114.7, 104.9, 69.8, 68.6, 66.7, 39.3, 22.8, ESI HRMS (MeOH) m/z calcd for $C_{18}H_{25}N_3O_7Na$ $[M+Na]^+$: 418.1585; found: 418.1605. Anal. Calcd for $C_{18}H_{25}N_3O_7$: C, 54.68; H, 6.33; N, 10.63. Found: C, 54.69; H, 6.40; N, 10.74%.

4.2. ESI-MS comparison measurements

All electrospray ionization mass spectra were recorded on a Micromass instrument equipped with an ESI source. The needle potential for the methanol solution was set to 4.0 kV for all experiments. Each spectrum taken was an average of 25–30 scans.

All solutions were prepared in methanol. The solutions containing chloride salt and two hosts had the concentration ratios of 1:1:1, and the host concentrations were 1×10^{-4} M for each host.

4.3. The X-ray structure investigations

The intensity data were collected on a Kuma KM4CCD diffractometer with a graphite-monochromated Mo Kα radiation (λ=0.71073 Å). The crystal was positioned at 65 mm from the KM4CCD camera, 600 frames were measured at 1° intervals with a counting time of 15 s. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. The structure was solved by the direct method and refined by full-matrix least squares on F^2 using SHELXL 97. The H atoms were located in geometrically calculated positions and were allowed to ride on their parent atom. CCDC data sets No. 264711, 264712, and 264713 for **4**, **9**, and **5**, respectively, contain 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 Center, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

*Crystal data for **4***: Crystals obtained in a vapor diffusive system MeOH/$CHCl_3$, 1:1/*n*-pentane; $C_{23}H_{29}N_3O_8$, M_r=475.5, monoclinic, $P2(1)/n$, a=8.4650(17), b=20.425(4), c=13.845(3) Å, α=90°, β=96.36(3)°, γ=90°, V=2379.1(8) Å^3, Z=4, D_c=1.338 g/cm^3, F_{000}=1008, T=293(2) K, μ=0.101 mm^{-1}, 4176 reflections collected, 2921 unique. Final GOF=1.129, $R1$=0.0577, $wR2$=0.1892 (all data).

*Crystal data for **5***: Crystals obtained in a vapor diffusive system MeOH/Et_2O; $C_{22}H_{28}N_4O_8$, M_r=476.5, monoclinic, $P2(1)/n$, a=8.3978(17), b=20.422(4), c=13.885(3) Å, α=90°, β=96.41(3)°, γ=90°, V=2366.1(8) Å^3, Z=4, D_c=1.337 g/cm^3, F_{000}=1008, T=150(2) K, μ=0.103 mm^{-1}, 17,400 reflections collected, 4157 unique. Final GOF=0.890, $R1$=0.0424, $wR2$=0.0832 (all data).

*Crystal data for **9***: Crystals obtained in a vapor diffusive system MeOH/$CHCl_3$, 1:1/*n*-pentane; $C_{28}H_{31}N_3O_8$, M_r=537.5, monoclinic, $P2(1)/c$, a=11.4801(7), b=14.5891(8), c=16.5399(3) Å, α=90°, β=95.23(4)°, γ=90°, V=2758.6(3) Å^3, Z=4, D_c=1.294 g/cm^3, F_{000}=1136, T=293(2) K, μ=0.096 mm^{-1}, 38,138 reflections collected, 4318 unique. Final GOF=1.138, $R1$=0.0530, $wR2$=0.1675 (all data).

Acknowledgements

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Superacid-catalyzed reactions of pyridinecarboxaldehydes

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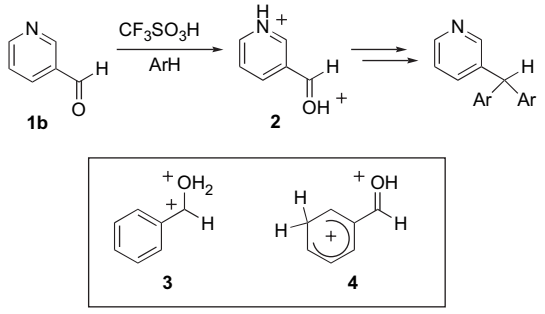
Abstract—A variety of pyridinecarboxaldehydes are shown to give condensation products in high yields (80–99%, 10 examples) by reacting with benzene and CF_3SO_3H (triflic acid). In the superacidic solution, pyridinecarboxaldehydes can react with deactivated arenes (*o*-dichlorobenzene and nitrobenzene) and with saturated hydrocarbons (methylcyclohexane and adamantane). Dicationic intermediates from pyridinecarboxaldehydes in superacid (FSO_3H–SbF_5) have been directly observed using low temperature ^{13}C NMR spectroscopy. Diprotonated pyridinecarboxaldehydes have also been studies using ab initio computational methods.

1. Introduction

We recently described the superacid-catalyzed chemistry of 3-pyridinecarboxaldehyde (**1b**), its reactions with deactivated arenes, and the involvement of dicationic electrophilic intermediates (Scheme 1).[1] Because of the similarities to the superelectrophilic systems like diprotonated benzaldehyde (**3**–**4**),[2] we proposed that dication **2** is a good model system for the superelectrophilic intermediates.[3] Since our report, many similar dicationic electrophilic systems have been described.[4] These reactive, dicationic electrophiles typically have a relatively stable cationic center (such as a pyridinium, ammonium, or phosphonium cation) adjacent to a cationic electrophilic site. We and others have shown that these dicationic electrophiles can exhibit dramatically increased electrophilic reactivities compared to analogous monocationic electrophiles.



Scheme 1.

In this paper, we provide a full report of our studies involving the superacid-catalyzed reactions of pyridinecarboxaldehydes (**1a**–**c**). The superacid-catalyzed condensation reactions of pyridinecarboxaldehydes with arenes are described and a general mechanism involving dicationic intermediates is proposed. These dicationic intermediates are also shown to be capable of reacting with saturated hydrocarbons. Direct observation of the dicationic species using low temperature NMR is also reported. The diprotonated species from 2-, 3-, and 4-pyridinecarboxaldehyde have also been studied using ab initio computational methods and these results are described. The results from these studies demonstrate that reactive dications can be formed in high concentrations and they exhibit electrophilic reactivities comparable to superelectrophiles.

2. Results and discussion

Some time ago, the condensations of pyridinecarboxaldehydes (**1a**–**c**) with benzene in H_2SO_4 were described in the patent literature.[5] Our previous report described the condensation of 3-pyridinecarboxaldehyde (**1b**) with benzene and CF_3SO_3H, and this Brønsted superacid was found to be an outstanding catalyst for the condensation.[1] In order to further demonstrate the utility of CF_3SO_3H in these types of condensation reactions, a series of pyridinecarboxaldehydes have been reacted with benzene in CF_3SO_3H (Table 1). The isomeric pyridinecarboxaldehydes (**1a**–**c**), and a number of substituted derivatives (**6**–**12**), give the condensation products in excellent yields. An *N*-methylated pyridiniumcarboxaldehyde also gives the condensation product (**21**) in high yield (Scheme 2). Although the yields have not been optimized, it has been determined that as little as 2.7 equiv of CF_3SO_3H can be used to convert **1a** to product **13a**

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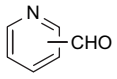
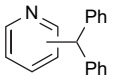
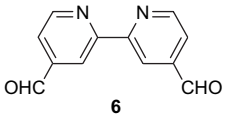
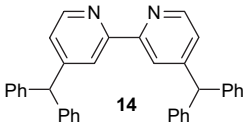
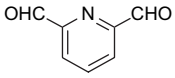
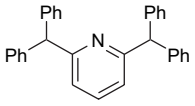
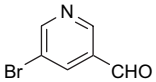
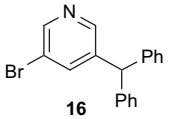
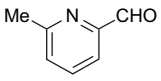
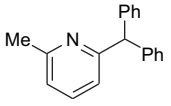
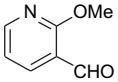
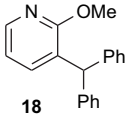
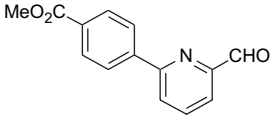
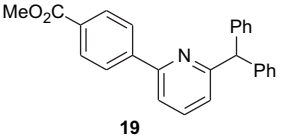
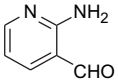
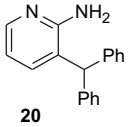
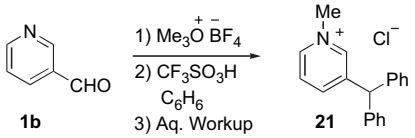
Table 1. Products and yields for the reactions of pyridinecarboxaldehydes (**1a–c**, **6–12**) with C_6H_6 and CF_3SO_3H

Starting material	Product	Yield (%)
		
1a, 2-isomer **1b**, 3-isomer **1c**, 4-isomer	**13a**, 2-isomer **13b**, 3-isomer **13c**, 4-isomer	88 99 93
 **6**	 **14**	80
 **7**	 **15**	82
 **8**	 **16**	92
 **9**	 **17**	90
 **10**	 **18**	99
 **11**	 **19**	89
 **12**	 **20**	91

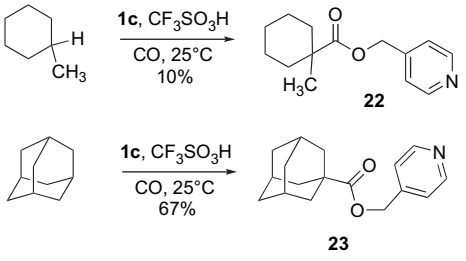
(>80% yield), and with larger quantities of CF_3SO_3H (15 equiv), the condensation reaction is complete within 5 min.[6] The condensation of **1a–13a** can be accomplished with H_2SO_4,[5] H_3PO_4,[5] and also $AlCl_3$,[7] but these acids give the hydroxy alkylation products (**13a–c**) in somewhat low yields (accompanied by unreacted **1a**). Recently, it was discovered that products **13a–c** are highly potent dopamine transporter inhibitors and it was proposed that these types of compounds may have therapeutic value in the treatment of cocaine abuse.[8] The triflic acid catalyzed reactions of pyridinecarboxaldehydes with benzene are effective, general route to these products.



Scheme 2.

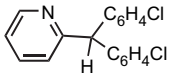
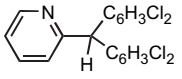
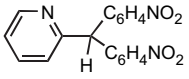
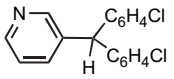
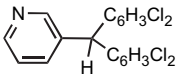
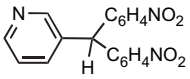
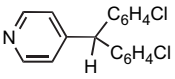
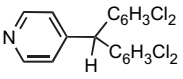
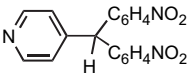
With less nucleophilic arenes, the pyridinecarboxaldehydes (**1a–c**) give hydroxy alkylation products from superacid (Table 2). The isomeric pyridinecarboxaldehydes were reacted with the deactivated arenes, chlorobenzene, *o*-dichlorobenzene, and nitrobenzene, in excess of CF_3SO_3H (100 equiv), and in all cases the condensation products were obtained. Remarkably, the pyridinecarboxaldehydes even react with nitrobenzene in a solution wherein the nitro group is largely protonated (protonated nitrobenzene, $pK_a=-11$).[9] Under similar conditions, benzaldehyde reacts with chlorobenzene in superacid to give some condensation product, but it does not react with either *o*-dichlorobenzene or nitrobenzene. Besides weak nucleophilic arenes, 4-pyridinecarboxaldehyde (**1c**) is also found to react with saturated hydrocarbons in superacid. When 4-pyridinecarboxaldehyde is dissolved in 6 equiv of CF_3SO_3H with 1.0 equiv of methylcyclohexane under CO pressure (750 psi; 25 °C), the functionalized product (**22**) is formed, al beit in low isolated yield (Scheme 3). Similarly, adamantane gives the ester product (**23**) in reasonable yield, along with a smaller amount of 1-adamantanecarboxylic acid. To verify that functionalization of the hydrocarbon is due to the reactivity of the carboxonium ion, methylcyclohexane was reacted with 6 equiv of CF_3SO_3H, CO (5 atm), and 4-pyridinemethanol. Under these conditions, there is no product (**22**) formed.

In order to characterize the electrophilic species arising from the pyridinecarboxaldehydes (**1a–c**), ab initio theoretical calculations were done along with spectroscopic studies. For the isomeric pyridinecarboxaldehydes (**1a–c**), 10 structures were located at potential energy minima on the energy surfaces for the *N*,*O*-diprotonated species (Fig. 1; all minimized structures possess C_1 symmetry). Geometry optimizations were done using density function theory and the hybrid functional B3LYP at the 6-311G** level.[10,11,12] Vibrational analyses were performed at the B3LYP/6-311G** level of theory and all optimized structures (**24–26**) were found to have zero imaginary frequencies. Zero-point-energy corrections were made to the single point energies for structures **24–26**. From 2-pyridinecarboxaldehyde (**1a**), four structures are found at energy minima: the conformational isomers of the *syn* stereoisomer (*syn*-**24a** and *syn*-**24b**) and *anti* stereoisomer (*anti*-**24a** and *anti*-**24b**) of the diprotonated



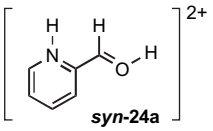
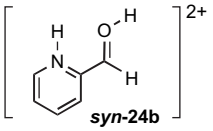
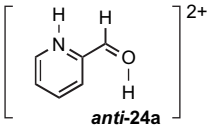
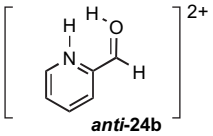
Scheme 3. Superacidic-functionalization of hydrocarbons with 4-pyridinecarboxaldehyde (**1c**).

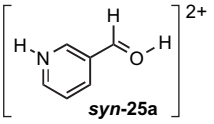
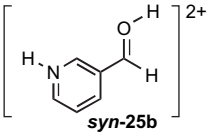
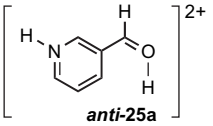
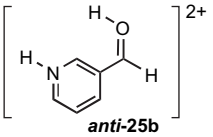
Table 2. Products and yields[a] from the reactions of pyridinecarboxaldehydes (**1a–c**) with deactivated arenes and CF_3SO_3H

Aldehyde	Chlorobenzene products[b]	Yield (%)	*o*-Dichlorobenzene products[c]	Yield (%)	Nitrobenzene products[d]	Yield (%)
1a		88		72		12
1b		85		87		10
1c		94		83		53

[a] Yields are reported as the mixture of isomers; result for **1b** is taken from Ref. 1.
[b] Reaction done at 25 °C.
[c] Reaction done at 80 °C.
[d] Reaction done at 140 °C.

aldehyde. The global energy minimum is found at the *syn*-**24b** structure, while the *syn*-**24a** structure is the next most stable structure, estimated to be 2.5 kcal/mol less stable than *syn*-**24b**. Diprotonation of 3-pyridinecarboxaldehyde (**1b**) also gives four structures at energy minima. The calculations find the global energy minimum at the *syn*-**25a**

structure	E + ZPE (Hartrees)	relative energy (kcal•mol^{-1})
 ***syn*-24a**	-362.095123	2.5
 ***syn*-24b**	-362.099126	0.0
 ***anti*-24a**	-362.083881	9.6
 ***anti*-24b**	-362.080414	11.7

structure	E + ZPE (Hartrees)	relative energy (kcal•mol^{-1})
 ***syn*-25a**	-362.109605	0.0
 ***syn*-25b**	-362.109488	0.1
 ***anti*-25a**	-362.098031	7.3
 ***anti*-25b**	-362.095243	9.0

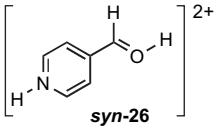
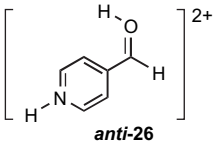
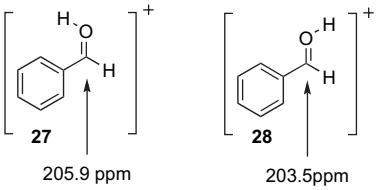
structure	E + ZPE (Hartrees)	relative energy (kcal•mol^{-1})
 ***syn*-26**	-362.105289	0.0
 ***anti*-26**	-362.093665	7.3

Figure 1. Calculated structures and energies for the diprotonated pyridinecarboxaldehydes (**24–26**) at the B3LYP/6-311G**//B3LYP/6-311G** level of theory.

structure, but the *syn*-**25b** structure is just 0.1 kcal/mol less stable. In the case of 4-pyridinecarboxaldehyde, the *syn*-**26** and *anti*-**26** structures (both C_1 point group) are found at energy minima, and the *syn*-**26** is more stable by 7.3 kcal/mol. These computational results are in accord with earlier studies related to protonated aldehydes. Experimental and theoretical results have previously shown that the *anti* stereoisomers of protonated aldehydes are less stable than the *syn* stereoisomers.[13] Interestingly, the monocationic carboxonium ions from benzaldehyde (**27**–**28**) are estimated to be 2.2 kcal/mol apart in relative energies for the *syn* and *anti* stereoisomers (Scheme 4).[2a] The dicationic carboxonium ions **24**–**26** show increasing relative energy differences for the *syn* and *anti* stereoisomers (7.3–11.7 kcal/mol).



Scheme 4.

The isomeric pyridinecarboxaldehydes were also studied by ^{13}C NMR in acidic solvents and the results are consistent with the formation of *N*,*O*-diprotonated structures in superacid (Table 3). When 2-pyridinecarboxaldehyde (**1a**) is dissolved in solutions of increasing acidity, the carbonyl (or carboxonium) carbon is progressively shifted down field from 181.9 ppm in CF_3CO_2H (H_o −2.7) to 203.6 ppm in SbF_5–FSO_3H (H_o<−18). The down field shifts indicate an increasing degree of protonation of the carbonyl group, and in SbF_5–FSO_3H, the chemical shift (203.6 ppm) is similar to other observed protonated aldehydes. For example, protonated benzaldehyde (**27** and **28**) gives carboxonium resonances at 203.5 and 205.9 ppm (Scheme 4).[2a] In our earlier communication, we described similar NMR experiments with 3-pyridinecarboxaldehyde (**1b**).[1] With increasing acidity, this compound also shows a dramatic down field shift of the carbonyl carbon. In the SbF_5–FSO_3H solution, however, two peaks are observed for the carbonyl carbon and several of the ring carbons. These doubled signals were initially thought to be from the *syn* and *anti* stereoisomers of the protonated aldehyde, because previous NMR studies of protonated aliphatic and aromatic aldehydes have observed both stereoisomers.[13] We now propose that the two observed ions are *not* the *syn* and *anti* stereoisomers, but rather the rotational isomers *syn*-**25a** and *syn*-**25b**. The computational studies indicated that these two rotational isomers are very close in energy, while the *syn* and *anti* isomers are energetically far apart. Evidently, a sizable energy barrier separates the conformational isomers *syn*-**25a** and *anti*-**25b**, because their inter-conversion is slow on the NMR time-scale at −80 °C.[13d] The NMR studies of 4-pyridinecarboxaldehyde (**1c**) also suggest the formation of the *N*,*O*-diprotonated species in superacid. The carbonyl ^{13}C resonance moves down field from 184.5 ppm in CF_3CO_2H to 211.2 ppm in SbF_5–FSO_3H solution. The ^{13}C NMR spectrum from SbF_5–FSO_3H solution clearly shows that a single species is generated from **1c** (Fig. 2). Computational results indicate that the *syn*-**26** structure would be heavily favored in an equilibration of diprotonated structures. Upon solvation in superacid, aldehyde **1c** is converted to the *syn*-**26** species, and at the highest levels of acidity (SbF_5–FSO_3H, H_o<−18) the conversion appears to be complete. The series of pyridinecarboxaldehydes (**1a**–**c**) give NMR spectra from superacid that are in accord with the results from the ab initio studies. For both **1a** and **1c**, calculations show that only one *N*,*O*-diprotonated species is located at or near the global minima, and the ^{13}C NMR spectra show only one species in each of the SbF_5–FSO_3H solutions. But calculations on the **1b** system show two species at or near the global minimum, and both ions are observed in the ^{13}C NMR.

Table 3. ^{13}C NMR data from pyridinecarboxaldehydes **1a**–**c** in acidic solution

Aldehyde	Acid system (H_o)	^{13}C NMR data, δ, ppm[a]
1a	CF_3CO_2H (−2.7)	181.9 (c), 148.4, 142.1, 140.0, 130.3, 128.4
	CF_3SO_3H (−14.1)	184.6 (c), 148.9, 142.1, 138.8, 131.1, 129.6
	FSO_3H (−15.1)	191.8 (c), 150.3, 144.4, 138.5, 133.7, 133.2
	SbF_5–FSO_3H (<−18)	203.6 (c), 150.6, 150.0, 145.3, 140.9, 133.0
1b	CF_3CO_2H	184.0 (c), 142.9, 140.2, 138.1, 129.2, 123.4
	CF_3SO_3H	193.3 (c), 147.1, 144.9, 142.3, 131.3, 127.5
	FSO_3H	201.0 (c), 149.7, 148.5, 146.1, 130.5, 129.5
	SbF_5–FSO_3H	208.6 (c), 155.8, 149.8, 144.6, 129.0, 125.2 207.1 (c), 151.4, 150.5, 148.6, 129.0, 125.2
1c	CF_3CO_2H	184.5 (c), 143.2, 138.3, 121.3
	CF_3SO_3H	194.6 (c), 142.1, 126.1, 122.8
	FSO_3H	199.6 (c), 143.9, 142.6, 127.0
	SbF_5–FSO_3H	211.2 (c), 143.3, 138.8, 130.4

(c) Indicates carbonyl (or carboxonium carbon) signal. Data for **1b** are taken from Ref. 1.

[a] Experiments with CF_3CO_2H or CF_3SO_3H were done at 25 °C; experiments with FSO_3H or SbF_5–FSO_3H were done at −70 °C with SO_2ClF diluent.

Based on the results of the NMR studies and the superacid-promoted reactions, a general mechanism is proposed that invokes these dicationic intermediates (Scheme 5). For example in the case of **1c**, the pyridine nitrogen is initially protonated to give the pyridinium cation (**29**) and subsequent protonation at the carbonyl oxygen yields the dicationic intermediate *syn*-**26**. Electrophilic attack of benzene then leads to the condensation products via dicationic intermediates **30** and **31**. In the case of 2-amino-3-pyridinecarboxaldehyde (**12**), the analogous tricationic electrophile (**33**) is likely generated from the dication **32**.[14] Given the low nucleophilicity of C_6H_6, it is highly unlikely that the condensation reaction occurs via the dication **32**, but must involve further protolytic activation of the carbonyl group. When 4-pyridinecarboxaldehyde (**1c**) is reacted with carbon monoxide and methylcyclohexane in CF_3SO_3H, the product is formed by hydride transfer from the cycloalkane to the dicationic carboxonium ion (Scheme 6). This proposed mechanism is in accord with another recent study showing the reduction of 3-pyridinecarboxaldehyde to 3-pyridilcarbinol and 3-methylpyridine from the reactions with

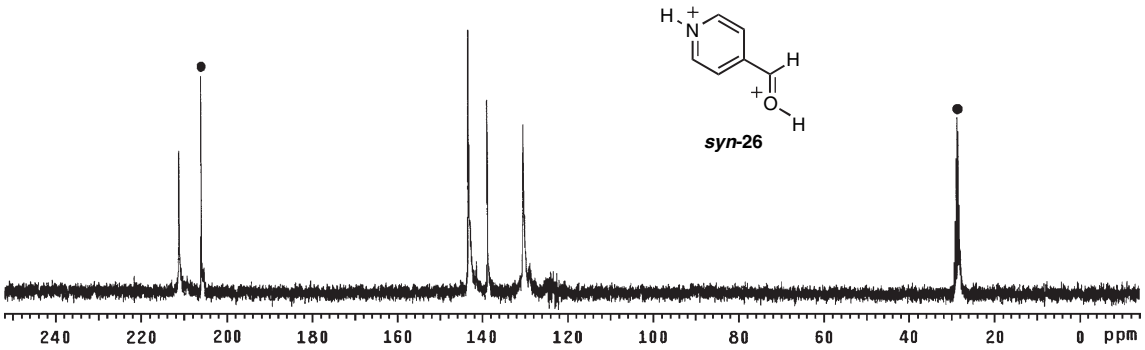
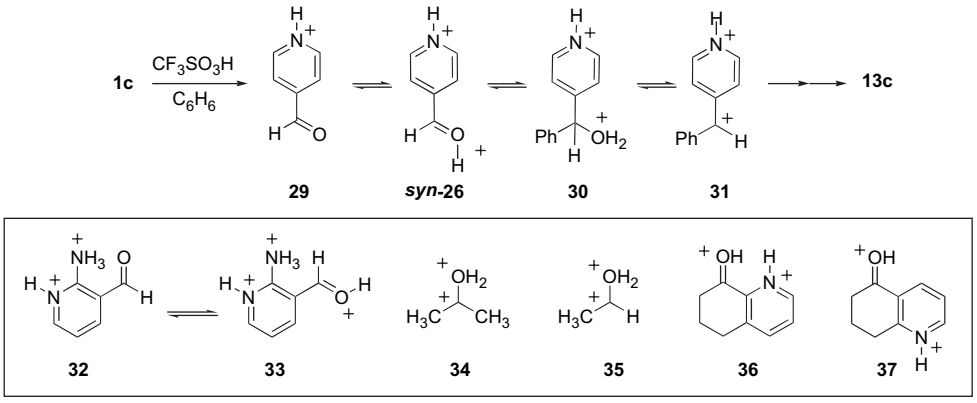
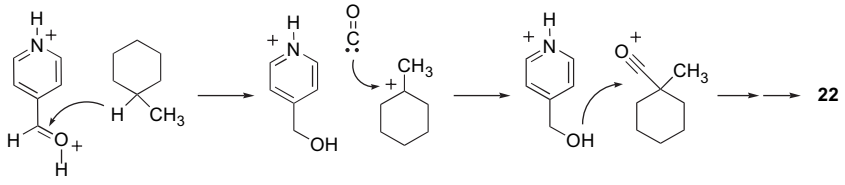


Figure 2. ^{13}C NMR spectrum of the dicationic product (*syn*-**26**) from 4-pyridinecarboxaldehyde (**1c**) and FSO_3H–SbF_5–SO_2ClF at −80 °C (• denotes external solvent, d_6-acetone).



Scheme 5. Proposed reaction mechanisms and intermediates in the electrophilic reactions of 4-pyridinecarboxaldehyde (**1c**) and related electrophiles.



Scheme 6.

cyclohexane and superacid or excess $AlCl_3$.[2c] In this recent study, the diprotonated species (**25**) is thought to be involved in hydride abstraction from cyclohexane. Because carboxonium ions are relatively weak electrophiles, there are few examples of carboxonium ions reacting with alkanes or cycloalkanes.[15] Superelectrophilic species like **34** and **35** are known to react with alkanes or cycloalkanes, while dicationic species like **36** and **37** have been shown to abstract hydride from cyclohexane–methylcyclopentane.[16]

In summary, a series of pyridinecarboxaldehydes are shown to give condensation products in excellent yields by reactions with arenes in the Brønsted superacid, CF_3SO_3H. The reactions involve dicationic intermediates, which exhibit very high electrophilic reactivities, attacking even *o*-dichlorobenzene, nitrobenzene, and some saturated hydrocarbons. Evidence for the involvement of dicationic intermediates comes from the direct observation of diprotonated species by low temperature ^{13}C NMR spectroscopy. For the diprotonated pyridinecarboxaldehydes, theoretical calculations show that the *syn*-carboxonium structures are strongly destabilized relative to the *anti*-forms, presumably due to the repulsive interaction of the cationic pyridinium ring and the carboxonium proton. These studies also show the importance of stable cationic groups in the structure–activity relationships of electrophilic systems. A high level of electrophilic reactivity can be achieved by the activation of the carboxonium group by the stable pyridinium cationic center.[17]

3. Experimental

3.1. General

The pyridinecarboxaldehydes were purchased from commercial suppliers and used as received. The trifluoromethanesulfonic acid (triflic acid) was purchased from the manufacturer and it was distilled from an Ar atmosphere prior to use. SbF_5 and triple distilled FSO_3H were purchased from commercial suppliers and used as received.

3.1.1. Procedure for the preparation of condensation products. The pyridinecarboxaldehyde (0.2 g, ca. 1 mmol) is dissolved in 1.0 mL of benzene, and 3 mL of CF_3SO_3H

is added. After 6 h, the mixture is poured over ice, the solution is neutralized with NaOH, and the products are extracted into $CHCl_3$. The organic extracts are then washed with H_2O, brine, and dried with $MgSO_4$. Concentration in vacuo provides the crude products, which are then purified by recrystallization or column chromatography.

3.1.2. Procedure for the reactions and functionalization of hydrocarbons. In a 125 mL Parr autoclave (glass-lined and flushed with dry Ar), 4-pyridinecarboxaldehyde (1 mmol) and methylcyclohexane (1 mmol) dissolved in 5 mL $CHCl_3$ and 3 mL CF_3SO_3H were added. The reactor is sealed and pressurized with carbon monoxide to 750 psi. After 12 h of stirring at 25 °C, the reactor was depressurized and its contents were poured into an ice-cold solution of CH_3OH and Na_2CO_3. Filtration and removal of the solvent gave crude product (**22**), which was further purified by column chromatography.

3.2. Analytical data for new compounds

3.2.1. 4,4′-Dibenzhydryl-[2,2′]bipyridinyl (14). Brown solid, mp 181–187 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 5.67 (s, 2H), 7.05 (d, J=3.9 Hz, 2H), 7.18–7.37 (m, J=20 Hz), 8.33 (s, 2H), 8.59 (d, J=4.7 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 56.6, 122.4, 124.6, 126.8, 128.6, 129.4, 142.2, 149.3, 153.9. HRMS: $C_{36}H_{28}N_2$, calcd 488.225249, found 488.223488.

3.2.2. 2,6-Dibenzhydryl-pyridine (15). Yellow solid, mp 94–101 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 5.66 (s, 2H), 7.06 (d, J=7.7 Hz, 2H), 7.28–7.35 (m, 20H), 7.57 (t, J=7.7 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 59.2, 121.4, 126.4, 128.3, 129.5, 136.9, 143.2, 162.4. MS: 411 (M+), 410, 332, 244, 165. HRMS: $C_{31}H_{25}N$, calcd 411.198700, found 411.198941.

3.2.3. 3-Benzhydryl-5-bromo-pyridine (16). Oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 5.60 (s, 1H), 7.16–7.18 (d, J=7.4 Hz, 2H), 7.28–7.41 (m, 6H), 7.63 (br s, 1H), 8.42 (d, J=1.2 Hz, 1H), 8.62 (d, J=1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 54.1, 120.8, 127.1, 128.8, 129.3, 139.2, 141.4, 142.0, 148.9, 149.1. MS: 325 (M+), 323, 244, 167. HRMS: $C_{18}H_{14}BrN$, calcd 323.030961, found 323.030937.

3.2.4. 2-Benzhydryl-6-methyl-pyridine (17). White solid, mp 53–58 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.63 (s, 1H), 5.91 (s, 1H), 6.97 (d, J=7.7 Hz, 1H), 7.02 (d, J=7.7 Hz, 1H), 7.27–7.38 (m, 10H), 7.48–7.51 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 24.6, 59.5, 121.0, 121.3, 126.6, 128.5, 129.6, 136.9, 143.1, 158.0, 162.5. MS: 259 (M^+), 258, 243, 181, 165. HRMS: $C_{19}H_{17}N$, calcd 259.136100, found 259.136453.

3.2.5. 3-Benzhydryl-2-methoxy-pyridine (18). White solid, mp 98–101 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 3.94 (s, 3H), 5.85 (s, 1H), 6.86 (dd, J=7.3, 5.0 Hz, 1H), 7.10–7.38 (m, 11H), 8.13 (dd, J=5.0, 1.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 49.7, 53.6, 116.6, 126.4, 126.9, 128.3, 128.8, 129.3, 138.5, 142.8, 144.7, 161.6. MS: 275 (M^+), 260, 242, 184, 167. HRMS: $C_{19}H_{17}NO$, calcd 275.131014, found 275.130983.

3.2.6. 4-(6-Benzhydryl-pyridin-2-yl)-benzoic acid methyl ester (19). White solid, mp 81–85 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.02 (s, 3H), 5.93 (s, 1H), 7.19–7.21 (m, 1H), 7.33–7.37 (m, 2H), 7.41–7.47 (m, 8H), 7.55–7.58 (m, 1H), 7.69–7.70 (m 2H), 8.18 (d, J=7.7 Hz, 1H), 8.35 (d, J=7.7 Hz, 1H), 8.84 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 52.3, 59.7, 118.2, 122.9, 126.7, 128.1, 128.5, 129.0, 129.6, 130.0, 130.7, 131.6, 137.4, 139.8, 143.3, 155.6, 162.9, 167.1. MS: 379 (M^+), 378, 348, 302, 241, 165. HRMS: $C_{26}H_{21}NO_2$, calcd 379.157229, found 379.157033.

3.2.7. 2-Amino-3-benzhydryl-pyridine (20). White solid, mp 133–135 °C ($CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.32 (s, 2H), 5.36 (s, 1H), 6.64 (dd, J=5.0, 7.5 Hz), 6.92 (d, J=7.1 Hz, 1H), 7.14 (d, J=7.1 Hz, 4H), 7.14–7.36 (m, 6H), 8.03 (d, J=4.0 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$), δ, ppm: 52.2, 114.5, 123.4, 127.1, 128.8, 129.4, 137.6, 141.3, 146.2, 156.6. MS: 260 (M^+), 259, 242, 181, 165. HRMS: $C_{18}H_{16}N_2$, calcd 260.131349, found 260.131390.

3.2.8. 3-Benzhydryl-1-methyl pyridinium triflate (21). White solid, mp 131–133 °C (Hexane–ether). ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm: 4.36 (s, 3H), 5.85 (s, 1H), 7.12–7.15 (m, 4H), 7.25–7.29 (m, 2H), 7.31–7.36 (m, 4H), 7.87 (dd, J=6.1, 8.1 Hz, 1H), 8.05 (d, J=8.2 Hz, 1H), 8.53 (s, 1H), 8.81 (d, J=6.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm: 48.8, 53.4, 120.7 (q, J_{C-F}=320 Hz), 127.7, 129.2, 129.3, 140.0, 143.8, 145.0, 145.3, 146.0. Calcd: C, 58.67; H, 4.43; N, 3.42; found: C, 58.63; H, 4.35; N, 3.40.

3.2.9. 1-Methyl-cyclohexanecarboxylic acid pyridin-4-yl-methyl ester (22). Oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm: 1.16 (s, 3H), 1.20–1.56 (m, 8H), 2.00–2.04 (m, 2H), 5.08 (s, 2H), 7.19–7.21 (m, 2H), 8.56 (s, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm: 23.1, 25.6, 35.4, 43.2, 63.9, 121.8, 145.5, 149.8, 177.2. MS: 233 (M+), 178, 125, 97.

3.2.10. Adamantane-1-carboxylic acid pyridin-4-yl-methyl ester (23). White solid, mp 55–56 °C (hexane–ether). ^{1}H NMR ($CDCl_3$, 500 MHz), δ, ppm: 1.66–1.74 (m, 6H), 1.92 (s, 6H), 1.99–2.03 (m, 3H), 5.09 (s, 2H), 7.23 (d, J=4.4 Hz, 2H), 8.57 (d, J=3.5 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz), δ, ppm: 27.9, 36.4, 38.8, 40.8, 63.7, 121.7, 146.1, 149.5, 176.9. MS: 271 (M^+), 227, 163, 135, 93.

Acknowledgements

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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.2006.04.022.

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The Ugi reaction with 2-substituted cyclic imines. Synthesis of substituted proline and homoproline derivatives

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Abstract—The Ugi three-component reaction with 2-substituted five-, six-, and seven-membered cyclic imines was investigated. The reaction opens a new route to substituted proline and homoproline derivatives. It was shown that the method is efficient for the one-step preparation of seminatural dipeptides containing natural amino acid residues, and fragments of substituted proline or pipecolinic acid. The scope and limitation of the approach are discussed.

1. Introduction

Unnatural non-proteinogenic α-amino acids are important substances for different areas of chemistry, biology and material science.[1] They have a wide biological activity and hence numerous medicinal applications. The replacement of natural amino acids in peptides with non-proteinogenic derivatives has become an important goal in synthetic organic chemistry because their incorporation into biologically relevant peptides may influence their properties dramatically.[2] The synthesis of proline peptidomimetics that mimic natural dipeptides is very attractive.[3] Proline is the most conformationally restricted amino acid. The proline residue plays an important role in protein secondary structure, and in many biological processes such as protein folding and protein recognition.[4] Proline isomerism can influence the receptor function of neurotransmitter-gated ion channels.[5] Substituted proline analogues were developed in order to constrain and control the peptide backbone in reverse turn motifs[6] or to alter the imide cis/trans ratio.[7] Pipecolinic acid (homoproline) is abundant in many natural products such as immunosuppressants or cyclic peptides with antifungal activity.[8] Pipecolinic acid residues accelerate the rate of cis–trans imide isomerism, and observe a higher preference for *cis*-imide bonds on the N-terminal of pipecolinic acid in comparison to proline residues.[8] Synthesis of 2-substituted proline or homoproline derivatives and their incorporation into natural peptides is an important goal for peptide chemistry.

Keywords: Ugi reaction; Multicomponent reaction; Imine; Amino acid; Isocyanide; Proline; Homoproline; Peptide.
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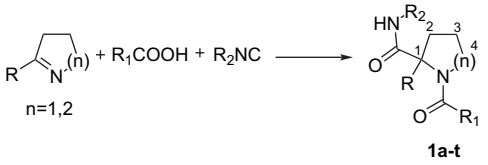
2. Results and discussion

Among the methods for the multicomponent synthesis of peptides or amino acids, the Ugi reaction is one of the most popular.[9] The Ugi reaction with non-substituted five- and six-membered cyclic aldimines was recently reported.[10] The use of 2-substituted cyclic ketimines in the Ugi MCR can give a short and very attractive synthesis of substituted proline derivatives and their higher six- and seven-membered analogues. This article is devoted in investigating the possibility of 2-substituted cyclic imines participating in the Ugi MCR (Scheme 1).



Scheme 1.

Starting cyclic imines with various aliphatic or aromatic substituents in the α-position can be easily prepared according to literature procedure from cheap, commercially available starting materials.[11] This can open broad possibilities for the syntheses of a variety of cyclic amino acid derivatives.

We decided to investigate the synthetic scope and limitations of the approach. Influence of the acid, isocyanide, and imine components on the yield of target cyclic amino acid was studied for this aim. We proposed that the structure of starting cyclic ketimines could most significantly affect the reaction path due to the considerable difference in the

Table 1. Influence of acid component on reaction time and yield (R=Me and R_2=Bn)

Entry	R_1	Product	pK_a	Reaction time (d)	Yield (%)
1	CH_3	—	4.75	5	0
2	Ph	**1a**	4.20	5	50
3	CH_2Cl	**1b**	2.85	3	80
4	$CHCl_2$	**1c**	1.48	3	73
5	CCl_3	**1d**	0.7	2.5	78
6	CF_3	**1e**	0.23	2	83

conformation behavior of five-, six-, and seven-membered nitrogen heterocycles.[12]

A model imine (2-methyl pyrroline) and benzylisocyanide were chosen to study the influence of the acid. We found that target amides of 2-methylproline can be prepared generally in good yield (Scheme 1, Table 1). However, the acidity of the carboxylic acid affects significantly the reaction time. The best result was observed in the case of trifluoroacetic acid TFA. In this case the reaction proceeds in reasonable time at room temperature to give the target amide in 83% yield. Another reason to use TFA is the possibility of subsequent deprotection of the amino acid nitrogen under mild conditions.[13] Acetic acid did not give any Ugi product.

The reaction is of general type. No restrictions on the structure of the isocyanide component were found (using model reaction with methyl pyrroline and TFA). As a rule, various isocyanides having alkyl and aryl substituents or ester groups gave substituted amides of 2-methylproline in high yields (Table 2).

It was found that the effect of the structure of the 2-substituted imine on the reaction path is much more important. Using a model benzylisocyanide and trifluoroacetic acid, we have investigated the relationship between the structure of substituents in the 2-position of the imine and the yield of the Ugi type product (Table 3). Imines with alkyl substituent react smoothly. Even in the case of sterically hindered 2-*tert*-butylpyrroline the target amide can be prepared in almost quantitative yield, however more prolonged reaction time was necessary. A very unusual result was observed in the case of 2-phenylpyrroline and other arylsubstituted imines. Instead of formation of the Ugi product the reaction is directed mainly to the trifluoroacylation of the imine. 2-Phenyl proline derivative **1n** is minor product in this case. For example, in the case of the 2-phenylpyrroline–TFA–benzylisocyanide system, the target Ugi amide was isolated in only 7% yield. We believe that the main reasons for the

Table 2. Influence of isocyanide component on the reaction (R=Me and R_1=CF_3)

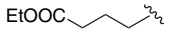
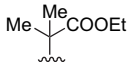
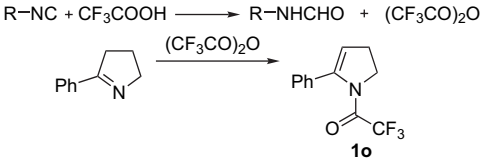
Entry	R_2	Product	Yield (%)
7	Bn	**1e**	83
8	4-Br–Ph	**1f**	72
9		**1g**	85
10		**1h**	50

Table 3. Influence of imine component on reaction time and yield (R_1=CF_3 and R_2=Bn)

Entry	R	Product	Reaction time (d)	Yield (%)
11	Me	**1e**	2	83
12	Bn	**1i**	3	45
13	Bu	**1j**	3	95
14	*i*-Pr	**1k**	4	60
15	Cyclopentyl	**1l**	4	50
16	*t*-Bu	**1m**	6	95
17	Ph	**1n**	5	7

formation of **1o** are the lower acidity of 2-phenylpyrroline compared to 2-alkylsubstituted pyrrolines, the lower electrophilicity of intermediate iminium salt, and finally, the possibility of conjugation of the enamide double bond with the phenyl ring in **1o**. The isocyanide behaves very interestingly in this reaction as a dehydrating agent to form trifluoroacetic anhydride, TFAA, from TFA.[14] The final step of this sequence is trifluoroacylation of 2-phenylpyrroline by TFAA to give enamide **1p** in 65% yield (Scheme 2). Our attempts to perform this reaction with other acids also gave the same results.

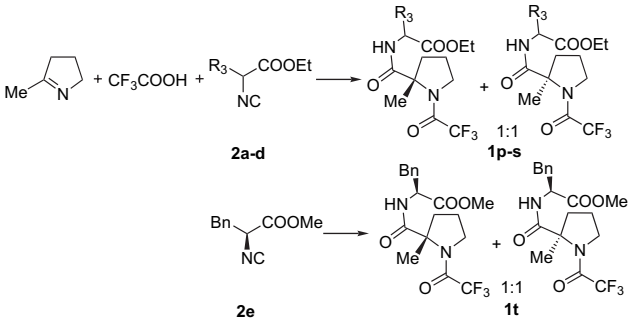


Scheme 2.

We have demonstrated that Ugi multicomponent reaction with 2-alkyl pyrrolines is a general approach to construct derivatives of 2-substituted proline, with a broad variety of such products prepared using this very simple procedure. In the case of isocyanides prepared from protected natural amino acids, this method opens a new route to seminatural dipeptides containing 2-substituted proline (as the acid building block) and a natural amino acid residue (as the amine building block). A crucial step in this synthesis is the preparation of a dipeptide with orthogonal protecting groups at each end. This opens up the possibility for the subsequent selective synthesis of tripeptides and longer peptides.

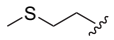
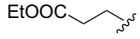
Usually no stereoinduction is observed in the case of chiral isocyanides in Ugi reactions in contrast to the Passerini reaction.[15] However, we proposed that the fixed conformation of cyclic imines could influence the possibility of a diastereoselective Ugi reaction with chiral isocyanides. Chiral isocyanide **2e** was prepared from L-phenylalanine by a literature procedure.[16]

We demonstrated that the method works for the one-step synthesis of some seminatural orthogonally protected dipeptides in good yield. Unfortunately, no induction was observed, and the reaction give a mixture of two diastereomers in a 1/1 ratio in the case of chiral isocyanide **2e**, and four diastereomers in the case of racemic isocyanides **2a–d** (by ^{1}H NMR spectroscopy) (Scheme 3). The results of the reaction of model 2-methyl pyrroline and TFA with various isocyanides **2a–e** are given in Table 4.

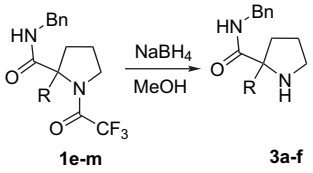


Scheme 3.

Table 4. Ugi reaction with isocyanide derivatives of natural amino acids

Entry	R_3	Product	Yield, %
18	Me	**1p**	65
19	Bn	**1q**	55
20		**1r**	52
21		**1s**	56

The possibility of selective deprotection was shown. Deprotection of **1e–m** results in N-unsubstituted amides **3a–f** (Scheme 4). The N-cleavage of trifluoroacetyl group was carried out under mild conditions in excellent yield (Table 5).

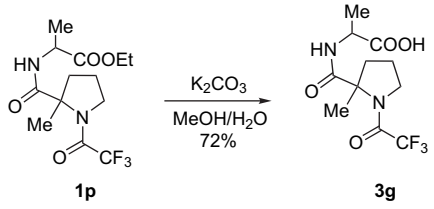


Scheme 4.

Table 5. Cleavage of TFA group

Entry	R	Product	Yield (%)
22	Me	**3a**	80
23	Bn	**3b**	90
24	Bu	**3c**	82
25	*i*-Pr	**3d**	81
26	Cyclopentyl	**3e**	83
27	*t*-Bu	**3f**	77

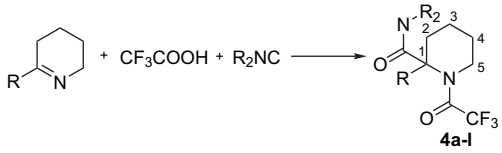
Similarly, the use of aq methanol/K_2CO_3 solution permits selective deprotection of the ester moiety to give the unprotected carboxylic acid (Scheme 5).



Scheme 5.

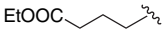
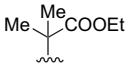
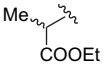
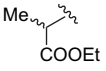
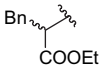
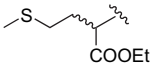
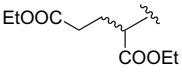
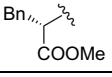
In addition to the 20 common natural amino acids there are a number of rare amino acids as which occur structural fragments of some natural products. Therefore, development of an effective synthesis of higher analogs of proline having six- and seven-membered rings is important. Pipecolinic acid (also known as homoproline) is a proline analogue, which contains a six-membered ring. It is found in several important natural products such as the immunosuppressant FK506, rapamycin, and cyclic peptides with antifungal activity.[8]

The Ugi reaction works is very well both in the case of 2-alkyl and 2-phenylpiperideines in contrast to the reaction with 2-aryl pyrrolines. As a result, a number of pipecolinic acid derivatives can be prepared using the same approach. Probably the difference in the reactivity of 2-substituted pyrrolines and 2-substituted piperideines in the Ugi reaction can be explained by the conformational peculiarities of five- and six-membered rings. In the case of pyrrolines the formation of enamides is more preferable due to lowering of vicinal interactions.[17] We found that it was also possible to synthesize orthogonally protected dipeptides containing a 2-substituted pipecolinic acid moiety (Scheme 6). In general no restriction for this synthesis was found and yields were generally high. Similarly to the reaction with chiral isocyanide **2e** for 2-substituted pyrrolines, the Ugi reaction with 6-ring imine (2-phenylpiperideine) is not diastereoselective, giving both diastereomers in a 1/1 ratio (Table 6, entry 36).



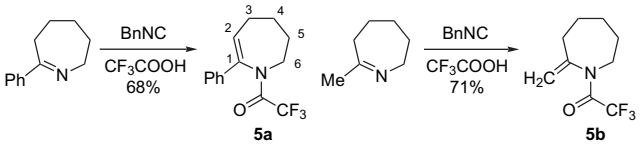
Scheme 6.

Table 6. Ugi synthesis of homoproline derivatives

Entry	R	R_2	Product	Yield (%)
28	Bu	Bn	**4a**	84
29	Ph	Bn	**4b**	79
30	Ph		**4c**	67
31	Ph		**4d**	71
32	Bu		**4e**	
32	Ph		**4f**	72
33	Ph		**4g** and **4h**[a]	84
34	Ph		**4i**	68
35	Ph		**4j**	69
36	Ph		**4k** and **4l**	84

[a] Mixture of two pairs of diastereomers in a 1:1 ratio was isolated.

We found that in the case of Ugi reactions with imines containing a seven-membered ring, no formation of the target amino acid derivatives was observed. Similarly to the reaction of 2-aryl pyrrolines only the formation of enamides take place both in the case of 2-phenyl and 2-methyl imines. Both reactions give the enamide as the only reaction product. In the case of 2-methylazepine, unpredictable elimination to form enamide **5b** having an exocyclic double bond was observed. These results confirmed that conformational peculiarities of five-, six-, and seven-membered cyclic imines are very important in the Ugi reaction. We demonstrated that only in the case of five- and six-membered 2-substituted imines the formation of 2-substituted proline and homoproline derivatives is possible (Scheme 7).



Scheme 7.

3. Conclusion

Thus, we have investigated the reaction of 2-substituted cyclic imines in Ugi reaction conditions. The reaction permits preparation of substituted proline and homoproline derivatives. It was shown that the method is efficient for the one-step preparation of seminatural dipeptides containing natural amino acid residues and fragments of substituted proline or pipecolinic acid. The significant difference in the reactivity of five-, six-, and seven-membered cyclic ketimines was demonstrated.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were determined in deuterated solvents on a Bruker VRX-400 spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from TMS. Deuterated solvent peaks were used as internal references: deutero-chloroform at 2.25 and 77.00 ppm and deutero-DMSO at 2.50 and 39.50 ppm. The IR spectra were measured using a UR-20 spectrometer. TLC was performed using 25 DC-Alufolien Kieselgel 60 F_{254} (Merck). Fluka Silica gel 60 (0.063–0.200 mm) was used for column chromatography. Commercial reagents and solvents were generally used as received.

4.2. General procedure for the Ugi reaction

The appropriate imine (1.1 mmol) and carboxylic acid (1 mmol) were dissolved in abs CH_2Cl_2 (2 ml). The isocyanide (1.0 mmol) was added and the solution was stirred for the appropriate time at room temperature. The solvent was removed in vacuo and the resulting crude product was purified by column chromatography (hexane/ethyl-acetate, 1:1).

4.2.1. 1-Benzoyl-*N*-benzyl-2-methylprolinamide (1a). Yield 50%, white solid, mp 87–88 °C [Found: C, 74.62; H, 6.66. $C_{20}H_{22}N_2O_2$ requires C, 74.51; H, 6.88%]; ν_{max} (Nujol) 2880, 1660, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.7 (1H, br, N*H*), 7.30–7.45 (5H, m, COPh), 7.20–7.35 (5H, m, Ph), 4.5 (2H, d, *J* 5.7 Hz, C*H*$_2$Ph), 3.40–3.55 (2H, m, *H*-4), 2.67–2.77 (1H, m, *H*-2), 1.85–1.92 (1H, m, *H*-2), 1.75–1.85 (2H, m, *H*-3), 1.80 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 174.75, 167.35, 137.15, 136.70, 131.28, 128.65, 127.40, 126.66, 126.16, 69.40, 48.57 (m), 43.61, 38.31, 23.77, 21.06.

4.2.2. *N*-Benzyl-1-(chloroacetyl)-2-methylprolinamide (1b). Yield 80%, colorless oil [Found: C, 61.36; H, 6.86. $C_{15}H_{19}ClN_2O_2$ requires C, 61.12; H, 6.50%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (liquid film) 2870, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.5 (1H, br, N*H*), 7.20–7.35 (5H, m, Ph), 4.41 and 4.45 (2H, both d, *J* 5.6 Hz, C*H*$_2$Ph), 4.03 (2H, d, *J* 1.5 Hz, C*H*$_2$Cl), 3.60–3.75 (2H, m, *H*-4), 2.51–2.63 (1H, m, *H*-2), 1.9–2.05 (1H, m, *H*-2), 1.71–1.93 (2H, m, *H*-3), 1.67 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.9, 165.78, 138.19, 128.43, 127.19, 68.72, 48.81 (m), 43.48, 42.90, 38.54, 23.36, 21.82.

4.2.3. *N*-Benzyl-1-(dichloroacetyl)-2-methylprolinamide (1c). Yield 73%, white solid, mp 107–108 °C [Found: C, 55.01; H, 5.72. $C_{15}H_{18}Cl_2N_2O_2$ requires C, 54.72; H, 5.51%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2870, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.33 (5H, m, Ph), 6.8 (1H, br, N*H*), 6.13 (1H, s, C*H*Cl$_2$), 4.43 (2H, d, *J* 5.3 Hz, C*H*$_2$Ph), 3.71–3.86 (2H, m, *H*-4), 2.50–2.63 (1H, m, *H*-2), 1.95–2.05 (1H, m, *H*-2), 1.75–1.87 (2H, m, *H*-3), 1.70 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.51, 162.47, 138.06, 128.54, 127.32, 127.23, 69.45, 66.15, 48.85 (m), 43.67, 38.38, 23.62, 21.54.

4.2.4. *N*-Benzyl-2-methyl-1-(trichloroacetyl)prolinamide (1d). Yield 78%, white solid, mp 111–112 °C [Found: C, 49.40; H, 5.08. $C_{15}H_{17}Cl_3N_2O_2$ requires C, 49.54; H, 4.71%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (Nujol) 2900, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (5H, m, Ph), 6.6 (1H, br, N*H*), 4.44 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.70–3.85 (2H, m, *H*-4), 2.40–2.50 (1H, m, *H*-2), 1.93–2.08 (2H, m, *H*-2 and *H*-3), 1.77–1.84 (1H, m, *H*-3), 1.70 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 172.47, 158.70, 138.02, 128.62, 127.55, 127.39, 93.58, 70.37, 51.31 (m), 43.83, 38.56, 24.61, 20.88.

4.2.5. *N*-Benzyl-2-methyl-1-(trifluoroacetyl)prolinamide (1e). Yield 83%, white solid, mp 94–95 °C [Found: C, 57.27; H, 5.72. $C_{15}H_{17}F_3N_2O_2$ requires C, 57.32; H, 5.45%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2880, 1680, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (5H, m, Ph), 6.65 (1H, br, N*H*), 4.42 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.70–3.85 (2H, m, *H*-4), 2.40–2.50 (1H, m, *H*-2), 1.93–2.08 (2H, m, *H*-2 and *H*-3), 1.77–1.84 (1H, m, *H*-3), 1.66 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 171.95, 155.65 (q, *J* 36.6), 137.99, 128.59, 127.34, 116.0 (q, *J* 288.4), 69.46, 48.57 (m), 43.71, 38.31, 23.87, 21.06.

4.2.6. *N*-(4-Bromophenyl)-2-methyl-1-(trifluoroacetyl)-prolinamide (1f). Yield 72%, white solid, mp 119–120 °C [Found: C, 44.50; H, 3.47. $C_{14}H_{14}BrF_3N_2O_2$ requires C, 44.35; H, 3.72%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 2900, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$)

8.3 (1H, br, N*H*), 7.48 (2H, d, *J* 8.6 Hz, *m*-Ph), 6.95 (2H, d, *J* 8.6 Hz, *o*-Ph), 3.32–3.38 (2H, m, *H*-4), 2.53–2.60 (2H, m, *H*-2), 1.83–1.89 (2H, m, *H*-3), 1.73 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 166.72, 154.54 (q, *J* 36.8), 135.71, 130.63, 125.42, 124.05, 116.2 (q, *J* 288.3), 77.62, 49.21 (m), 38.99, 23.96, 21.50.

4.2.7. Ethyl 4-{[2-methyl-1-(trifluoroacetyl)prolyl]amino}-butanoate (1g). Yield 85%, colorless oil [Found: C, 49.39; H, 6.20. $C_{14}H_{21}F_3N_2O_4$ requires C, 49.70; H, 6.26%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2950, 1720, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.7 (1H, br, N*H*), 4.07 (2H, q, *J* 7 Hz, $COOCH_2Me$), 3.67–3.85 (2H, m, *H*-4), 3.26 (2H, q, *J* 5.6 Hz, $CH_2CH_2CH_2COOCH_2CH_3$), 2.30–2.42 (3H, m, *H*-2 and $CH_2CH_2CH_2COOCH_2Me$), 1.90–2.07 (2H, m, *H*-2 and *H*-3), 1.73–1.85 (3H, m, *H*-3 and $CH_2CH_2CH_2COOCH_2Me$), 1.63 (3H, s, *Me*), 1.20 (3H, t, *J* 7.1 Hz, CH_2Me); δ_C (400 MHz, $CDCl_3$) 173.69, 172.12, 155.52 (q, *J* 36.6), 115.2 (q, *J* 288.6), 69.44, 60.44, 48.52 (m), 39.47, 38.40, 31.76, 24.98, 23.83, 20.96, 14.04.

4.2.8. Ethyl 2-methyl-1-(trifluoroacetyl)prolyl-2-methyl-alaninate (1h). Yield 50%, white solid, mp 65–66 °C [Found: C, 50.01; H, 6.30. $C_{14}H_{21}F_3N_2O_4$ requires C, 49.70; H, 6.26%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2930, 1750, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9 (1H, br, N*H*), 4.15 (2H, q, *J* 7.1 Hz, $COOCH_2Me$), 3.67–3.85 (2H, m, *H*-4), 2.4–2.48 (1H, m, *H*-2), 1.91–2.12 (2H, m, *H*-2 and *H*-3), 1.70–1.80 (1H, m, *H*-3), 1.65 (3H, s, *Me*), 1.44 (6H, s, CMe_2), 1.22 (3H, t, *J* 7.1 Hz, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 174.51, 170.99, 155.66 (q, *J* 36.7), 115.2 (q, *J* 288.3), 69.70, 61.46, 56.68, 48.62 (m), 38.12, 24.38, 24.18, 23.81, 21.11, 13.94.

4.2.9. *N*,2-Dibenzyl-1-(trifluoroacetyl)prolinamide (1i). Yield 45%, white solid, mp 89–90 °C [Found: C, 64.59; H, 5.42. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2910, 1680, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.38 (8H, m, Ph and Ph), 7.07 (2H, dd, *J* 2.2, *J* 5.7 Hz, *o*-Ph), 6.9 (1H, br, N*H*), 4.42–4.55 (2H, m, $NHCH_2Ph$), 3.65–3.75 (2H, m, *H*-4), 3.10–3.20 (2H, m, CH_2Ph), 2.35–2.47 (1H, m, *H*-2), 2.03–2.10 (1H, m, *H*-2), 1.70–1.85 (1H, m, *H*-3), 1.32–1.44 (1H, m, *H*-3); δ_C (400 MHz, $CDCl_3$) 172.03, 155.65 (q, *J* 36.6), 138.60, 137.99, 130.33, 128.59, 127.50, 127.34, 126.88, 116.0 (q, *J* 288.4), 70.55, 48.57 (m), 43.70, 39.07, 23.95.

4.2.10. *N*-Benzyl-2-butyl-1-(trifluoroacetyl)prolinamide (1j). Yield 95%, white solid, mp 84–85 °C [Found: C, 60.34; H, 6.62. $C_{18}H_{23}F_3N_2O_2$ requires C, 60.66; H, 6.50%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (Nujol) 2890, 1670, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.40 (5H, m, Ph), 4.33–4.57 (2H, m, CH_2Ph), 3.85–3.93 (1H, m, *H*-4), 3.57–3.62 (1H, m, *H*-4), 2.65–2.73 (1H, m, *H*-2), 2.10–2.25 (2H, m, $CH_2CH_2CH_2CH_3$), 1.91–2.02 (2H, m, *H*-2 and *H*-3), 1.75–1.85 (1H, m, *H*-3), 1.05–1.35 (4H, m, $CH_2CH_2CH_2CH_3$), 0.86 (3H, t, $CH_2CH_2CH_2Me$); δ_C (400 MHz, $CDCl_3$) 171.79, 156.53 (q, *J* 36.6), 138.20, 128.58, 127.27, 116.0 (q, *J* 288.4), 74.21, 48.57 (m), 43.66, 34.53, 33.46, 26.10, 23.69, 22.63, 13.80.

4.2.11. *N*-Benzyl-2-isopropyl-1-(trifluoroacetyl)prolinamide (1k). Yield 60%, colorless oil [Found: C, 59.85; H, 6.40. $C_{17}H_{21}F_3N_2O_2$ requires C, 59.64; H, 6.18%]; R_f (50% EtOAc/hexane) 0.70; ν_{max} (liquid film) 2950, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, N*H*), 7.22–7.35 (5H, m, Ph), 4.53–4.60 (1H, m, CH_2Ph), 4.32–4.40 (1H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.50–3.58 (1H, m, *H*-4), 3.13–3.23 (1H, m, *H*-2), 2.77–2.83 (1H, m, *H*-2), 1.86–2.03 (2H, m, *H*-3), 1.65–1.73 (1H, m, C*H*), 0.87 (3H, d, *J* 7 Hz, *Me*), 0.83 (3H, d, *J* 7 Hz, *Me*); δ_C (400 MHz, $CDCl_3$) 171.32, 157.65 (q, *J* 36.6), 138.37, 128.54, 127.21, 127.18, 116.53 (q, *J* 288.4), 79.85, 49.99 (m), 43.64, 29.23, 27.38, 23.47, 17.63, 16.18.

4.2.12. *N*-Benzyl-2-cyclopentyl-1-(trifluoroacetyl)prolinamide (1l). Yield 50%, white solid, mp 88–89 °C [Found: C, 62.12; H, 6.44.$C_{19}H_{23}F_3N_2O_2$ requires C, 61.95; H, 6.29%]; R_f (50% EtOAc/hexane) 0.65; ν_{max} (Nujol) 2920, 1690, 1630 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.9 (1H, br, N*H*), 7.22–7.35 (5H, m, Ph), 4.53–4.60 (1H, m, CH_2Ph), 4.32–4.40 (1H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.50–3.58 (1H, m, *H*-4), 3.30–3.58 (1H, m, *H*-2), 2.82–2.87 (1H, m, *H*-2), 1.90–2.00 (2H, m, *H*-3), 1.52–1.75 (7H, m, cpt), 1.20–1.35 (2H, m, cpt); δ_C (400 MHz, $CDCl_3$) 171.88, 157.06 (q, *J* 36.6), 138.35, 128.54, 127.16, 116.3 (q, *J* 288.4), 78.32, 49.92 (m), 43.63, 41.40, 29.14, 28.71, 27.06, 26.55, 25.37, 23.38.

4.2.13. *N*-Benzyl-2-*tert*-butyl-1-(trifluoroacetyl)prolinamide (1m). Yield 95%, white solid, mp 85–86 °C [Found: C, 60.40; H, 6.72. $C_{18}H_{23}F_3N_2O_2$ requires C, 60.66; H, 6.50%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 2910, 1680, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.8 (1H, br, N*H*), 7.20–7.33 (5H, m, Ph), 4.43–4.51 (2H, m, CH_2Ph), 3.87–3.95 (1H, m, *H*-4), 3.45–3.55 (1H, m, *H*-4), 2.87–2.95 (1H, m, *H*-2), 1.83–1.93 (2H, m, *H*-2 and *H*-3), 1.53–1.65 (1H, m, *H*-3), 1.13 (9H, s, *t*-Bu); δ_C (400 MHz, $CDCl_3$) 171.56, 158.66 (q, *J* 36.9), 138.09, 128.59, 127.53, 127.27, 116.7 (q, *J* 288.1), 84.32, 50.99 (m), 43.98, 38.39, 34.88, 27.84, 23.27.

4.2.14. *N*-Benzyl-2-phenyl-1-(trifluoroacetyl)prolinamide (1n). Yield 7%, white solid, mp 100–101 °C [Found: C, 63.43; H, 5.09. $C_{20}H_{19}F_3N_2O_2$ requires C, 63.82; H, 5.09%]; R_f (50% EtOAc/hexane) 0.75; ν_{max} (Nujol) 3000, 1690, 1660 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.18–7.33 (8H, m, Ph and Ph), 7.07–7.12 (2H, m, Ph), 4.50–4.57 (2H, m, CH_2Ph), 4.35–4.43 (1H, m, CH_2Ph), 3.97–4.05 (1H, m, *H*-4), 3.87–3.97 (1H, m, *H*-4), 3.10–3.20 (1H, m, *H*-2), 1.86–2.05 (3H, m, *H*-2 and *H*-3); δ_C (400 MHz, $CDCl_3$) 170.34, 156.56 (q, *J* 36.3), 138.06, 137.89, 128.75, 128.57, 127.93, 127.45, 127.29, 125.50, 116.0 (q, *J* 288.6), 77.11, 49.37 (m), 44.11, 40.75, 24.28.

4.2.15. Ethyl 2-methyl-1-(trifluoroacetyl)prolylalaninate (1p), mixture of diastereomers, ratio 1:1. Yield 65%, white solid, mp 69–70 °C [Found: C, 47.83; H, 6.12. $C_{13}H_{19}F_3N_2O_4$ requires C, 48.15; H, 5.91%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2920, 1740, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.7, 6.8 (1H, br, N*H*), 4.48 (1H, m, C*H*), 4.17–4.25 (2H, m, $COOCH_2CH_3$), 3.70–3.87 (2H, m, *H*-4), 2.37–2.48 (1H, m, *H*-2), 1.91–2.10 (2H, m, *H*-2 and *H*-3), 1.76–1.85 (1H, m, *H*-3), 1.68,

1.59 (3H, s, *Me*), 1.38 (3H, m, CH*Me*), 1.25–1.27 (3H, m, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 172.81, 172.76, 171.55, 171.42, 155.97 (q, *J* 36.7), 116.0 (q, *J* 288.3), 69.58, 69.16, 61.49, 61.46, 53.40, 53.24, 48.63 (m), 38.33, 38.24, 23.94, 23.78, 21.10, 20.94, 14.02, 14.00.

4.2.16. Ethyl 2-methyl-1-(trifluoroacetyl)prolylphenylalaninate (1q), mixture of diastereomers, ratio 1:1. Yield 55%, white solid, mp 66–67 °C [Found: C, 56.64; H, 5.45. $C_{19}H_{23}F_3N_2O_4$ requires C, 56.99; H, 5.79%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2940, 1740, 1710, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.07–7.30 (5H, m, Ph), 6.6, 6.5 (1H, br, N*H*), 4.83 (1H, m, C*H*), 4.17 (2H, q, *J* 7.1 Hz, $COOCH_2CH_3$), 3.65–3.80 (2H, m, *H*-4), 3.05–3.20 (2H, m, CH_2Ph), 2.30–2.40 (1H, m, *H*-2), 1.83–2.01 (2H, m, *H*-2 and *H*-3), 1.72–1.83 (1H, m, *H*-3), 1.65, 1.62 (3H, s, *Me*), 1.25 (t, *J* 7.1 Hz, $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 171.46, 171.43, 171.26, 171.19, 155.97 (q, *J* 36.7), 135.88, 135.72, 129.37, 129.29, 128.46, 129.39, 127.05, 126.99, 116.0 (q, *J* 288.3), 69.52, 69.46, 61.47, 53.40, 53.24, 48.49 (m), 38.41, 38.15, 37.76, 37.66, 23.67, 21.06, 20.91, 13.99.

4.2.17. Ethyl 2-methyl-1-(trifluoroacetyl)prolylmethioninate (1r), mixture of diastereomers, ratio 1:1. Yield 52%, yellow oil [Found: C, 46.83; H, 6.15. $C_{15}H_{23}F_3N_2O_4S$ requires C, 46.87; H, 6.03%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2980, 1730, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9, 7.0 (1H, br, N*H*), 4.63 (1H, m, C*H*), 4.17 (2H, m, CH_2CH_3), 3.70–3.90 (2H, m, *H*-4), 2.35–2.60 (3H, m, *H*-2, $CH_2CH_2SCH_3$), 2.12–2.20 (1H, m, *H*-2), 2.09, 2.08 (3H, s, SCH_3), 1.94–2.06 (3H, m, *H*-3, CH_2CH_2SMe), 1.80–1.88 (1H, m, *H*-3), 1.68, 1.69 (3H, s, *Me*), 1.27–1.35 (3H, m, CH_2Me); δ_C (400 MHz, $CDCl_3$) 171.71, 171.69, 171.58, 155.60 (q, *J* 36.7), 116.5 (q, *J* 288.5), 69.45, 69.99, 61.54, 52.06, 51.95, 48.44 (m), 38.37, 38.16, 31.04, 30.76, 29.78, 29.75, 23.87, 23.70, 20.79, 20.71, 15.24, 13.93.

4.2.18. Diethyl 2-methyl-1-(trifluoroacetyl)prolylglutamate (1s), mixture of diastereomers, ratio 1:1. Yield 56%, yellow oil [Found: C, 49.48; H, 6.04. $C_{17}H_{25}F_3N_2O_6$ requires C, 49.75; H, 6.14%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2990, 1730, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.9, 7.1 (1H, br, N*H*), 4.50 (1H, m, C*H*), 4.07–4.22 (4H, m, $COOCH_2CH_3$ and $COOCH_2CH_3$), 3.70–3.92 (2H, m, *H*-4), 2.32–2.46 (3H, m, *H*-2, CH_2CH_2COOEt), 2.12–2.25 (1H, m, *H*-2), 1.93–2.10 (3H, m, H-3 and CH_2CH_2COOEt), 1.80–1.90 (1H, m, *H*-3), 1.68, 1.67 (3H, s, *Me*), 1.20–1.27 (6H, m, $COOCH_2Me$ and $COOCH_2Me$); δ_C (400 MHz, $CDCl_3$) 173.43, 173.37, 172.07, 172.01, 171.60, 157.5 (q, *J* 36.5), 116.0 (q, *J* 288.6), 69.52, 68.99, 61.54, 60.71, 52.45, 52.32, 48.50 (m, C-4), 38.60, 38.37, 30.21, 30.18, 26.33, 26.50, 23.95, 23.76, 20.86, 20.79, 14.05, 14.03.

4.2.19. Methyl 2-methyl-1-(trifluoroacetyl)prolyl-L-phenylalaninate (1t), mixture of diastereomers, ratio 1:1. Yield 55%, colorless oil, crystallizes on standing [Found: C, 55.90; H, 5.60. $C_{18}H_{21}F_3N_2O_4$ requires C, 55.96; H, 5.48%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2940, 1740, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.07–7.30 (5H, m, Ph), 6.6, 6.5 (1H, br, N*H*), 4.83–4.88 (1H, m, C*H*), 3.65–3.80 (5H, m, *H*-4, COO*Me*), 3.05–3.20 (2H, m, CH_2Ph), 2.27–2.42 (1H, m, *H*-2), 1.85–2.00 (2H, m, *H*-2 and *H*-3), 1.72–1.83 (1H, m, *H*-3), 1.65, 1.63 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 171.82, 171.73, 171.55, 155.97 (q, *J* 36.7), 135.79, 135.64, 129.37, 129.26, 128.58, 129.52, 127.18, 126.11, 116.0 (q, *J* 288.3), 69.49, 69.43, 53.38, 53.19, 48.54 (m, C-4), 38.44, 38.16, 37.78, 37.65, 23.74, 21.09, 20.90.

4.3. General procedure for deprotection 1e–m

The appropriate amides **1e**–**m** (0.5 mmol) were dissolved in abs MeOH (5 ml). The $NaBH_4$ (0.25 mmol) was added and the solution was stirred for the appropriate time at room temperature. The solvent was removed in vacuo and the resulting crude residue was treated with 2 ml of 2 M aq K_2CO_3. Product was extracted with ethyl-acetate (3×10 ml), dried over K_2CO_3, and evaporate in vacuo.

4.3.1. *N*-Benzyl-2-methylprolinamide (3a). Yield 80%, yellow oil [Found: C, 71.20; H, 8.48. $C_{13}H_{18}N_2O$ requires C, 71.53; H, 8.31%]; R_f (2% NH_3(aq)/CH_3CN) 0.6; ν_{max} (liquid film) 2960, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, t, *J* 5.9 Hz, CH_2Ph), 3.03–3.10 (1H, m, *H*-4), 2.77–2.83 (1H, m, *H*-4), 2.25–2.37 (1H, m, *H*-2), 1.60–1.80 (3H, m, *H*-2 and *H*-3), 1.43 (3H, s, *Me*); δ_C (400 MHz, $CDCl_3$) 177.24, 138.84, 128.47, 127.32, 127.06, 66.50, 47.03, 42.96, 37.61, 26.47, 25.94.

4.3.2. *N*,2-Dibenzylprolinamide (3b). Yield 90%, yellow oil [Found: C, 77.77; H, 7.23. $C_{19}H_{22}N_2O$ requires C, 77.52; H, 7.53%]; R_f (2% NH_3(aq)/CH_3CN) 0.6; ν_{max} (liquid film) 2960, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.0 (1H, br, CON*H*), 7.05–7.35 (10H, m, Ph and Ph), 4.27–4.45 (2H, m, $PhCH_2NH$), 3.67 (1H, d, *J* 13.3 Hz, CH_2Ph), 2.97–3.05 (1H, m, *H*-4), 2.82–2.88 (1H, m, *H*-4), 2.70 (1H, d, *J* 13.3 Hz, $PhCH_2$), 2.23–2.30 (1H, m, H-2), 1.83–1.92 (2H, m, *H*-2 and *H*-3), 1.67–1.80 (1H, m, *H*-3); δ_C (400 MHz, $CDCl_3$) 176.12, 138.55, 137.08, 127.79, 128.41, 127.44, 127.03, 126.70, 70.01, 46.53, 43.49, 43.03, 37.11, 25.61.

4.3.3. *N*-Benzyl-2-butylprolinamide (3c). Yield 82%, yellow oil [Found: C, 73.62; H, 8.95. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2980, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.4 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, d, *J* 6 Hz, CH_2Ph), 2.96–3.05 (1H, m, *H*-4), 2.75–2.82 (1H, m, *H*-4), 2.20–2.27 (1H, m, *H*-2), 1.96–2.04 (1H, m, *H*-2), 1.60–1.73 (3H, m, *H*-3 and $CH_2CH_2CH_2Me$), 1.43–1.50 (1H, m, $CH_2CH_2CH_2Me$), 1.15–1.30 (4H, m, $CH_2CH_2CH_2Me$), 0.85 (3H, t, *J* 7 Hz, *Me*); δ_C (400 MHz, $CDCl_3$) 176.59, 138.89, 128.46, 127.44, 127.08, 69.94, 47.04, 43.04, 38.99, 36.92, 27.06, 26.09, 22.96, 13.88.

4.3.4. *N*-Benzyl-2-isopropylprolinamide (3d). Yield 81%, yellow oil [Found: C, 73.13; H, 8.95. $C_{15}H_{22}N_2O$ requires C, 73.13; H, 9.00%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2950, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.22–7.35 (5H, m, Ph), 4.40 (2H, d, *J* 5.9 Hz, CH_2Ph), 2.94–3.03 (1H, m, *H*-4), 2.73–2.80 (1H, m, *H*-4), 2.13–2.27 (2H, m, *H*-2 and C*H*), 1.60–1.76 (3H, m, *H*-2 and *H*-3), 0.89 (6H, m, *Me* and *Me*); δ_C (400 MHz,

$CDCl_3$) 176.33, 138.82, 128.55, 127.39, 126.96, 73.09, 47.21, 42.89, 34.64, 34.59, 26.33, 18.69, 16.99.

4.3.5. *N*-Benzyl-2-cyclopentylprolinamide (3e). Yield 83%, yellow oil [Found: C, 75.13; H, 8.98. $C_{17}H_{24}N_2O$ requires C, 74.96; H, 8.88%]; R_f (2% NH_3(aq)/CH_3CN) 0.7; ν_{max} (liquid film) 2980, 2780 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.3 (1H, br, CON*H*), 7.23–7.38 (5H, m, Ph), 4.30–4.40 (2H, m, C*H*$_2$Ph), 2.92–3.01 (1H, m, *H*-4), 2.75–2.81 (1H, m, *H*-4), 2.42–2.51 (1H, m, *H*-2), 2.20–2.30 (1H, m, *H*-2), 1.45–1.76 (9H, m, C*H*, *H*-3 and cpt), 1.15–1.35 (2H, m, cpt); δ_C (400 MHz, $CDCl_3$) 176.56, 138.77, 128.43, 127.55, 126.88, 71.56, 47.17, 45.74, 42.76, 34.78, 26.37, 27.06, 26.52, 25.40.

4.3.6. *N*-Benzyl-2-*tert*-butylprolinamide (3f). Yield 77%, yellow oil [Found: C, 73.62; H, 8.95. $C_{16}H_{24}N_2O$ requires C, 73.81; H, 9.29%]; R_f (2% NH_3(aq)/CH_3CN) 0.65; ν_{max} (liquid film) 2960, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 8.5 (1H, br, CONH), 7.22–7.35 (5H, m, Ph), 4.40 (2H, m, C*H*$_2$Ph), 2.94–3.0 (1H, m, *H*-4), 2.75–2.85 (1H, m, *H*-4), 2.24–2.33 (1H, m, *H*-2), 1.60–1.80 (3H, m, *H*-2 and *H*-3), 1.04 (9H, s, *t*-Bu); δ_C (400 MHz, $CDCl_3$) 175.74, 138.95, 128.44, 127.56, 127.03, 75.73, 47.05, 43.16, 35.87, 31.19, 26.43, 26.28.

4.3.7. 2-Methyl-1-(trifluoroacetyl)prolylalanine (3g), mixture of isomers. To a stirred solution of amide **1p** 157 mg (0.5 mmol) in a mixture of MeOH/H_2O (1:1, 5 ml), 69 mg (0.25 mmol) K_2CO_3 was added and the solution was stirred for 24 h at room temperature. The solvent was removed in vacuo and the resulting crude residue was treated with 0.2 ml of 50% aq CF_3COOH and product was extracted with ethyl-acetate (3×5 ml) and evaporated in vacuo to yield 72% **3g** as yellow oil [Found: C, 44.65; H, 5.12. $C_{11}H_{15}F_3N_2O_4$ requires C, 44.60; H, 5.10%]; R_f (5% MeOH/CH_3CN) 0.7; ν_{max} (liquid film) 2950, 1690 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 7.90, 7.85 (1H, s, N*H*), 4.15–4.25 (1H, m, CH), 3.65–3.85 (2H, m, H-4), 2.03–2.15 (1H, m, H-2), 1.81–2.00 (3H, m, *H*-2 and *H*-3), 1.59, 1.48 (3H, s, *Me*), 1.20–2.30 (3H, m, *Me*CH); δ_C (400 MHz, DMSO-d_6) 174.18, 174.13, 171.37, 171.25, 153.95 (q, *J* 36.4), 116.12 (q, *J* 288.4), 68.89, 68.77, 48.21, 47.85, 38.07, 38.01, 23.37, 20.29, 19.99, 17.03, 16.67.

4.3.8. *N*-Benzyl-2-butyl-1-(trifluoroacetyl)piperidine-2-carboxamide (4a). Yield 84%, white solid, mp 91–29 °C [Found: C, 62.00; H, 6.90. $C_{19}H_{25}F_3N_2O_2$ requires C, 61.61; H, 6.80%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (Nujol) 2970, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.37 (5H, m, Ph), 6.10 (1H, br, N*H*), 4.46 (2H, d, *J* 5.5 Hz, C*H*$_2$Ph), 3.60–3.70 (1H, m, *H*-5), 3.39–3.49 (1H, m, *H*-5), 2.42–2.52 (1H, m, *H*-2), 1.95–2.06 (1H, m, *H*-2), 1.60–1.90 (6H, m, *H*-3 and C*H*$_2$CH$_2$CH$_2$CH$_3$ and CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.22–1.39 (3H, m, CH$_2$CH$_2$C*H*$_2$CH$_3$ and *H*-4), 1.09–1.20 (1H, m, *H*-4), 0.87 (3H, t, *J* 7.0 Hz, CH$_2$CH$_2$CH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 171.98, 155.75 (q, *J* 36.4), 138.25, 128.71, 127.60, 127.45, 116.0 (q, *J* 288.6), 66.65, 43.82, 42.71 (m), 34.35, 30.48 (C-2), 25.99, 22.85, 21.97, 16.55, 13.94.

4.3.9. *N*-Benzyl-2-phenyl-1-(trifluoroacetyl)piperidine-2-carboxamide (4b). Yield 79%, white solid, mp 99–100 °C [Found: C, 64.65; H, 5.42. $C_{21}H_{21}F_3N_2O_2$ requires C, 64.61; H, 5.42%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (Nujol) 2960, 1700, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.05–7.35 (10H, m, Ph and Ph), 5.8 (1H, br, NH), 4.37–4.45 (1H, m, PhCH_2), 4.22–4.27 (1H, m, PhCH_2), 3.73–3.83 (1H, m, H-5), 3.23–3.30 (1H, m, H-5), 2.55–2.64 (1H, m, H-2), 2.23–2.32 (1H, m, H-2), 1.67–1.83 (2H, m, H-3), 1.52–1.63 (1H, m, H-4), 1.26–1.40 (1H, m, H-4); δ_C (400 MHz, $CDCl_3$) 171.16, 158.13 (q, *J* 36.6), 138.31, 133.66, 129.66, 128.81, 128.72, 127.60, 127.51, 127.40, 117.0 (q, *J* 288.6), 70.40, 44.29, 43.65 (m), 34.68, 23.53, 18.66.

4.3.10. Ethyl 4-({[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}amino)butanoate (4c). Yield 67%, colorless oil [Found: C, 57.60; H, 6.16. $C_{20}H_{25}F_3N_2O_4$ requires C, 57.96; H, 6.08%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2990, 1720, 1690, 1670 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.33–7.47 (3H, m, Ph), 7.22–7.27 (2H, m, Ph), 5.6 (1H, br, N*H*), 4.05 (2H, q, *J* 7.1 Hz, COOC*H*$_2$CH$_3$), 3.78–3.88 (1H, m, *H*-5), 3.23–3.32 (1H, m, *H*-5), 3.16–3.23 (2H, q, *J* 6.3 Hz, C*H*$_2$CH$_2$CH$_2$COOEt), 2.58–2.67 (1H, m, *H*-2), 2.27–2.34 (1H, m, *H*-2), 2.24 (2H, t, *J* 7.1, CH$_2$CH$_2$C*H*$_2$COOEt), 1.55–1.85 (5H, m, *H*-3 and CH$_2$C*H*$_2$CH$_2$COOEt and *H*-4), 1.21–1.45 (1H, m, *H*-4), 1.19 (3H, t, *J* 7.1 Hz, COOCH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.84, 170.66, 157.38 (q, *J* 35.9), 136.06, 129.12, 128.14, 126.95,115.6 (q, *J* 289.1), 69.81, 60.03, 43.03 (m), 39.08, 33.85, 31.17, 23.92, 23.00, 18.09, 13.84.

4.3.11. Ethyl 2-methyl-*N*-{[2-phenyl-1-(trifluoroacetyl)-piperidin-2-yl]carbonyl}alaninate (4d). Yield 71%, colorless oil [Found: C, 57.77; H, 6.15. $C_{20}H_{25}F_3N_2O_4$ requires C, 57.96; H, 6.08%]; R_f (50% EtOAc/hexane) 0.6; ν_{max} (liquid film) 2980, 1710, 1700, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.22–7.43 (5H, m, Ph), 6.4 (1H, br, N*H*), 4.07–4.19 (2H, m, COOC*H*$_2$CH$_3$), 3.72–3.85 (1H, m, *H*-5), 3.37–3.45 (1H, m, *H*-5), 2.51–2.60 (1H, m, *H*-2), 1.17–2.24 (1H, m, *H*-2), 1.74–1.88 (2H, m, *H*-3), 1.58–1.7 (2H, m, *H*-4), 1.50 (3H, s, CMe*Me*), 1.42 (3H, s, C*Me*Me), 1.22 (3H, t, *J* 7.1 Hz, COOCH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 174.20, 169.52, 157.85 (q, *J* 35.9), 134.14, 129.11, 128.11, 126.73, 117.7 (q, *J* 289.1), 70.08, 61.31, 56.59, 43.36, 34.77, 24.50, 23.75, 23.14, 18.32, 13.98.

4.3.12. Ethyl *N*-{[2-butyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}alaninate (4e), mixture of diastereomers, ratio 1:1. Yield 78%, white solid, mp 83–84 °C [Found: C, 53.50; H, 7.16. $C_{17}H_{27}F_3N_2O_4$ requires C, 53.68; H, 7.15%]; R_f (50% EtOAc/hexane) 0.60; ν_{max} (Nujol) 2980, 1740, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 6.47, 6.33 (1H, br, N*H*), 4.46–4.57 (1H, m, C*H*), 4.12–4.25 (2H, m, COOC*H*$_2$CH$_3$), 3.65–3.75 (1H, m, *H*-5), 3.33–3.47 (1H, m, *H*-5), 2.33–2.50 (1H, m, *H*-2), 1.95–2.10 (1H, m, *H*-2), 1.60–1.90 (7H, m, *H*-3, *H*-2, C*H*$_2$CH$_2$CH$_2$Me and CH$_2$C*H*$_2$CH$_2$Me), 1.35–1.45 (3H, m, *Me*), 1.30–1.35 (2H, m, CH$_2$CH$_2$C*H*$_2$Me), 1.27–1.30 (3H, t, *J* 7.6 Hz, COOCH$_2$*Me*), 1.05–1.17 (1H, m, *H*-4), 0.85–0.93 (3H, m, CH$_2$CH$_2$CH$_2$*Me*); δ_C (400 MHz, $CDCl_3$) 173.11, 171.50, 171.37, 157.38 (q, *J* 35.9), 115.7 (q, *J* 289.1), 66.69, 66.04, 61.53, 48.47, 48.28, 42.68, 42.32, 33.87, 33.67, 30.32, 30.10, 25.88, 22.86, 22.01, 21.69, 18.30, 18.27, 16.52, 16.16, 14.07, 13.98.

4.3.13. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}alaninate (4f), mixture of diastereomers, ratio 1:1. Yield 72%, white solid, mp 96–97 °C [Found: C, 57.05; H, 5.51. $C_{19}H_{23}F_3N_2O_4$ requires C, 56.99; H, 5.79%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.50 (5H, m, Ph), 5.9, 6.4 (1H, br, N*H*), 4.41–4.52 (1H, m, C*H*), 4.10 (2H, q, *J* 7.1 Hz, COOCH_2Me), 3.75–3.90 (1H, m, *H*-5), 3.21–3.42 (1H, m, *H*-5), 2.52–2.64 (1H, m, *H*-2), 2.20–2.40 (1H, m, *H*-2), 1.72–1.87 (2H, m, *H*-3), 1.55–1.69 (1H, m, *H*-4), 1.38–1.52 (1H, m, *H*-4), 1.15–1.4 (6H, m, *Me*, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.76, 172.43, 170.32, 169.98, 157.8 (q, *J* 36.0), 136.79, 135.68, 129.45, 129.20, 128.37, 128.28, 127.31, 127.78, 116.8 (q, *J* 289.2), 69.86, 61.38, 61.26, 48.74, 48.67, 43.61, 43.18 (m), 34.52, 34.07, 23.43, 23.14, 18.66, 18.18, 18.06, 17.59, 14.04, 13.94.

4.3.14. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}phenylalaninate (4g and 4h). Yield 84%, ratio of the diastereomers 1:1.

Diastereomer 1: white solid, mp 96–97 °C [Found: C, 63.05; H, 5.61. $C_{25}H_{27}F_3N_2O_4$ requires C, 63.02; H, 5.71%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.41 (6H, m, Ph and Ph), 6.78–7.01 (4H, m, Ph), 6.2 (1H, br, N*H*), 4.68–4.75 (1H, m, C*H*), 4.00 (2H, q, *J* 7.1 Hz, $COOCH_2CH_3$), 3.63–3.75 (1H, m, *H*-5), 3.25–3.35 (1H, m, *H*-5), 3.15–3.23 (1H, m, CH_2Ph), 2.73–2.85 (1H, m, CH_2Ph), 2.33–2.45 (1H, m, *H*-2), 2.03–2.12 (1H, m, *H*-2), 1.60–1.75 (2H, m, *H*-3), 1.45–1.60 (1H, m, *H*-4), 1.23–1.38 (1H, m, *H*-4), 1.19 (3H, t, *J* 7.1 Hz, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 170.98, 170.13, 156.5 (q, *J* 35.9), 136.41, 136.17, 129.30, 129.10, 128.28, 128.15, 126.73, 126.66, 116.5 (q, *J* 289.2), 69.87, 61.42, 53.57, 43.53 (m), 37.55, 34.52, 23.44, 18.65, 13.94.

Diastereomer 2: white solid, mp 112–113 °C [Found: C, 63.12; H, 5.67. $C_{25}H_{27}F_3N_2O_4$ requires C, 63.02; H, 5.71%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (Nujol) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.35 (3H, m, Ph), 7.15–7.20 (2H, m, Ph), 6.91–7.05 (3H, m, Ph), 6.76–6.83 (2H, Ph), 5.90 (1H, br, N*H*), 4.70–4.80 (1H, m, C*H*), 4.01 (2H, q, *J* 7.1 Hz, COOCH_2Me), 3.63–3.74 (1H, m, *H*-5), 3.12–3.21 (1H, m, *H*-5), 2.70–2.97 (2H, m, CH_2Ph), 2.40–2.50 (1H, m, *H*-2), 2.20–2.38 (1H, m, *H*-2), 1.62–1.75 (2H, m, *H*-3), 1.43–1.57 (1H, m, *H*-4), 1.23–1.35 (1H, m, *H*-4), 1.1 (3H, t, *J* 7.1 Hz, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 171.03, 170.22, 156.6 (q, *J* 35.9), 136.50, 136.21, 129.33, 129.09, 128.28, 128.13, 126.68, 126.65, 116.4 (q, *J* 289.2), 69.89, 61.43, 53.61, 43.49 (m), 37.56, 34.52, 23.47, 18.44, 13.97.

4.3.15. Ethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}methioninate (4i), mixture of diastereomers, ratio 1:1. Yield 68%, yellow oil [Found: C, 54.50; H, 5.55. $C_{21}H_{27}F_3N_2O_4S$ requires C, 54.77; H, 5.91%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2990, 1730, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.20–7.50 (5H, m, Ph), 6.4, 6.2 (1H, br, N*H*), 4.52–4.67 (1H, m, C*H*), 4.07–4.15 (2H, m, COOCH_2Me), 3.75–3.90 (1H, m, *H*-5), 3.21–3.40 (1H, m, *H*-5), 2.50–2.60 (1H, m, *H*-2), 2.32–2.48 (3H, m, *H*-2 and $CH_2CH_2SCH_3$), 2.15–2.29 (2H, m, C$H_2$$CH_2$SMe), 1.95–2.03 (3H, s, CH_2CH_2S*Me*), 1.67–1.83 (2H, m, *H*-3), 1.52–1.63 (1H, m, *H*-4), 1.26–1.40 (1H, m, *H*-4), 1.15–1.25 (3H, m, $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 174.20, 169.52, 158.00 (q, *J* 35.9), 137.14, 129.11, 128.11, 126.73, 116.5 (q, *J* 289.3), 70.08, 61.31, 56.89, 42.36 (m), 34.77, 24.50, 23.75, 23.14, 22.88, 18.32 (C-3), 13.98.

4.3.16. Diethyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}glutamate (4j), mixture of diastereomers, ratio 1:1. Yield 69%, yellow oil [Found: C, 56.50; H, 6.05. $C_{23}H_{29}F_3N_2O_6$ requires C, 56.78; H, 6.01%]; R_f (50% EtOAc/hexane) 0.50; ν_{max} (liquid film) 2990, 1720, 1690, 1680 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.23–7.50 (5H, m, Ph), 6.4, 6.1 (1H, br, N*H*), 4.47–4.56 (1H, m, C*H*), 4.00–4.17 (4H, m, $COOCH_2CH_3$ and $COOCH_2CH_3$), 3.77–3.90 (1H, m, *H*-5), 3.24–3.40 (1H, m, *H*-5), 2.50–2.60 (1H, m, *H*-2), 2.20–2.44 (3H, m, *H*-2 and CH_2CH_2COOEt), 2.13–2.18 (2H, m, CH_2CH_2COOEt), 1.73–1.90 (2H, m, *H*-3), 1.56–1.67 (1H, m, *H*-4), 1.34–1.50 (1H, m, *H*-4), 1.15–1.28 (6H, m, $CH_2CH_2COOCH_2$*Me* and $COOCH_2$*Me*); δ_C (400 MHz, $CDCl_3$) 172.30, 172.49, 171.53, 171.13, 170.62, 170.28, 157.53 (q, *J* 35.9), 136.40, 135.58, 129.33, 129.18, 128.45, 128.30, 127.23, 126.80, 116.3 (q, *J* 289.7), 69.77, 69.73, 61.46, 61.32, 60.43, 60.28, 52.14, 50.00, 43.47, 43.02 (m), 34.35, 34.00, 29.93, 27.03, 26.63, 23.35, 23.02, 18.50, 18.03, 13.94.

4.3.17. Methyl *N*-{[2-phenyl-1-(trifluoroacetyl)piperidin-2-yl]carbonyl}-L-phenylalaninate (4k and 4l). Yield 84%, ratio of the diastereomers 1:1.

Diastereomer 1: colorless oil, crystallizes on standing [Found: C, 62.35; H, 5.45. $C_{24}H_{25}F_3N_2O_4$ requires C, 62.33; H, 5.45%]; R_f (50% EtOAc/hexane) 0.55; ν_{max} (liquid film) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.2–7.34 (6H, m, Ph and Ph), 6.98–7.05 (4H, m, Ph), 6.2 (1H, br, N*H*), 4.78–4.85 (1H, m, C*H*), 3.72–3.82 (1H, m, *H*-5), 3.65 (3H, s, COO*Me*), 3.3–3.4 (1H, m, *H*-5), 3.15–3.23 (1H, m, CH_2Ph), 2.9–2.97 (1H, m, CH_2Ph), 2.42–2.53 (1H, m, *H*-2), 2.08–2.18 (1H, m, *H*-2), 1.70–1.85 (2H, m, *H*-3), 1.58–1.69 (1H, m, *H*-4), 1.34–1.44 (1H, m, *H*-4); δ_C (400 MHz, $CDCl_3$) 171.50, 170.19, 156.5 (q, *J* 35.9), 136.36, 136.03, 129.17, 129.08, 128.33, 128.13, 126.85, 126.66, 116.4 (q, *J* 289.1), 69.80, 53.44, 52.22, 43.50 (m), 37.44, 34.48, 23.38, 18.58.

Diastereomer 2: colorless oil, crystallizes on standing [Found: C, 62.30; H, 5.48. $C_{24}H_{25}F_3N_2O_4$ requires C, 62.33; H, 5.45%]; R_f (50% EtOAc/hexane) 0.45; ν_{max} (liquid film) 2960, 1730, 1700, 1690 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.30–7.42 (3H, m, Ph), 7.21–7.27 (2H, m, Ph), 7.05–7.14 (3H, m, Ph), 6.84–6.90 (2H, m, Ph), 6.0 (1H, br, N*H*), 4.82–4.89 (1H, m, C*H*), 3.71–3.80 (1H, m, *H*-5), 3.65 (3H, s, *Me*), 3.2–3.29 (1H, m, *H*-5), 2.95–3.08 (2H, m, CH_2Ph), 2.46–2.56 (1H, m, *H*-2), 2.28–2.35 (1H, m, *H*-2), 1.65–1.82 (2H, m, *H*-3), 1.54–1.65 (1H, m, *H*-4), 1.31–1.42 (1H, m, *H*-4); δ_C (400 MHz, $CDCl_3$) 171.54, 169.90, 157.00 (q, *J* 36.0), 135.76, 135.43, 129.30, 128.91, 128.39, 127.05, 126.71, 116.5 (q, *J* 289.1), 69.84, 53.01, 51.99, 43.50 (m), 37.19, 34.13, 23.15, 18.34.

4.3.18. 7-Phenyl-1-(trifluoroacetyl)-2,3,4,5-tetrahydro-1*H*-azepine (5a). Yield 68%, yellow oil [Found: C, 62.33; H,

5.34. $C_{14}H_{14}F_3NO$ requires C, 62.54; H, 5.24%]; R_f (30% EtOAc/hexane) 0.70; ν_{max} (liquid film) 1690, 1640 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 7.25–7.40 (5H, m, Ph), 6.45 (1H, m, C*H*), 4.4–4.7 (2H, m, *H*-6), 2.3–2.4 (2H, m, *H*-3), 1.80–2.13 (3H, m, *H*-4, *H*-5), 1.31–1.45 (1H, m, *H*-5); δ_C (400 MHz, $CDCl_3$) 154.5 (q, *J* 36.1), 142.51, 136.50, 128.67, 128.33, 127.30, 124.09, 115.9 (q, *J* 289.1), 48.80, 28.66, 26.59, 23.72.

4.3.19. 2-Methylene-1-(trifluoroacetyl)azepane (5b). Yield 71%, yellow oil [Found: C, 52.23; H, 5.74. $C_9H_{12}F_3NO$ requires C, 52.17; H, 5.84%]; ν_{max} (liquid film) 1690, 1650 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 5.15 (1H, s, H*H*C=C), 5.03 (1H, s, *H*HC=C), 3.57–3.68 (2H, m, *H*-6), 2.40–2.50 (2H, m, *H*-2), 1.71–1.81 (2H, m, *H*-3), 1.55–1.69 (4H, m, *H*-4 and *H*-5); δ_C (400 MHz, $CDCl_3$) 155.6 (q, *J* 36.3), 138.15, 116.90 (q, *J* 289.1), 109.82, 48.56, 34.29, 28.13, 26.08, 23.65.

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Novel tandem multi-component reactions in the stereoselective synthesis of highly functionalised pyrrolidines

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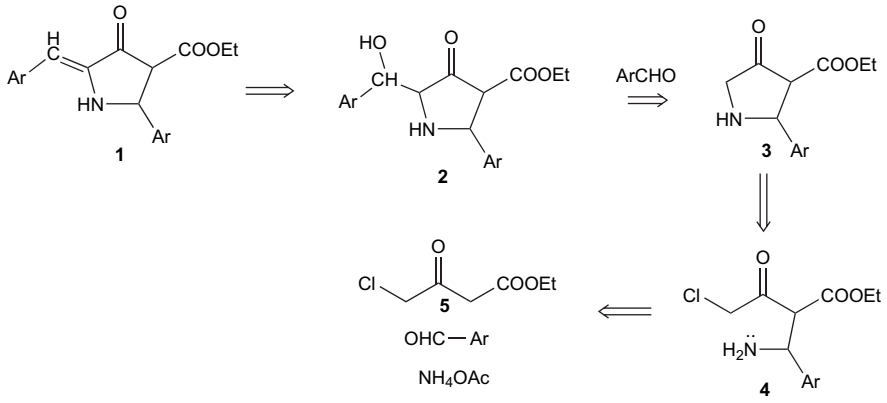
Abstract—The four-component reaction of ethyl 4-chloroacetoacetate with aromatic aldehydes and ammonium acetate in a 1:2:1 molar ratio provided a simple and rapid access to highly functionalised pyrrolidines, ethyl 1-acetyl-4-hydroxy-5-[hydroxy(aryl)methyl]-2-aryl-2,3-dihydro-1*H*-pyrrole-3-carboxylates stereoselectively. This transformation presumably occurs via a tandem Mannich-substitution-acetylation-aldol sequence of reactions.

1. Introduction

Pyrrolidines constitute an important class of five-membered ring heterocycles with remarkable biological properties,[1] such as antitumour,[2] analgesic,[3,4] antidepressant,[5] antihistaminic,[6] anti-inflammatory[7] and anti-parkinson.[8,9] Apart from its pharmaceutical applications, the pyrrolidine moiety has also witnessed wide use as a chiral auxiliary for asymmetric synthesis[10] and as a catalyst for asymmetric epoxidation.[11] The widespread occurrence of substituted pyrrolidine motif amongst biologically significant natural products and pharmaceuticals has stimulated great interest in its synthetic methods.[12] Numerous strategies for the synthesis of pyrrolidines such as intramolecular cyclisations involving radical,[13] anionic[14] or transition metal catalysed[15] processes are known.

Tandem reactions[16–18] are multi-step one pot processes providing a rapid access to complex molecules without isolation and purification of the products of the intermediates, thus rendering the synthetic protocols, efficient, elegant, expedient, economic and eco-friendly. Hence, a one pot tandem sequence of reactions was planned for the synthesis of ethyl 4-oxo-2-aryl-5-[(*E*)-1-arylmethylidene]-3-pyrrolidine-carboxylates (**1**) by a four-component reaction of ethyl 4-chloroacetoacetate (**5**), aromatic aldehydes and ammonium acetate (Scheme 1). Pyrrolidine (**1**), with unsaturated carbonyl and ester functionalities, could be a useful synthon



Scheme 1. Retrosynthesis of pyrrolidines (**1**).

Keywords: Pyrrolidine; Ethyl 4-chloroacetoacetate; Tandem; Mannich; Aldol; X-ray; Aldehyde.
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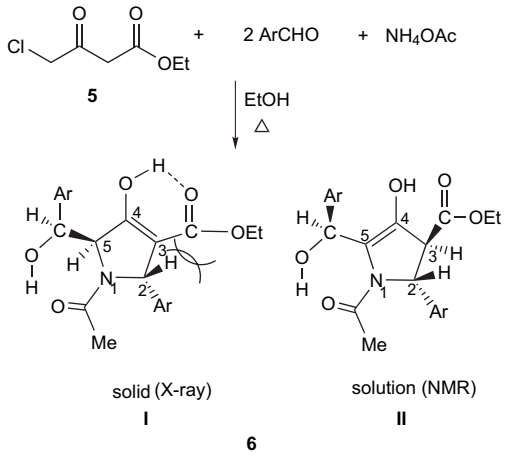
in further transformations that lead to more elaborate heterocycles.

2. Results and discussion

The reaction of ethyl 4-chloroacetoacetate (**5**), aromatic aldehydes and ammonium acetate was carried out in ethanol with initial heating, followed by stirring at ambient temperature. This reaction afforded pyrrolidines (**6**) diastereoselectively, which are different from the anticipated **1** in that (i) pyrrolidines (**6**) were obtained in aldol form and (ii) the pyrrolidine nitrogen has been acetylated during the reaction (Scheme 2).



6	Ar	Yield (%)
a	C_6H_5	51
b	4-MeC_6H_4	60
c	4-ClC_6H_4	62
d	4-MeOC_6H_4	54
e	4-FC_6H_4	54
f	2-MeC_6H_4	48
g	2-ClC_6H_4	65
h	2-MeOC_6H_4	47

Scheme 2. Formation of pyrrolidines (**6**) by tandem reactions.

The structure of the pyrrolidine in solution (Scheme 2) has been arrived at from one- and two-dimensional NMR spectroscopic data as illustrated for a representative example **6a**. The protons, H-2 and H-3, give a pair of doublets at 5.58 and 4.75 ppm, respectively, with a *J* value of 2.7 Hz. The small *J* value of 2.7 Hz for the protons in the five-membered ring points to a *trans* relationship between these protons, which in turn, shows that the 2-phenyl and the 3-ester groups are also *trans* to each other. The hydroxyl and methine protons of the –CHOH group linked to C-5 of the pyrrolidine ring give doublets with a *J* value of 9.8 Hz at 6.83 and 5.36 ppm, respectively. The assignment of these protons was confirmed by the addition of D_2O, which led to disappearance of the doublet at 6.83 ppm and the emergence of a clear singlet at 5.36 ppm. The methyl and methylene (diastereotopic) protons of the ester functionality give a triplet (*J*=7.2 Hz) and a multiplet at 1.02 and 3.89–4.03 ppm, respectively. The methyl protons of the *N*-acetyl and the OH proton linked to C-4 give a singlet at 1.48 ppm and a broad

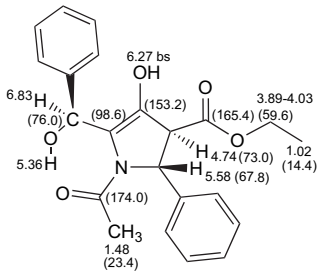


Figure 1. ^1H and ^{13}C chemical shifts of **6a**.

signal at 6.27 ppm, respectively. The OH signal at 6.27 ppm in $CDCl_3$ moves downfield to 6.70 ppm upon addition of a drop of DMSO-d_6, which discloses the absence of significant intramolecular hydrogen bonding in $CDCl_3$ solution. An unambiguous assignment of the carbon signals of the proton bearing carbons (except aromatic) viz., C-2, C-3, CH_3(CO), CH_3–CH_2 and CH(OH) was made on the basis of the proton chemical shifts and the respective C,H-COSY correlations. The proton and carbon chemical shifts, and HMBC correlations are depicted in Figure 1 and 2, respectively. The above observations, in conjunction with the chemical shifts of C-4 and C-5 and the HMBC correlations, are all in accord with structure **II** depicted in Figure 2.

The structure of the pyrrolidine determined by X-ray crystallographic studies (Fig. 3) shows that **6a** exists in another enol form **I** in the solid state (Scheme 2). Probably, crystal packing and intermolecular interactions favour tautomer **I** in the solid state, while the stability of the individual tautomeric molecules lead to the preference of tautomer **II** in solution. The 2-aryl group and the 3-ester functionality of enol **II** may interact sterically to a lesser extent than those of the enol form **I**, as in the former, the larger dihedral angle between

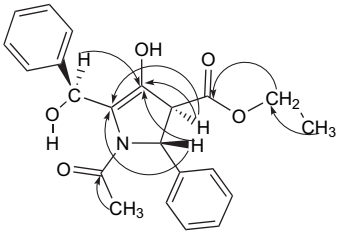


Figure 2. HMBC correlations of **6a**.

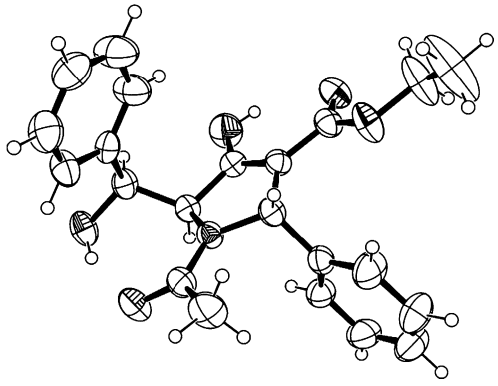


Figure 3. X-ray crystal structure of **6a**.

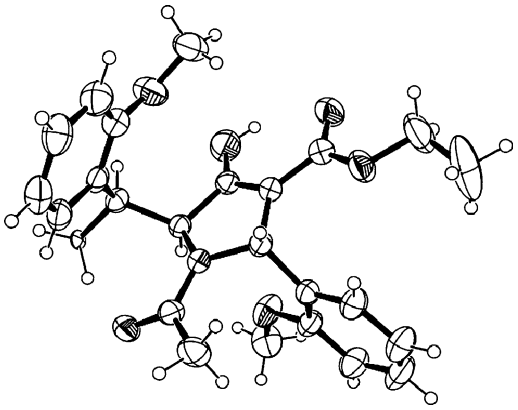


Figure 4. X-ray crystal structure of **6h**.

the aryl and ester groups minimises steric interaction than in the latter. The structure for **6h** in solid state deduced from X-ray crystallographic studies also is similar to **6a** (Fig. 4).

2.1. Product selectivity

The reaction of ethyl 4-chloroacetoacetate, substituted aromatic aldehydes and ammonium acetate could, in principle, afford either a pyrrolidine [(an aldol **2** or an α,β-unsaturated system **1**], or a 2,6-diaryl-5-chloro-4-ethoxycarbonylpiperidin-4-one (**7**, Fig. 5). It is of interest to find that the reaction is product-selective furnishing exclusively the *N*-acetylpyrrolidine aldol (**6**). The intramolecular substitution in **4** furnishing pyrrolidine (**6**) is probably favoured by entropy over the formation of the piperidone (**7**). The formation of the latter would require an intermolecular reaction between the initially formed amine (**4**) and the aromatic aldehyde forming an iminium ion followed by ring closure.

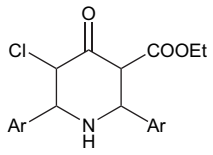


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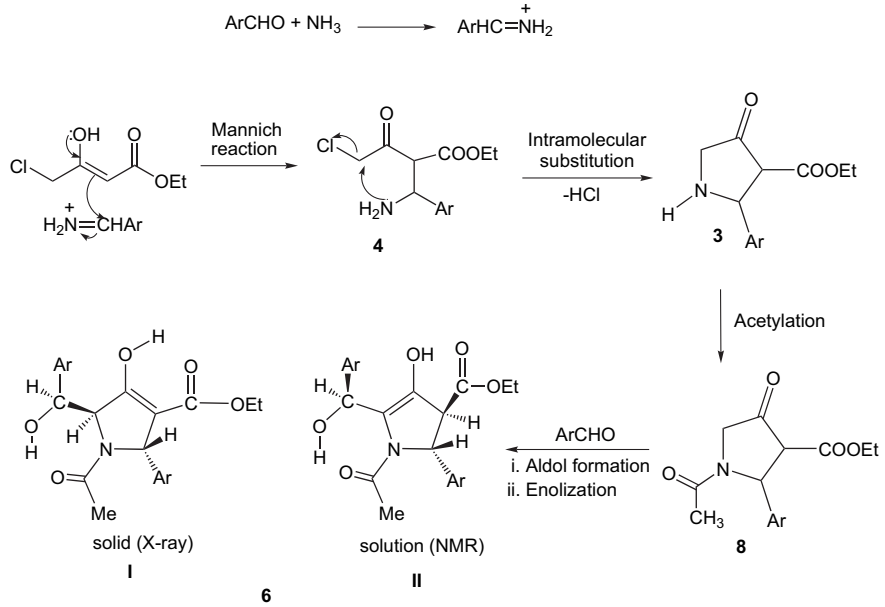
Figure 5.

A plausible mechanism for the formation of **6** is depicted in Scheme 3. The acetylation of **3** leading to **8** appears surprising under the reaction conditions. The reaction mixture after the initial heating was allowed to proceed at ambient temperature in an open vessel for 8–12 days, which led to a slow evaporation of the ethanol solvent and concentration of the reaction mixture to a paste. Probably, the hydrochloric acid liberated during the displacement reaction and the acetate present in the reaction mixture effect the N-acetylation of **3**. This reaction proceeds very slowly, as the nitrogen can also be protonated leading to a low concentration of the free amine, hence a long reaction time, viz. 8–12 days is required to afford yields of 48–62% that are good considering the number of steps involved.

2.2. Stereoselectivity

In the enol form of pyrrolidines (**6**) found in solution, there are three stereogenic centres; suggesting eight possible stereoisomers. However, it is found that one diastereomer is exclusively formed in this reaction. The *trans*-relationship between the 2-aryl and 3-ester functions of the enol form **II** of **6** is ascribable to its enhanced stability relative to *cis*, as the latter is bound to suffer from steric interactions between the almost eclipsing ester and aryl groups. Correspondingly, the transition state leading to the *trans*-product might require less free energy of activation than its *cis* isomer. From the absence of even trace amounts of the *cis*-diastereomer of **6** as found from NMR spectroscopic data of solution obtained by dissolving the crystals of **6** in



Scheme 3. Mechanism for the formation of pyrrolidines (**6**).

$CDCl_3$, it is clear that the enolisation at C-3 found for **6** in the solid state does not lead to isomerisation of the *trans* isomer to the *cis* in solution. The stereoselectivity observed from the aldol reaction of **8** with the aldehyde to furnish aldol (**6**) with one particular relative configuration for the hydroxymethyl carbon attached to C-5 relative to that of the C-2 and C-3 presumably arises from the difference in the steric interactions and/or extent of hydrogen bonding on the diastereo faces of the pyrrolidine.

3. Conclusion

The present work describes a four-component one pot tandem sequence providing a rapid access to the highly substituted pyrrolidines (**6**) in a stereoselective manner from simple starting materials under mild reaction conditions. In view of the importance of pyrrolidine sub-structure as a pharmacophore, investigations are in progress in our group with a view to (i) construct more complex heterocycles using pyrrolidines (**6**) as synthons and (ii) synthesise enantiomerically pure/enriched pyrrolidines using this protocol.

4. Experimental

4.1. General methods

Melting points of the pyrrolidines are uncorrected. Unless stated otherwise, solvents and chemicals were obtained from commercial sources and used without further purification. Flash chromatography was performed on silica gel (230–400 mesh). NMR spectra were recorded on a 300 MHz Bruker (Avance) NMR spectrometer. Chemical shifts were reported as δ values (ppm) relative to tetramethylsilane. Infrared spectra were recorded in a JASCO FTIR spectrometer. Elemental analyses of **6** were performed on a Perkin–Elmer 2400 Series II Elemental CHNS Analyser. The products, **6a** and **6h**, were recrystallised from ethanol.

4.2. General procedure for the preparation of ethyl 1-acetyl-4-hydroxy-5-[hydroxy-(aryl)-methyl]-2-aryl-2,3-dihydro-1*H*-pyrrole-3-carboxylates (6)

Ethyl 4-chloroacetoacetate (0.609 g, 3.7 mmol) was dissolved in ethanol (10 mL). Freshly distilled aromatic aldehyde (7.4 mmol) and ammonium acetate (0.285 g, 3.7 mmol) were added and the solution was heated until the solution turned yellow. The reaction mixture was then kept at room temperature for 8–12 days to ensure completion of the reaction, which was monitored using TLC. The reaction mixture was extracted with chloroform (25 mL), washed with water, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel using pet. ether/ethyl acetate (4:1 v/v) as the eluent.

4.2.1. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(phenyl)-methyl]-2-phenyl-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6a)

Isolated as a pale yellow solid (0.719 g, 51%), mp=210 °C; IR (KBr) ν 3652, 3322, 1677, 1623, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.02 (3H, t, J=7.2 Hz), 1.48 (3H, s), 3.89–4.03 (2H, m), 4.75 (1H, d, J=2.7 Hz), 5.36 (1H, d, J=9.8 Hz), 5.58 (1H, d, J=2.7 Hz), 6.27 (1H, br s), 6.83 (1H, d, J=9.8 Hz), 7.10–7.31 (10H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.4, 23.4, 59.7, 67.9, 73.1, 76.0, 98.6, 125.9, 127.7, 127.9, 128.0, 128.3, 128.6, 139.6, 142.7, 153.2, 165.4, 174.1.

Anal. Calcd for $C_{22}H_{23}NO_5$: C, 69.28; H, 6.08; N, 3.67; obsd C, 69.29; H, 6.17; N, 3.79.

4.2.2. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(4-methyl-phenyl)-methyl]-2-(4-methyl-phenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6b)

Isolated as a pale yellow solid (0.909 g, 60%), mp=177 °C; IR (KBr) ν 3405, 3309, 1670, 1616, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.06 (3H, t, J=7.2 Hz), 1.50 (3H, s), 2.28 (3H, s), 2.36 (3H, s), 3.90–4.02 (2H, m), 4.78 (1H, d, J=2.6 Hz), 5.33 (1H, d, J=9.1 Hz), 5.55 (1H, d, J=2.6 Hz), 6.22 (1H, br s), 6.76 (1H, d, J=9.1 Hz), 7.00 (4H, AB pattern), 7.14 (4H, AB pattern); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.5, 21.5, 21.6, 23.5, 59.6, 67.7, 73.0, 75.9, 98.4, 125.8, 127.6, 129.0, 129.2, 136.6, 137.4, 137.5, 139.9, 153.3, 165.5, 174.1.

Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42; obsd C, 70.36; H, 6.53; N, 3.51.

4.2.3. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(4-chloro-phenyl)-methyl]-2-(4-chlorophenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6c)

Isolated as a pale yellow solid (1.03 g, 62%), mp=208 °C; IR (KBr) ν 3494, 3353, 1681, 1619, 1560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.07 (3H, t, J=7.2 Hz), 1.49 (3H, s), 3.93–4.03 (2H, m), 4.78 (1H, d, J=2.9 Hz), 5.23 (1H, d, J=9.8 Hz), 5.52 (1H, d, J=2.9 Hz), 6.70 (1H, d, J=9.8 Hz), 7.05 (2H, d, J=8.4 Hz), 7.21 (4H, AB pattern), 7.30 (2H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.4, 23.4, 59.9, 67.2, 73.0, 75.7, 98.1, 127.3, 128.5, 128.9, 129.0, 133.8, 138.0, 141.2, 153.1, 165.2, 174.0.

Anal. Calcd for $C_{22}H_{21}Cl_2NO_5$: C, 58.68; H, 4.70; N, 3.11; obsd C, 58.71; H, 4.65; N, 3.16.

4.2.4. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(4-methoxy-phenyl)-methyl]-2-(4-methoxy-phenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6d)

Isolated as a pale yellow solid (0.881 g, 54%), mp=159 °C; IR (KBr) ν 3480, 3359, 1678, 1616, 1563 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.05 (3H, t, J=7.2 Hz), 1.52 (3H, s), 3.76 (3H, s), 3.83 (3H, s), 3.89–4.00 (2H, m), 4.75 (1H, d, J=2.4 Hz), 5.30 (1H, d, J=9.0 Hz), 5.53 (1H, d, J=2.4 Hz), 6.30 (1H, br s), 6.76 (2H, d, J=8.4 Hz), 6.85 (2H, d, J=8.4 Hz), 6.98 (1H, d, J=9.0 Hz), 7.01 (2H, d, J=8.4 Hz), 7.18 (2H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.5, 23.5, 55.6, 59.6, 67.3, 72.9, 75.8, 98.6, 113.7, 113.9, 127.1, 128.8, 131.7, 135.0, 153.1, 159.2, 159.3, 165.5, 174.1.

Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17; obsd C, 65.32; H, 6.11; N, 3.22.

4.2.5. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(4-fluorophenyl)-methyl]-2-(4-fluorophenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6e)

Isolated as a pale yellow solid (0.833 g, 54%), mp=196 °C; IR (KBr) ν 3492, 3355, 1679, 1621, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 1.04 (3H, t, J=7.2 Hz), 1.50 (3H, s), 3.88–4.10 (2H, m), 4.74 (1H, d, J=2.6 Hz), 5.32 (1H, d, J=8.4 Hz), 5.55 (1H, d, J=2.6 Hz), 6.45 (1H, br s), 6.92 (1H, d, J=8.4 Hz), 7.05–7.27 (8H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.4, 23.4, 59.8, 67.2, 73.0, 75.8, 98.2, 115.2, 115.6, 127.6, 129.3, 135.2, 138.5, 153.2, 160.9, 164.2, 174.1.

Anal. Calcd for $C_{22}H_{21}F_2NO_5$: C, 63.30; H, 5.07; N, 3.36; obsd C, 63.33; H, 4.98; N, 3.31.

4.2.6. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(2-methylphenyl)-methyl]-2-(2-methyl-phenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6f)

Isolated as a pale yellow solid (0.727 g, 48%), mp=167 °C; IR (KBr) ν 3478, 3315, 1673, 1626, 1571 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, J=7.2 Hz), 1.56 (3H, s), 2.43 (3H, s), 2.48 (3H, s), 3.92 (2H, q, J=7.2 Hz), 4.21 (1H, br s), 5.38 (1H, d, J=3.0 Hz), 5.54 (1H, d, J=3.0 Hz), 5.84 (1H, s), 6.78–6.93 (1H, m), 7.02–7.10 (3H, m), 7.17–7.26 (3H, m), 7.58–7.61 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.3, 19.7, 19.8, 23.0, 59.6, 62.1, 69.5, 70.4, 99.3, 126.0, 126.6, 126.9, 127.2, 127.6, 128.2, 130.2, 131.2, 136.0, 136.2, 138.0, 141.6, 153.5, 165.7, 172.5.

Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.40; H, 6.65; N, 3.42; obsd C, 70.45; H, 6.62; N, 3.39.

4.2.7. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(2-chlorophenyl)-methyl]-2-(2-chlorophenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6g)

Isolated as a pale yellow solid (1.08 g, 65%), mp=188 °C; IR (KBr) ν 3421, 3278, 1671, 1631, 1569 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.98 (3H, t, J=7.2 Hz), 1.62 (3H, s), 3.83–4.00 (2H, m), 5.18 (1H, d, J=7.5 Hz), 5.60 (1H, s), 5.66 (1H, s), 5.84 (1H, d, J=7.5 Hz), 7.04 (1H, d, J=7.0 Hz), 7.12–7.22 (2H, m), 7.25–7.39 (5H, m), 7.59 (1H, dd, J=7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.3, 22.9, 59.7, 62.5, 70.3, 71.7, 127.0, 128.1, 128.5, 129.2, 129.4, 129.6, 130.0, 132.8, 137.6, 140.6, 153.5, 165.1, 174.0.

Anal. Calcd for $C_{22}H_{21}Cl_2NO_5$: C, 58.68; H, 4.70; N, 3.11; obsd C, 58.62; H, 4.73; N, 3.07.

4.2.8. Ethyl 1-acetyl-4-hydroxy-5-[hydroxy(2-methoxyphenyl)-methyl]-2-(2-methoxy-phenyl)-2,3-dihydro-1*H*-pyrrole-3-carboxylate (6h)

Isolated as a pale yellow solid (0.767 g, 47%), mp=154 °C; IR (KBr) ν 3415, 3315, 1673, 1616, 1562 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ_H 0.95 (3H, t, J=7.2 Hz), 1.54 (3H, s), 3.68 (3H, s), 3.77 (3H, s), 3.82–4.11 (2H, m), 5.48 (1H, s), 5.67 (1H, d, J=8.7 Hz), 6.00 (1H, br s), 6.28 (1H, br s), 6.76–6.86 (3H, m), 6.94–6.99 (2H, m), 7.16 (1H, t, J=8.0 Hz), 7.27 (1H, t, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_c 14.4, 22.5, 55.0, 55.9, 59.2, 71.1, 72.3, 110.3, 120.6, 127.8, 128.4, 129.0, 155.4, 156.6, 157.0, 165.8, 173.5.

Anal. Calcd for $C_{24}H_{27}NO_7$: C, 65.29; H, 6.16; N, 3.17; obsd C, 65.24; H, 6.19; N, 3.12.

4.3. X-ray crystallographic determination of compounds 6a and 6h

Data were collected at room temperature on an Enraf-Nonius MACH 3 four-circle diffractometer (Mo Kα radiation, λ=0.71073 Å) for compounds **6a** and **6h**. The data collection, integration and data reduction for **6a** and **6h** were performed using CAD-4 EXPRESS[19] and XCAD4[20] programs and an empirical absorption correction was applied using ψ scan method.[21] The unit cell parameters were determined by a least square fitting of 25 randomly selected strong reflections and an empirical absorption correction was applied using the azimuthal scan method. The structures were solved by direct methods (SHELXS 97)[22] and subsequent Fourier synthesis and refined by full matrix least squares on SHELXL 97[23] for all non-hydrogen atoms for **6a** and **6h**. All hydrogen atoms were placed in calculated positions.

Compound ***6a***—$C_{22}H_{23}NO_5$, M=381.41, monoclinic, space group $P2_1/C$, a=8.840(8) Å, b=21.463(14) Å, c=11.533(9) Å, V=2049.2(5) $Å^3$, Z=4, $f(000)$=808, μ=0.088 mm^{-1}, D_c=1.236 mg/m^3. The reflections collected were 4057 of which 3592 unique [$R_{(int)}$=0.00294]; 1988 reflections $I>2\sigma(I)$, R_1=0.0551 and wR_2=0.1554 for 1988 [$I>2\sigma(I)$] and R_1=0.1214 and wR_2=0.1923 for all (3592) intensity data. Goodness of fit=1.015, residual electron density in the final Fourier map was 0.412 and −0.311 $eÅ^{-3}$. CCDC number is 296789.

Compound ***6h***—$C_{24}H_{27}NO_7$, M=441.18, monoclinic, space group $P2_1/n$, a=11.640(5) Å, b=11.995(8) Å, c=17.570(14) Å, β=107.19° (20) V=2343(5) $Å^3$, Z=4, $f(000)$=936, μ=0.092 mm^{-1}, D_c=1.251 mg/m^3. The reflections collected were 4789 of which 4123 unique [$R_{(int)}$=0.0166]; 2490 reflections $I>2\sigma(I)$, R_1=0.0481 and wR_2=0.1265 for 2490 [$I>2\sigma(I)$] and R_1=0.0971 and wR_2=0.1526 for all (4123) intensity data. Goodness of fit=1.0120, residual electron density in the final Fourier map was 0.36 and −0.40 $eÅ^{-3}$. CCDC number is 296790.

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Syriacin, a novel unusual sulfated ceramide glycoside from the freshwater sponge *Ephydatia syriaca* (Porifera, Demospongiae, Spongillidae)

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Abstract—Syriacin, a novel unusual sulfated ceramide glycoside with branched very-long-chain fatty acid, i.e., (all *Z*)-34*S*-methylhexatriaconta-5,9,12,15,18,21-hexaenoic acid, has been isolated from the freshwater sponge *Ephydatia syriaca*. Its structure was identified by means of extensive spectroscopic analysis (IR, UV, 2D NMR, MS, CD) and chemical degradation. Syriacin showed antifeeding activity against goldfish at natural concentration (~10 μg/ml).

1. Introduction

Sponges, an ancient and highly successful group of animals, common inhabitants of the benthos, have been living in the waters of the world for more than 600 million years, and can be found in all marine and many freshwater habitats.[1] In addition to many marine forms, the freshwater sponges belonging to the genus *Ephydatia* are typical representatives of Spongillidae and occur in different rivers and lakes around the world. A few natural compounds have been isolated from this genus.[2] *Ephydatia fluviatilis* contains almost exclusively Δ^5-sterols. In addition, *E. fluviatilis* contains sterols with the 24β configuration, which predominate over the 24α-epimers.[3] Phospholipids and fatty acids were also studied in *E. fluviatilis*.[4] Multibranched, polyunsaturated and very-long-chain fatty acids have been isolated from *Ephydatia syriaca*.[5,6]

This report is part of our investigation of marine and freshwater sponges[2,4,5] in the framework of a comprehensive program on the chemistry and biotoxicity of natural compounds. We isolated a novel unusual sulfated ceramide, named syriacin, with very-long-chain branched fatty acid having six double bonds.

2. Results and discussion

The extract of the freshwater sponge *E. syriaca*, which was collected in August 2003, in the Jordan River, was subjected to gel filtration chromatography on Sephadex LH-20. The fractions were further purified by gradient RP-HPLC to give glycoside (**1**, see Fig. 1), which was identified by its IR, MS, UV, CD, and ^{1}H and ^{13}C NMR spectroscopic data and by chemical degradation.

The IR spectrum of compound **1** has absorption bands at 3300–3400 (hydroxy groups), 1540, 1640, 3250 (amide),

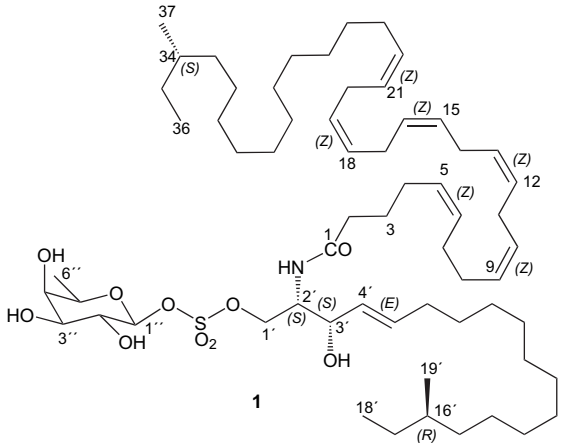

Figure 1. Structure of syriacin (**1**), a sulfated ceramide glycoside from the freshwater sponge *E. syriaca*.

Keywords: Ceramide; Glycoside; Sulfate; Freshwater sponge; *Ephydatia syriaca*; Antifeeding activity.
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1450, 2850, 2900 (the aliphatic chain), and 1070, 1230 (sulfate group) cm^{-1}.

The high-resolution mass spectrum of **1** shows a pseudomolecular ion peak $[M+Na]^+$ at *m/z* 1082.7666, which corresponds to the molecular formula $C_{62}H_{109}NO_{10}S$. The presence of a sulfate group was supported by the ion peaks at *m/z* 96 (SO_4) and 80 (SO_3) in FABMS.

The sulfate group was located at the C-1′ position from low-field shifts of the methylene signals of H-1′ (δ 4.28 and 4.18) and C-1′ (δ 74.2) (chemical shifts of typical ceramide are δ 62.6 and δ 3.94 and/or 3.68, respectively).[7]

The presence of the ester linked sulfo group was further confirmed enzymatically. β-D-Galactosidase from *E. coli* (EC 3.2.1.23) was used to hydrolyze compound **1** to afford fucose (**3**) and sulfoceramide (**1a**). The reaction mixture was lyophilized and then analyzed by FABMS; the corresponding ion at *m/z* 936.7090 $C_{56}H_{99}NO_6SNa$ $[M+Na]^+$ was identified. Although the enzyme used for the hydrolysis was not β-D-fucosidase (EC 3.2.1.38), β-D-galactosidase is known to be insensitive to substitution in position 6 of the substrate[8] and can be used for the purpose.

Another enzyme used for splitting **1** was β-D-glucuronidase (EC 3.2.1.31) from the keyhole limpet, which exhibited a high sulfatase (EC 3.1.6.1) activity. FABMS analysis of the reaction mixture showed that the spectrum contains sulfofucose (**3a**) ion at *m/z* 267.0151 $C_6H_{12}O_8SNa$ $[M+Na]^+$. The two enzymatic reactions thus clearly show that the sulfate group forms a bridge between fucose and the ceramide.

The ^1H NMR spectrum revealed the presence of two secondary methyls at δ 0.82 and 0.83, respectively, six heteroatom-bearing methines, four of them in hexose, and an oxygenated methylene protons at δ 4.18 and 4.28, two trans olefinic protons at δ 5.57 and 5.69, 12 cis olefinic protons (δ 5.38–5.45), and a huge methylene envelope at δ 1.25–1.40 (Table 1). The ^1H NMR spectrum also showed, in the methyl region, two triplets at δ 0.85 and δ 0.86, respectively (ethyl termini). Interpretation of the ^1H–^1H COSY and HMQC spectra resulted in three partial structures, two of which were connected to long aliphatic chains.

The amide broad singlet at δ 6.51 allowed us to assign all the protons of the polar part of the sphingosine through the COSY spectrum. The lack of substitution of the fatty acid residue in α position was revealed by the presence of a characteristic triplet at δ ~2.2 of the α-protons of acyl in the ^1H NMR spectrum of **1**, and an intense correlation peak with the amide NH signal in the ROESY spectrum. In addition, both H_2-2′ and NH were shown to be coupled with the amidic carbon atom at δ 172.4 (C-1) in the HMBC spectrum. This correlation between H-2′ and C-1 not only confirmed the position of the nitrogen atom but also connected the two partial structures through an amide bond. Two olefinic protons at 5.57 and 5.69, respectively were found to be trans configuration, because the coupling constant was 15 Hz.

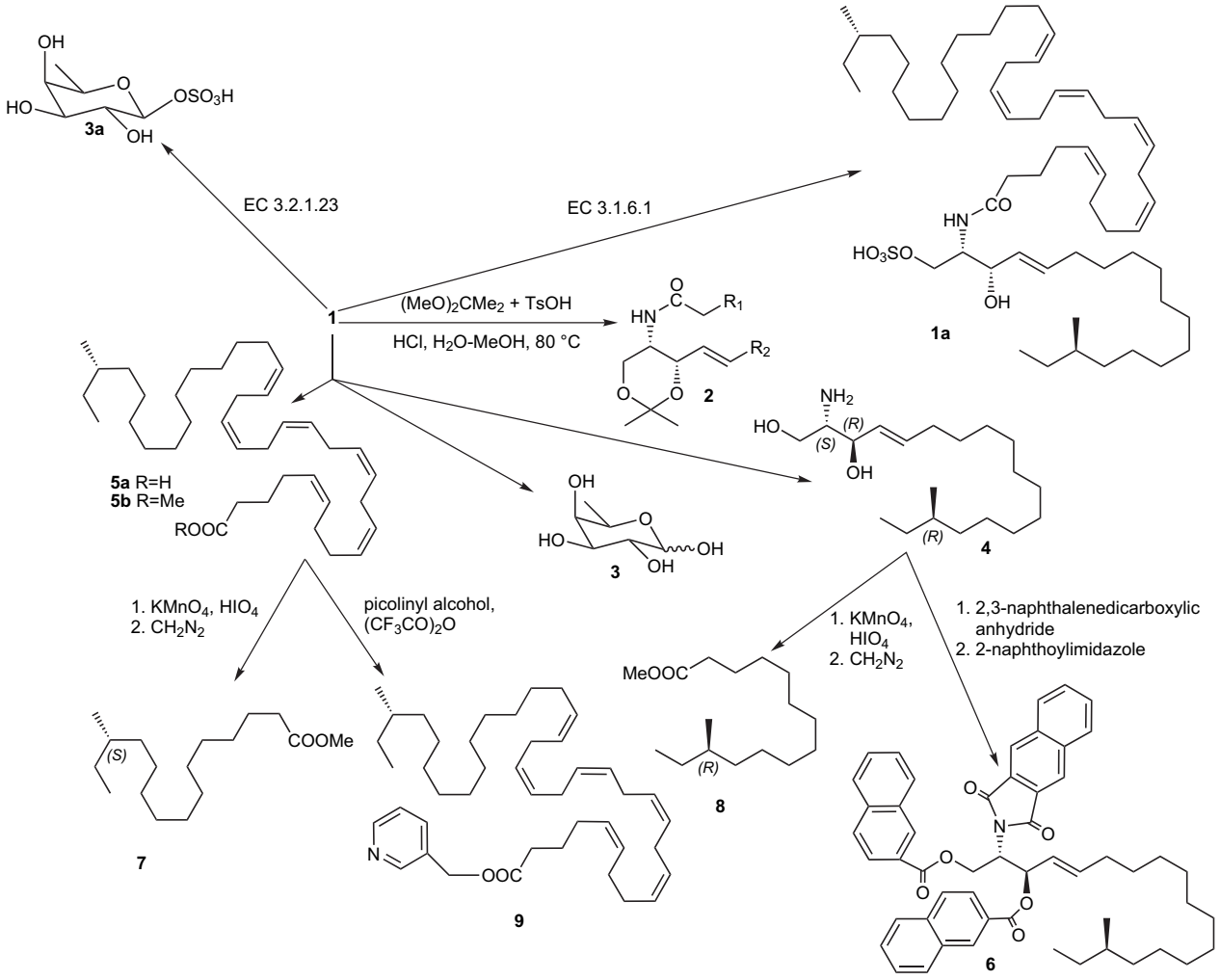
The ^{13}C NMR spectrum of **1** showed 14 olefinic carbons at δ 126–135, one anomeric carbon at δ 101.6, methylene carbons at δ 29.0–31.5, and two secondary methyls (δ 20.7 and 21.2, respectively; both quartets), further supporting the nature of **1**. Additionally, the carbon resonances at δ 74.2, 51.6, 78.3, 131.2, and 134.8 revealed the presence of a dihydroxyaminoene system in **1**.

Table 1. ^1H and ^{13}C NMR data of syriacin (**1**) (measured in $CDCl_3$)

No.	^1H NMR	^{13}C NMR
1	—	172.4
2	2.18 (2H, t, *J*=6.3 Hz)	36.9
3	1.61 (2H, m)	25.6
4, 23	1.90 (4H, m)	27.2–27.9
5, 6, 9, 10, 12, 13, 15, 16, 18, 19, 21, 22	5.38–5.45 (12H, m)	126.0–135.0
7, 8	2.00–2.10 (4H, m)	31.2
11, 14, 17, 20	2.60–2.75 (8H, m)	25.0–26.0
24–32, 35	1.25–1.40 (20H, m)	29.0–31.5
33	1.24 (2H, m)	37.1
34	1.61 (1H, m)	35.4
36	0.85 (3H, t, *J*=7.1 Hz)	12.4
37	0.83 (3H, d, *J*=6.8 Hz)	21.2
1a′	4.18 (1H, dd, *J*=10.5, 5.2 Hz)	74.2
1b′	4.28 (1H, dd, *J*=10.5, 8.4 Hz)	
2′	4.01 (1H, ddd, *J*=8.6, 8.4, 5.2 Hz)	51.6
3′	4.14 (1H, dd, *J*=8.6, 7.2 Hz)	78.3
4′	5.57 (1H, dd, *J*=7.2, 15.0 Hz)	131.2
5′	5.69 (1H, dt, *J*=15.0, 6.9 Hz)	134.8
6′	1.96 (2H, m)	34.3
7′–15′, 17′	1.25–1.40 (20H, m)	29.0–31.5
16′	1.65 (1H, m)	35.4
18′	0.86 (3H, t, *J*=7.2 Hz)	11.6
19′	0.82 (3H, d, *J*=6.7 Hz)	20.7
NH	6.51 (1H, br s)	—
1″	5.28 (1H, d, *J*=7.5 Hz)	101.6
2″	4.26 (1H, dd, *J*=7.5, 8.5 Hz)	73.6
3″	4.39 (1H, dd, *J*=3.4, 8.5 Hz)	75.1
4″	4.15 (1H, dd, *J*=3.4, 1.4 Hz)	74.4
5″	4.42 (1H, dq, *J*=1.4, 6.7 Hz)	72.5
6″	1.52 (1H, d, *J*=6.7 Hz)	16.6

In the saccharide unit, the coupling system in the ^1H–^1H COSY spectrum of **1** started from the anomeric proton signal. This was established by tracing and joining the coupling points among C-1″–C-6″; this revealed contiguous coupling between H-1″ and H-2″, H-2″ and H-3″, H-3″ and H-4″, and H-5″ and 5″-Me. The coupling constants of the anomeric protons H-1″ ($J_{1''-2''}$=7.5 Hz) and H-2″ ($J_{2''-3''}$=8.5 Hz) of **1** suggest its axial orientation. The double-doublet signal of H-4″ suggested that H-4″ was equatorial. Selected NOE difference experiments were used to confirm the configuration of the monosaccharide residues in **1**, irradiation at H-5″ resulted in NOE enhancement at H-3″, confirming that both hydrogens were axial and that 5″-Me was equatorial. Finally, based on these spectral data, it was concluded that the monosaccharide unit of **1** was β-fucopyranose (6-deoxy-galactose). The presence of a β-fucopyranose moiety in **1** was confirmed by comparing the ^{13}C NMR chemical shifts of the monosaccharide unit with those of known monosaccharides.[9]

The relative stereochemistry of **1** was elucidated by chemical derivatization (Scheme 1). The sulfate group of **1** was easily removed by treatment with 2,2-dimethoxypropane under acidic conditions to furnish acetonide **2**. The *anti*-relationship of H-2′ and H-3′ in **2** was inferred from the coupling constant between H-2′ and H-3′ (*J*=8.6 Hz) as well as



Scheme 1. Reaction scheme of degradation compounds from syriacin (**1**).

from ROESY cross peaks between H-3′/H_3-21 and H-1b′/H_3-21 (Fig. 2).

Glycosphingolipids are often present in minute quantities in living organisms as inseparable mixtures of homologues with branched and unsaturated chains. Unfortunately, despite the progress of NMR and MS, chemical degradation is still an essential step in the study of these compounds. The degradation procedure for compound **1** that we used is quite complex and is summarized in Scheme 1. In order to determine the structures of the saccharide, sphingosine, and fatty acyl units of **1**, which would lead to a gross structure, compound **1** was subjected to acidic hydrolysis, and the reaction

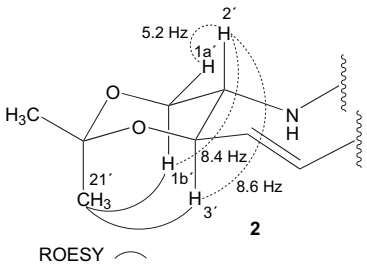


Figure 2. Coupling constants and ROESY correlations of acetonide (**2**).

products were partitioned between CH_2Cl_2 and H_2O/MeOH, giving an aqueous layer consisting of a saccharide (fraction 1) and an organic layer composed of a fatty acid and sphingosine (fraction 2).

The saccharide fraction (1) was used to determine the absolute configuration of the saccharide. The $[\alpha]_D^{21}$ of our fucopyranose (**3**) was +74.0; literature[10] reported $[\alpha]_D^{23}$ −76 for L or +75 for D form.

Fraction 2, containing the fatty acid (**5a**) and the long-chain aminodiol (**4**), was separated on silica gel column. The first eluted fraction 2a was analyzed as methyl ester (**5b**) by GC–MS and was shown to contain a branched polyunsaturated chain, which was further identified by MS, NMR, and chemical degradation (Scheme 1).

The presence of a double bond(s) in the molecule **9** (prepared from **5a**) causes a significant alteration in the mass spectrum, see Figure 3. The cationic site on the picolinyl nitrogen significantly reduces the double bond migrations and enabled us to locate the position of double bond(s). While this technique is universally applicable to all PUFA (polyunsaturated fatty acids), additional fragment ions present in the mass spectra of this picolinyl ester complicated the

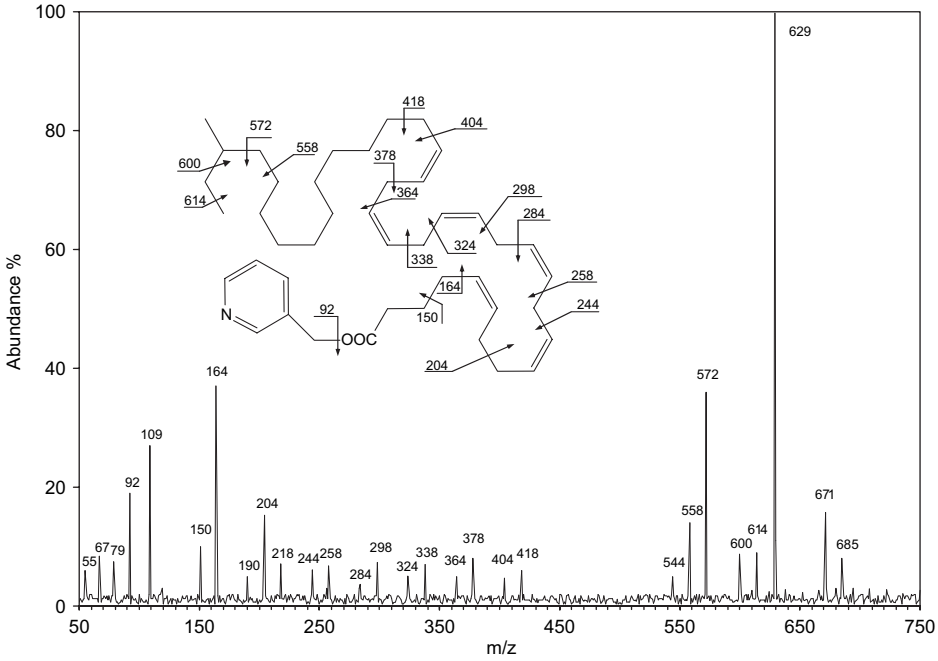


Figure 3. The APCI/MS of picolinyl ester of (all *Z*)-34*S*-methylhexatriaconta-5,9,12,15,18,21-hexaenoic acid.

clear interpretation of the exact position of branching. Oxidative splitting was therefore used to determine the branching position.

The methyl ester of PUFA (**5b**) was not conjugated, as shown by the UV data (see Section 4). The double-bond stereochemistry was established by IR. All double bonds were *Z* because the IR spectrum of the PUFA exhibited absorption at 723 cm^{-1} and no absorption in the 960–980 cm^{-1} region.[11] This stereochemistry was further confirmed by ^{13}C NMR, since the allylic carbons (C-11, C-14, C-17, and C-20) resonated between 25 and 26 ppm (Table 1).[12] Consequently, the above data and deductions completed the sketchy features of the structure of the PUFA, with the exception of the absolute stereochemistry of the branching chain.

The absolute stereochemistry of the long-chain base was established using a method developed earlier.[13] The aminodiol (**4**) was converted by a two-step derivatization to 1,3-binaphthoate-2-*N*-naphthimido-sphingosine (**6**) and its circular dichroism spectrum was measured. The use of two different strongly absorbing chromophores leads to characteristic exciton split CD curves, which depend on the absolute skew of interacting chromophores and the pair wise additivity principle. In order to obtain diagnostic CD reference curves for all four sphingosine diastereomers, numerous bichromophoric combinations, including new chromophores, have been tested over the years,[13,14] we chose O-derivatization and N-derivatization with different chromophores.

In a non-polar solvent both the shapes and amplitudes of CD curves are distinctly different. The (2*S*,3*R*)-*erythro* derivative **6** exhibits a simple negative naphthimide/naphthoate exciton couplet with a negative Cotton effect at 254 μm ($\Delta\varepsilon$ −28) and a positive Cotton effect at 238 μm ($\Delta\varepsilon$ +65). The difference in $\Delta\varepsilon$ values may come from the presence of an extra methyl at C-16′ in **6**.

Both compounds (**4** and **5a**) were subjected to Lemieux oxidation with $KMnO_4/NaIO_4$ to convert sphingosine to a carboxylic acid with four less carbon atoms and the PUFA to a mixture of mono- and dicarboxylic acids. The obtained fatty acids were methylated with CH_2N_2 and analyzed by GC–MS; the results are reported below.

The methyl 13-methylpentadecanoate (**7**) was identified as the longest compound after splitting of PUFA (**5a**), while methyl 12-methyltetradecanoate (**8**) originated from sphingosine (**4**). The optical rotation values of both compounds were opposite; $[\alpha]_D^{23}$ for compound **7** was therefore +3.1; the literature value for free *S*-acid is $[\alpha]_D$ +3.3.[15] The $[\alpha]_D^{21}$ value of **8** was −4.7, which is in accordance with literature data ($[\alpha]_D$ −5.6 for *R* and +5.07 for *S*).[16] This value was a great surprise because this stereochemistry is unnatural (starting unit is probably derived from D-isoleucine). Thereby the absolute stereostructure of **1**, including both positions 34 and 16′, was finally determined as shown in Figure 1.

Based on our results, it was established that the isolated cerebroside occurred as a 2′*S*-(all *Z*)-34*S*-methylhexatriaconta-5,9,12,15,18,21-hexaenoylamino 3′*R*-hydroxy-16′*S*-methyl-octadece-4′*E*-enyl β-D-fucopyranosyl sulfate. The structure of the main product can be described by formula **1**.

Sponges, with their sessile lifestyle and soft unprotected body tissues, are in a strong need of chemical defenses. Accordingly, aquarium assays performed by previously described methods[17] showed that syriacin **1** at a concentration of 10 μg/mL, i.e., slightly below the natural concentration (17.2 μg/mL in our experiments), reduces feeding by goldfish to 13.4±0.6% of the syriacin-free control value (see

Section 4); this strong bioactivity suggests a role in the chemical defense of *E. syriaca*.

Ceramide 1-sulfates with structures similar to compound **1** but with different *N*-acyl moieties have been isolated from Bryozoa *Watersipora cucullata* as new potent inhibitors of human DNA topoisomerase I,[18] while sulfated ceramides isolated from the marine sponge *Discodemia calyx*[19] and from *Zoanthus* sp. (Coelenterata)[20] were found to be inhibitors of neuraminidase. *E. syriaca* syriacin contains a unique very-long-chain fatty acid with six double bonds—34-methylhexatriaconta-5,9,12,15,18,21-hexaenoic acid. Other very-long-chain fatty acids isolated from different freshwater sponges include, e.g., 5,9,23-triacontatrienoic acid (*Baicalospongia bacillifera*, *B. intermedia*, *Cortispongilla barroisi*, *E. syriaca*, *Lubomirskia baicalensis*, *Nudospongilla* sp.), 15,18,21,24-triacontatetraenoic and 15,18,21,24,27-triacontapentaenoic fatty acids (*B. bacillifera*, *B. intermedia* and *L. baicalensis*).[2]

The unusual branched starter units for the biosynthesis of branched chain fatty acids are obtained from the branched chain amino acids L-valine, L-leucine, and L-isoleucine via their corresponding catabolites.[21] Investigations of the biosynthesis of (2*S*)-methylbutanoate esters in apples[22] confirmed that (2*S*)-isoleucine was the precursor of (2*S*)-methylbutanoate. Isoleucine was also a precursor of anteiso-fatty acids in rat skin,[23] all four possible stereoisomers being selectively used for the biosynthesis of these acids. This study suggested the selective biosynthesis of the (*S*)-enantiomer of anteiso-fatty acid in rat skin from DL-isoleucine.

Why isoleucine and alloisoleucine are incorporated into the syriacin molecule is not known. One of the possibilities is isomerization of isoleucine to form alloisoleucine, as described with coronamic acid, an ethylcyclopropyl amino acid derived from isoleucine.[24]

In our case a branched fatty acid was biosynthesized from leucine, which is in agreement with the (*S*)-configuration on carbon C-34. By contrast, sphingosine has (*R*)-configuration on carbon C-16′, which is in agreement with its biosynthesis from alloisoleucine. This configuration is unusual and, to our knowledge, no sphingosine with *R* anteiso-configuration has been found in the nature.

3. Conclusion

To the best of our knowledge, this is the first report of a sulfated ceramide containing an (*R*)-branched long-chain base and (*S*)-branched VLCPUFA (very-long-chain polyunsaturated fatty acids) from living organisms.

4. Experimental

4.1. General

General experimental procedures: UV–vis spectra were measured in MeOH within the range of 210–550 nm in a Cary 118 (Varian) apparatus. A Perkin–Elmer (Perkin–Elmer, Norwalk, CT, USA) model 1310 IR spectrophotometer was used for scanning IR spectroscopy as neat films. Circular dichroism (CD) spectroscopy was carried out under dry N_2 on a Jasco-500A spectropolarimeter at 24 °C. NMR spectra were recorded on a Bruker AMX 500 spectrometer (Bruker Analytik, Karlsruhe, Germany) at 500.1 MHz (^{1}H), 125.7 MHz (^{13}C). High- and also low-resolution MS were recorded using a VG 7070E-HF spectrometer (70 eV). HR-FABMS (positive ion mode) were obtained with a PEG-400 matrix. GC–MS of the fatty acid methyl esters were done using a Finnigan 1020 B (Finnigan MAT, San Jose, CA, USA) single-state quadrupole GC–MS instrument in the EI mode.

4.2. LC–MS/APCI

The LC–MS/APCI of picolinyl ester was realized as mentioned previously[25]—briefly: the HP 1090 series (HP 1090 series, Hewlett Packard, USA) was used with two columns (HIRPB-250AM 250×2.1 mm i.d., 5 mm phase particle). A quadrupole mass spectrometer system Navigator (Finnigan MAT, San Jose, CA, USA) had vaporizer temperature 400 °C, capillary heater temperature 220 °C, corona current 5 mA, sheath gas high-purity nitrogen, pressure ca. 380 kPa, and auxiliary gas (also nitrogen) flow rate 1500 ml/min. Ions with *m*/*z* 50–1500 were scanned with a scan time of 0.5 s, flow rate 0.37 ml/min. Picolinyl esters were separated using a gradient solvent program with acetonitrile/dichloromethane (90:10) and linear from 10 to 40 min acetonitrile/dichloromethane (70:30).

4.3. Chromatography of fatty acid methyl esters

GC–MS of FAME was done on a Finnigan 1020 B in EI mode. Splitless injection was 100 °C, and a fused silica capillary column (Supelcowax 10; 60 m×0.25 mm i.d., 0.25 mm film thickness; Supelco, Prague) was used. The temperature program was as follows: 100 °C for 1 min, subsequently increasing at 20 °C/min to 180 °C and at 2 °C/min to 280 °C, which was maintained for 1 min. The carrier gas was helium at a linear velocity of 60 cm/s. All spectra were scanned within the range *m*/*z* 50–800. The mass spectra of methyl esters agreed with previously published data.[26,27]

4.4. Animal material

The freshwater sponge *E. syriaca* was collected in August 2003 in the spring of the Jordan River, Israel. The voucher specimens are deposited in the collection of the third author (V. M. Dembitsky). Fresh sponge was put into ethanol and stored at −10 °C under nitrogen.

4.5. Isolation

Sponge was extracted three times by butanol; the extracts were chromatographed on a Sephadex LH-20 column with chloroform/methanol 3:2 and then separated by RP-HPLC on a Discovery C18 column (Supelco) particle size 5 μm, length×i.d. (250 mm×21.2 mm) using a linear gradient from 20% H_2O and 80% acetonitrile to 1% H_2O and 99% acetonitrile over 25 min, with a flow rate of 9.9 ml/min and monitoring by a variable wavelength detector at 208 nm. The yield of compound **1** was 26.5 mg in the crude extract.

4.6. Syriacin (1)

Colorless powder (26.5 mg); $[\alpha]_D^{23}$ −18.3 (*c* 0.04, MeOH); UV λ_{max} (MeOH, nm) (log ε): 218 (3.07); IR (film, cm^{-1}) ν_{max} 3300–3400 (OH), 1540, 1640, 3250 (CONH), 1450, 2850, 2900 (CH_2), and 1070, 1230 (SO_4) cm^{-1}; HR-FABMS (*m/z*): 1082.7666 $[M+Na]^+$, calcd for $[C_{62}H_{109}NO_{10}S+Na]^+$ 1082.7668; NMR data, see Table 1.

4.7. Acetonide (2)

A mixture of **1** (1.8 mg), 2,2-dimethoxypropane (0.1 ml), and *p*-TsOH (catalytic amounts) in CH_2Cl_2 (0.5 ml) was stirred at room temperature for 3 h. After addition of triethylamine (10 µl) and H_2O (2 ml), the reaction mixture was extracted with ether (3×2 ml). The ether extract was evaporated and chromatographed on a silica gel column with $CHCl_3$/MeOH (100:1) to yield (1.3 mg, i.e., 87%) of acetonide **2**. ^1H NMR ($CDCl_3$) δ 1.66 (2H, m, H-3), 1.99 (2H, m, H-6′), 3.68 (1H, dd, *J*=5.2, 13.6 Hz, H-1a′), 3.77 (1H, dd, *J*=8.4, 13.6 Hz, H-1b′), 3.79 (1H, ddd, *J*=8.4, 8.6, 5.2 Hz, H-2′), 2.24 (2H, m, H-2), 4.32 (1H, dd, *J*=8.6, 6.9 Hz, H-3′), 5.34 (1H, dd, *J*=15.0, 6.9 Hz, H-4′), 5.71 (1H, dt, *J*=15.0, 6.9 Hz, H-5′); HR-FABMS (*m/z*): 896.7833 $[M+Na]^+$, calcd for $[C_{59}H_{103}NO_3+Na]^+$ 896.7836.

4.8. Enzymatic cleavage of 1

Tris buffer solution (3 ml, 200 mM), pH 6.3 and **1** (1 mg) in deionized water (2 ml) were mixed and further equilibrated at 37 °C. After 10 min, 100 units of sulfatase solution (β-D-glucuronidase (EC 3.2.1.31) from the keyhole limpet) was added and mixed for 5 min. The solution was lyophilized and analyzed by mass spectrometry.

Citrate buffer (3 ml, 400 mM), pH 3.5 and **1** (1 mg) in deionized water (2 ml) were mixed and further equilibrated at 25 °C. After 10 min, 100 units of sulfatase solution (β-D-galactoside (EC 3.2.1.23) from the *E. coli*) was added and mixed for 15 min. The solution was lyophilized and analyzed by mass spectrometry.

4.9. Hydrolysis of 1

Compound **1** (24.0 mg) was dissolved in 1 M HCl (1 ml) in 50% MeOH and the solution was kept for about 12 h at 80 °C in a sealed tube. The reaction mixture was dried under nitrogen, and partitioned between $CHCl_3$ and H_2O/MeOH (8:2). The aqueous layer was concentrated to give a saccharide (fraction 1). The organic layer was concentrated and dissolved in a small quantity of $CHCl_3$ and the solution was passed through a silica gel column. Elution with 1% pyridine in $CHCl_3$ (15 ml) gave a mixture of acids (fraction 2a), and subsequent elution with 1% pyridine in MeOH afforded a sphingosine (fraction 2b).

4.9.1. Fraction 1. The water from fraction 1 was evaporated to dryness and an α,β-anomeric mixture (2.1 mg, 56%) of D-fucopyranose $[\alpha]_D^{21}$ +74.0 (*c* 0.15, MeOH) was obtained as a colorless syrup.

4.9.2. Fraction 2a. The component (11.0 mg) after hydrolysis of compound **1** was identified by APCI/MS as picolinyl ester (**9**) and also as methyl ester (**5b**) by ^1H, ^{13}C NMR, MS, and chemical degradation. Methyl ester (**5b**) was prepared by treatment of **5a** (9.5 mg) with diazomethane—yield 9.5 mg.

The free fatty acid (1.5 mg) was dissolved in diethyl ether (1 ml) and converted into the mixed anhydride derivatives by reaction with trifluoroacetic anhydride (0.1 ml) at 30 °C for 8 h. The excess reagent was evaporated, 10% solution of nicotinyl alcohol in tetrahydrofuran (0.25 ml) was added and the mixture was left at 50 °C for 2 h. Diethyl ether (1 ml) and hexane (0.2 ml) were added and the mixture was washed with water (0.2 ml), 1 M HCl (0.2 ml, three times), and water (0.2 ml, three times) and dried. The solvents were evaporated under reduced pressure and picolinyl ester was further analyzed by LC–MS/APCI.

The component **5b** was further identified by UV, IR, ^1H, ^{13}C NMR, MS, and chemical degradation: UV λ_{max} (MeOH, nm) (log ε) 209 (3.36); IR (neat) λ_{max} 3500 (OH), 3010 (=CH), 2950, 2930, 2870, 1710 (C=O), 1460, 1435, 1410, 1380, 1370, 1240, 940, 720 (HC=CH, *Z*) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (3H, t, *J*=6.8 Hz, H-36), 1.09 (3H, d, *J*=6.9 Hz, H-37), 1.24 (2H, m, H-33), 1.26–1.39 (18H, m, H-25, -32, -35), 1.61 (1H, m, H-34), 1.90 (4H, m, H-4, -23), 2.00–2.10 (4H, m, H-7, -8), 2.18 (2H, m, H-2), 1.61 (2H, m, H-3), 2.32 (2H, m, H-24), 2.60–2.75 (8H, m, H-11, -14, -17, 20), 3.62 (3H, s, OCH_3), 5.38–5.45 (12H, m, H-5, -6, -9, -10, -12, -13, -15, -16, -18, -19, -21, -22); ^{13}C NMR ($CDCl_3$) δ 12.4 (C-36), 21.2 (C-37), 25.0–26.0 (C-11, -14, -17, -20), 25.6 (C-3), 27.2–27.9 (C-4, -23), 29.0–31.0 (C-25, -32, -35), 31.2 (C-7, -8), 31.4 (C-24), 35.4 (C-34), 37.1 (C-33), 36.9 (C-2), 53.2 (OCH_3), 128.0–129.5 (C-5, -6, -9, -10, -12, -13, -15, -16, -18, -19, -21, -22), 173.0 (C-1); HREIMS (*m/z*): 552.4903 $[M]^+$, calcd for $[C_{38}H_{64}O_2]^+$ 552.4906.

To a solution of **5b** (4.0 mg) in 1 ml of *t*-BuOH were added 0.04 M solution of K_2CO_3 (0.2 ml), an aqueous solution of 0.023 M $KMnO_4$ (0.4 ml), and 0.09 M $NaIO_4$ (0.4 ml). The reaction was allowed to proceed at 37 °C for 18 h. After acidification with 2.5 M H_2SO_4, the solution was decolorized with a saturated solution of Na_2SO_3 and extracted twice with 4 ml of ether. The combined extracts were dried and the resulting carboxylic acid was methylated with CH_2N_2. The methyl ester (**7**) was analyzed by GC–MS: methyl (*S*)-13-methylpentadecanoate (**7**), yield 1.2 mg (60%) $[\alpha]_D^{24}$ +3.1 (*c* 0.09, $CHCl_3$), literature data[16] $[\alpha]_D^{21}$ +3.3; HREIMS (*m/z*): 270.2556 $[M]^+$, calcd for $[C_{17}H_{34}O_2]^+$ 270.2559.

4.9.3. Fraction 2b. A first portion of fraction 2b (3.1 mg) of the sphingosine (**4**) from compound **1** was subjected to oxidative cleavage with $KMnO_4$/$NaIO_4$ as described above. GC–MS analysis of the resulting methyl ester gave the methyl (*R*)-12-methyltetradecanoate (**8**); $[\alpha]_D^{24}$ −4.7 (*c* 0.08, $CHCl_3$) literature[18] $[\alpha]_D^{22}$ −5.6 (*c* 2.06, $CHCl_3$); HREIMS (*m/z*) 256.2401 $[M]^+$, calcd for $[C_{16}H_{32}O_2]^+$ 256.2402.

A second portion (3.0 mg) of the sphingosine (**4**) and freshly sublimed 2,3-naphthalenedicarboxylic acid anhydride (3 mg) were dissolved in anhydrous pyridine (1 ml) and refluxed

under stirring for 12 h. The reaction mixture was purified by preparative TLC (hexane/EtOAc 1:1, strongly fluorescent band at R_f ~0.60). The obtained *N*-naphthimido derivative of sphinganines was dissolved in anhydrous acetonitrile (0.2 ml), and 2-naphthoylimidazole (10 mg) and a catalytic amount of 1,8-diazabicyclo-[5.4.0]undec-7-ene were added. The reaction mixture was stirred under argon for 2 h, then dried and purified by preparative TLC (hexane/EtOAc 3:1, strongly fluorescent band at R_f ~0.65) to obtain the pure compound **6** (yield 2.7 mg, 35%); CD (MeCN, nm) λ_{max} 238.5 ($\Delta\varepsilon$ +33.3), 260.0 (−42.3); HR-FABMS (*m*/*z*) 824.3924 $[M+Na]^+$, calcd for $[C_{53}H_{55}NO_6Na]^+$ 824.3927.

4.10. Antifeeding activity assay

Purified syriacin **1** was dissolved in a minimal volume of methanol and mixed with alginate-based food matrix[17] (100 μl) until all organic and water-soluble components were distributed uniformly throughout the paste. The alginate food matrix was then dispensed by a 0.1 ml syringe into a $CaCl_2$ solution (0.25 M), forming a strand that was allowed to harden for 2 min. The hardened strand was rinsed with filtered water and cut into 3 mm pellets with a scalpel. Control pellets were prepared identically but without the addition of natural or synthetic compounds. Feeding assays were performed with goldfish (*Carassius auratus*).

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Unique chlorine effect in regioselective one-pot synthesis of 1-alkyl-/allyl-3-(*o*-chlorobenzyl) uracils: anti-HIV activity of selected uracil derivatives

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Abstract—2,4-Bis(trimethylsilyloxy)pyrimidines **1/2** on reaction with *o*-chlorobenzyl chlorides in 1,2-dichloroethane in the presence of I_2 undergo single step 1,3-dibenzylation to provide 1,3-bis(*o*-chlorobenzyl)pyrimidine-2,4-diones. The reactions of **1** with allyl/alkyl bromide followed by subsequent addition of *o*-chlorobenzyl chloride provide a simple one-pot synthesis of 1,3-unsymmetrical pyrimidine-2,4-diones. Amongst these, 1,3-bis(*o*-chlorobenzyl)uracil (**6a**) shows anti-HIV-1 activity.

1. Introduction

Due to the clinical toxicities involved in the use of nucleoside inhibitors of reverse transcriptase (NRTIs)[1] and high frequency of viral mutations, the use of non-nucleoside inhibitors of reverse transcriptase (NNRTIs)[2] (enzyme responsible for encoding viral RNA to host DNA) has been overcoming the use of nucleoside inhibitors. The presence of hydrophobic residues lining the non-nucleoside binding pocket (NNBP) of HIV-1 RT has necessitated the development of NNIs with allyl/benzyl/alkyl groups at suitable sites of nucleobases which could facilitate the π–π or π–CH interactions with the amino acid residues of the enzyme.[3,4] The presence of these moieties generally enhances the potency profile of lead drug molecules e.g., the presence of allyl/amidophenyl/thiophenyl/aminophenyl moieties at the end of N-1 chain of HEPT along with a thiophenyl/benzyl group at C-6 of pyrimidine has led to higher anti-HIV-1 activity than that observed with HEPT.[5,6] It was envisaged that the presence of hydrophobic moieties at N-1 and N-3 of pyrimidinedione might enhance the anti-HIV activities of the resulting compounds. 1,3-Disubstituted pyrimidinediones are little explored for their anti-HIV activities, which might be due to the difficulty in synthesis of such compounds. This led us to design and synthesise new molecules with an allyl/alkyl/benzyl substituent at N-1 and a benzyl group at N-3 of the pyrimidinedione.

During the synthesis of N-1, N-3 unsymmetrically substituted pyrimidine-2,4-diones, we have observed that the alkylation of 2,4-bis(trimethylsilyloxy)pyrimidine (**1**) stops at N-1 substitution stage.[7] The present work shows that alkylation of **1** with *o*-chlorobenzyl chlorides on prolonged heating provide N-1 and N-3 dialkylated products. This unique ability of N-3 *o*-chlorobenzylation has been exploited for the synthesis of 1-allyl-/alkyl-/benzyl-3-(*o*-chlorobenzyl) pyrimidine-2,4-diones. The mechanism for such unique ability of *o*-chlorobenzyl chlorides to promote the benzylation at N-3 of 1-substituted pyrimidine-2,4-diones has been discussed. The selected 1,3-substituted pyrimidine-2,4-diones have been evaluated for their in vitro anti-HIV activities.

2. Results and discussion

2,4-Bis(trimethylsilyloxy)pyrimidine (**1**) on refluxing with 2-chlorobenzyl chloride (**3a**) (3 equiv) in 1,2-dichloroethane (1,2-DCE) in the presence of I_2 (0.1 equiv) for 96 h, after the usual work-up and column chromatography gave two compounds **4a** (<1%) and **6a** (74%). Compound **6a**, mp 72 °C, M^+ *m/z* 361, 363, 365 (100:60:10), shows the signals of H-5 and H-6 protons as doublets at δ 5.74 and 7.24 and N-1 and N-3 CH_2 as singlets at δ 4.97 and 5.22 along with aromatic protons in its ^{1}H NMR spectrum and the presence of 10 positive (due to CH), two negative (due to CH_2) and six quaternary carbons in ^{13}C normal and DEPT-135 spectra, which corroborate the structure **6a** (Scheme 1).

Similarly, the refluxing of solutions of **1** with 2,4-dichlorobenzyl chloride **3b** and 2,6-dichlorobenzyl chloride **3c** in 1,2-DCE in the presence of I_2 for 96 h gave 1,3-disubstituted

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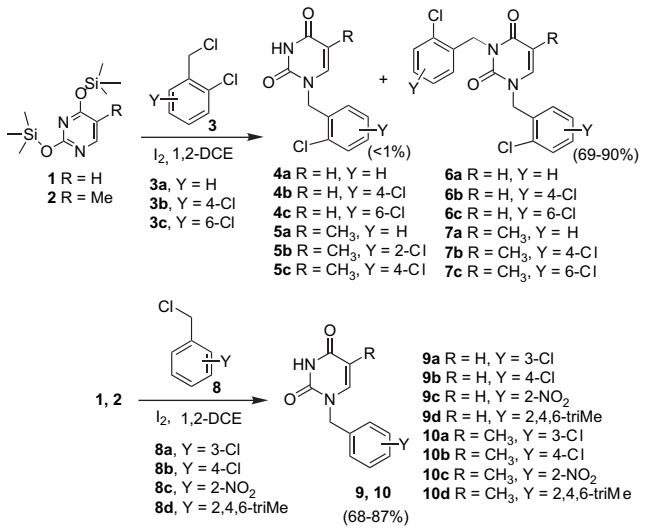


Scheme 1.

uracil derivatives **6b** and **6c**, respectively. In these reactions, only traces (<1%) of **4b** and **4c** were isolated (Table 1). Furthermore, the reactions of 2,4-bis(trimethylsilyloxy)-5-methylpyrimidine (**2**) with **3a–c** gave the respective 1,3-bis(*o*-chlorobenzyl)thymines **7a–7c** along with small amounts of **5a–5c** (Scheme 1, Table 1).

However, the reactions of **1** and **2** with 3-chloro-/4-chloro-/2-nitro-/2,4,6-trimethyl-benzyl chlorides (**8a–8d**) (3 equiv) did not provide respective 1,3-disubstituted uracil/thymine derivatives even on prolonged refluxing (7 days) and the reactions stopped at the 1-substituted stage yielding N_1-substituted uracils **9(a–d)** and **10(a–d)** (Scheme 1, Table 1).

Amongst various substituted benzyl halides **3(a–c)** and **8(a–d)**, which were made to react with **1** and **2**, only **3(a–c)** gave dibenzylated products **6** and **7**, while in all other cases the reaction stops at the N_1-substitution stage. These results clearly point to the unique role of *o*-chlorine in benzyl halides **3(a–c)** in yielding 1,3-dibenzyl pyrimidine-2,4-diones **6** and **7**. The reasons for this differential reactivity remain unexplained.

The monitoring of reactions of **1** with **3a/3b/3c** by ^{1}H NMR spectroscopy unravels the plausible mechanism in transferring *o*-chlorobenzyl group at N-3. The ^{1}H NMR spectrum of the reaction mixture of **1** and 2-chlorobenzyl chloride **3a**, recorded by quenching the reaction after 48 h, shows two sets of signals each due to H-5 (at δ 5.74 and 5.89), N_1-CH_2 (two singlets δ 4.97 and 5.06) and two singlets due to N_3-CH_2 (at δ 5.22 and 5.47) in the 96:4 ratio (entry 1, Table 2). The major component on the basis of ^{1}H NMR spectrum has been assigned the structure **6a**. The minor component could be due to **11a/12a** formed due to O-alkylation at C_2=*O* or C_4=*O* (Scheme 2). Similarly, the reaction of **1** with 2,4-dichlorobenzyl chloride **3b** on work-up after 48 h, in its ^{1}H NMR spectrum shows two sets of signals each due to H-5 (δ 5.85 and 5.95), N_1-CH_2 (δ 5.01 and 5.12) and N_3-CH_2 (δ 5.21 and 5.48) protons in 75:25 ratio (entry 2, Table 2). The ^{1}H NMR spectrum of the reaction of **1** with 2,6-dichlorobenzyl chloride **3c** recorded after 48 h of reaction shows three singlets each due to N_1-CH_2 at δ 5.20, 5.28 and 5.35, N_3-CH_2 at δ 5.40, 5.46 and 5.68 in the ratio 27:24:49 indicating it to be a mixture of three components.

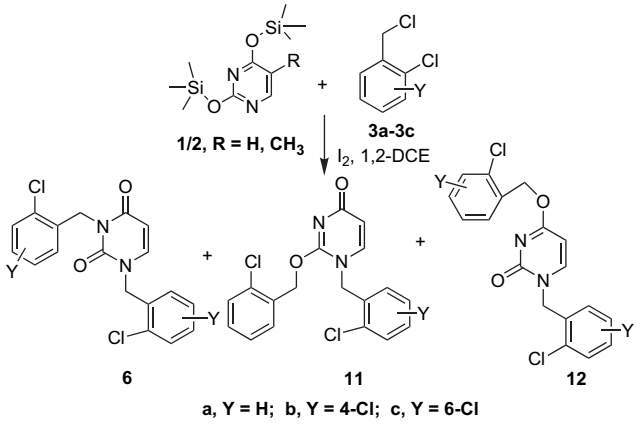
Table 1. Reactions of 1/2 with substituted 2-chlorobenzyl chlorides

Entry	R in 1/2	Benzyl halide	Rx time (h)	N_1-alkylated, yield %	N_1,N_3-alkylated, yield %
1	H	**3a**	96	**4a** (<1)	**6a** (74)
2	H	**3b**	96	**4b** (<1)	**6b** (82)
3	H	**3c**	96	**4c** (<1)	**6c** (89)
4	CH_3	**3a**	96	**5a** (<1)	**7a** (72)
5	CH_3	**3b**	96	**5b** (<1)	**7b** (76)
6	CH_3	**3c**	96	**5c** (<1)	**7c** (67)
7	H	**8a**	96	**9a** (74)	—
8	H	**8b**	96	**9b** (78)	—
9	H	**8c**	96	**9c** (74)	—
10	H	**8d**	96	**9d** (68)	—
11	CH_3	**8a**	96	**10a** (79)	—
12	CH_3	**8b**	96	**10b** (82)	—
13	CH_3	**8c**	96	**10c** (82)	—
14	CH_3	**8d**	96	**10d** (87)	—

Table 2. Product distribution ratio for the reaction of 1/2 with substituted benzyl chlorides quenched after 48 h (Scheme 2)

Entry	R in **1/2**	Benzyl halide	Product ratio (**6**: **11**+**12**)	Product **6** (yield %[a])
1	H	**3a**	96:4	**6a** (70)
2	H	**3b**	75:25	**6b** (70)
3	H	**3c**	27:73	**6c** (72)

[a] Yield after work-up with 4 M HCl.



Scheme 2.

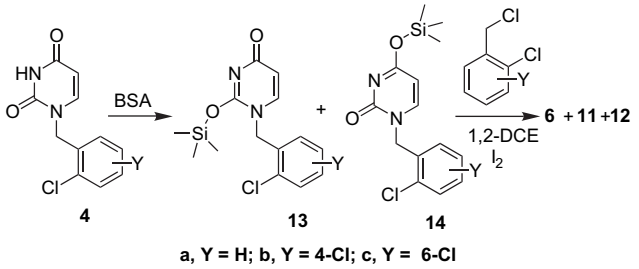
However, TLC of these mixtures shows the presence of only one component and even on repeated chromatography these could not be separated.

The crude reaction mixtures obtained after 48 h of refluxing of **1** with **3(a–c)** on further heating with 4 M HCl at 80 °C for 1 h gave pure products **6a–6c** (Table 2) along with small quantities of respective 1-(*o*-chlorobenzyl)uracil derivatives **4(a–c)** (<1%). Alternatively, these reaction mixtures on further heating in 1,2-DCE for >24 h underwent rearrangement to 1,3-disubstituted uracil derivatives **6a–6c**.

These observations indicate that probably after N-1 alkylation, the *ortho*-chlorobenzyl promotes N-3, C_2=O and C_4=O alkylation to provide mixture of N_3-alkyl derivative

6 and *O*-alkyl derivatives **11** and **12** (Scheme 2), which on heating in HCl or 1,2-DCE undergo rearrangement to provide **6**.

The participation of intermediates **11** and **12** has been further confirmed by silylation of **4**(**a**–**c**) and subsequent alkylation with *o*-chlorobenzyl chlorides **3**(**a**–**c**). Compound **4a** on heating with *N*,*O*-bis(trimethylsilyl)acetamide (BSA) gave a clear solution, which confirms its complete silylation. ^{1}H NMR ($CDCl_3$) spectrum of this silylated mixture shows the presence of two NCH_2 signals at δ 4.93 and 5.07 and two H-5 doublets at δ 5.61 and 5.79 in 22:78 ratio and confirms it to be a mixture of C_2=O and C_4=O silylated derivatives **13** and **14** (Scheme 3). The mixture of **13** and **14** on refluxing with 2-chlorobenzyl chloride in the presence of I_2 on work-up after 48 h provided a mixture of **6a** and **11/12**. Similarly, **4b** and **4c** on silylation showed the presence of **13b**, **14b** and **13c**, **14c** in their ^{1}H NMR spectra. The silylated pyrimidines **13** and **14** on subsequent refluxing with *o*-chlorobenzyl chlorides for 48 h provided mixtures of **6**, **11** and **12** in nearly similar ratios as observed in direct alkylation of **1** as given in Table 2.

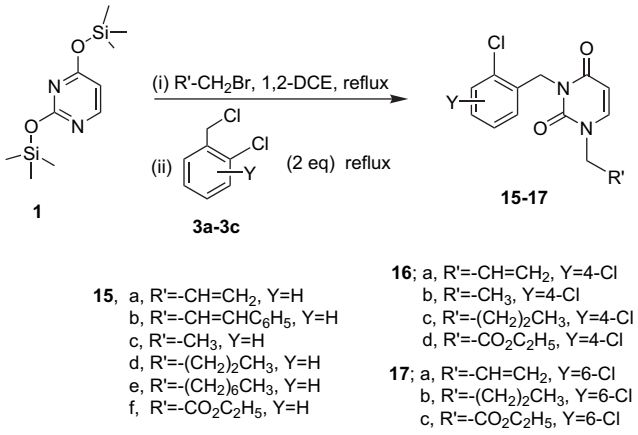


Scheme 3.

Therefore, **1** initially undergoes regioselective alkylation at N-1 and then 2-chloro-/2,4-dichloro-/2,6-dichloro-benzyl chloride causes alkylation at N-3, C_2=O and C_4=O to provide a mixture of **6**, **11** and **12**, which on heating undergoes rearrangement to the respective 1,3-disubstituted uracil derivatives **6a**–**6c**. This provides a simple approach for the 1,3-disubstituted uracil and thymine derivatives under neutral or mild acidic conditions. Significantly, in the case of reactions of **2** with 2-chlorobenzyl chlorides **3a**–**3c**, even after work-up at different intervals of time, the formation of respective *O*-alkylated products **11** and **12** was not observed.

This ability of *o*-chlorobenzyl chlorides to promote N_3-benzylation of *O*-silylated uracil derivatives has been advantageously used for the one-pot synthesis of 1-alkyl/allyl/3-(*o*-chlorobenzyl) uracil derivatives (Scheme 4). The reactions of **1** with various alkyl/allyl/benzyl halides and subsequent in situ reactions with *o*-chlorobenzyl chlorides provide 1,3-unsymmettrically substituted uracil derivatives.

The refluxing of **1** with allyl bromide (1.5 equiv) in 1,2-DCE containing I_2 (0.1 equiv) provided *O*-silylated derivatives of 1-allyluracil (TLC comparison with authentic sample). Then, **3a** (2 equiv) was added to the reaction mixture and refluxing was continued (Scheme 4). The reaction mixture on work-up and column chromatography gave a pale yellow liquid **15a** (73%), [M^+ *m*/*z* 277, 279 (3:1)] (entry 1, Table 3,). Similarly, the reaction of **1** with allyl bromide (1.5 equiv) followed by subsequent reaction with **3b** and **3c** (2 equiv)



Scheme 4.

Table 3. Percentage yield and melting points of 1-allyl/arylmethyl/alkyl-3-(*o*-chlorobenzyl) uracil derivatives (**15**–**17**)

Entry	Y	R′	Yield (%)	Mp (°C)
1	H	$CH{=}CH_2$	**15a** (73)	liq
2	H	$CH{=}CHC_6H_5$	**15b** (72)	110
3	H	CH_3	**15c** (63)	liq
4	H	$(CH_2)_2CH_3$	**15d** (78)	liq
5	H	$(CH_2)_6CH_3$	**15e** (67)	liq
6	H	$CO_2C_2H_5$	**15f** (64)	liq
7	4-Cl	$CH{=}CH_2$	**16a** (62)	94
8	4-Cl	CH_3	**16b** (70)	98
9	4-Cl	$(CH_2)_2CH_3$	**16c** (63)	94
10	4-Cl	$CO_2C_2H_5$	**16d** (64)	120
11	6-Cl	$CH{=}CH_2$	**17a** (65)	110
12	6-Cl	$(CH_2)_2CH_3$	**17b** (62)	140
13	6-Cl	$CO_2C_2H_5$	**17c** (62)	120

provided the respective compounds **16a** and **17a** (entries 7 and 11, Table 3).

To check the competition between the allyl bromide and *o*-chlorobenzyl chloride for N-3 alkylation, **1** was refluxed with 1.2 equiv of allyl bromide for 24 h and then 2 equiv each of allyl bromide and *o*-chlorobenzyl chloride was added and the reaction mixture was refluxed for 48 h. The reaction mixture on work-up provided only **15a** (73%). 1,3-Diallyluracil was not isolated from the reaction mixture. The reaction of **1** with cinnamyl bromide (1.5 equiv) and subsequent alkylation with 2-chlorobenzyl chloride gave uracil derivative **15b** (72%). Similarly, the reactions of **1** with various alkyl/alkyl ester halides followed by addition of 2 equiv of **3a/3b/3c** provided respective compounds **15**–**17** (Scheme 4, Table 3).

2.1. In vitro anti-HIV activities

The in vitro anti-HIV activities of the six selected compounds in terms of 50% effective concentration against HIV cytopathic effects and 50% inhibitory concentration for cell growth have been evaluated against human immunodeficiency virus (HIV). The biological results as inhibition of HIV-1 replication in T4 lymphocytes (CEM-SS cell line) are given in Table 4.

Among the compounds tested (**6a**–**6c**, **15a**, **16a**, **17a**) for anti-HIV-1 activity, **6a** possessing 2-chlorobenzyl groups

Table 4. Inhibition of HIV-1 replication in T4 lymphocytes (CEM-SS cell line) by compounds **6a–6c** and **15a**, **16a**, **17a**

Compd	IC_{50}[a] (μM)	EC_{50}[b] (μM)	TI[c]
6a	36.4	9.19	3.65
6b	35.5	>200	<0.17
6c	35.4	>200	<0.17
15a	121	>200	<0.6
16a	111	>200	<0.5
17a	42.7	>200	<0.2
HEPT	740	7	106
AZT	20	0.016	1250

[a] Concentration of compound required to achieve 50% inhibition of cell growth.
[b] Compound dose required to achieve 50% protection of T4 lymphocyte cells from HIV-1 induced cytopathogenecity.
[c] Therapeutic Index (TI=IC_{50}/EC_{50}).

at N-1 and N-3 of uracil shows highest anti-HIV-1 activity with EC_{50}=9.19 μM, which is comparable to HEPT (7.0 μM) but lacks the selectivity. The replacement of *o*-chlorobenzyl group at N-1 with allyl moiety (**15a**, **16a**, **17a**) results in total loss of anti-HIV activity. The presence of another chlorine atom at 4 or 6 positions of the benzyl group in **6b** and **6c** increases the effective concentration required to achieve 50% protection of HIV infected cells while the IC_{50} values of these compounds are parallel with **6a**. It seems as if the presence of a phenyl moiety at N-1 is the essential requirement for these compounds to exhibit anti-HIV-1 activities.

3. Conclusions

2,4-Bis(trimethylsilyloxy)pyrimidines **1** on reaction with allyl/arylmethyl/alkyl/alkoxycarbonylmethyl halides followed by reactions with 2-chloro/2,4-dichloro-/2,6-dichloro benzyl chlorides provides simple one-pot methodology for the synthesis of 1-allyl-/alkyl-/benzyl-3-(*o*-chlorobenzyl) uracil derivatives.

4. Experimental

4.1. General

Melting points were determined in capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were run on JEOL JNM-AL spectrometer at 300 MHz and 75 MHz, respectively, using $CDCl_3$ as solvent and TMS as an internal standard. In ^{13}C NMR spectral data, +ve signals correspond to CH_3 and CH and −ve signals correspond to CH_2 carbons in DEPT-135 spectrum. *J* values are given in Hertz. Mass spectra were recorded at CDRI, Lucknow. IR spectra were recorded by using $CHCl_3$ or KBr (solid) as medium. CHN analysis was performed on thermoelectron CHN analyser EA1112.

4.2. General procedure for the reactions of 1/2 with benzyl chlorides 3(a–c) and 8(a–d)

Procedure **A**: A solution of 2,4-bis-(trimethylsilyloxy)pyrimidine (**1/2**) (0.01 mol), the appropriate benzyl chloride (0.03 mol) and I_2 (0.001 mol) in 1,2-DCE (20 ml) was refluxed for 96 h. After completion of the reaction (TLC), the cooled reaction mixture was treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel using ethyl acetate and hexane mixtures as eluents to isolate the pure compounds.

4.2.1. 1-(2-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (4a). <1%; White solid, mp 209 °C (lit.[7] mp 210 °C).

4.2.2. 1,3-Bis(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (6a). 74%; White solid, mp 72 °C (CH_3CN); FAB mass *m/z* 361, 363, 365 (100:62:10) (M^+); ^1H NMR ($CDCl_3$): δ 4.97 (2H, s, CH_2), 5.22 (2H, s, CH_2), 5.74 (1H, d, *J*=7.8 Hz, C5-H), 6.91–7.01 (1H, m, ArH), 7.11–7.17 (2H, m, ArH), 7.24–7.43 (6H, m, 5ArH, C-6H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 42.23 (−ve, CH_2), 49.95 (−ve, CH_2), 101.81 (+ve, 5-CH), 126.59 (+ve, ArCH), 126.73 (+ve, ArCH), 127.42 (+ve, ArCH), 128.23 (+ve, ArCH), 129.55 (+ve, ArCH), 129.97 (+ve, ArCH), 130.57 (+ve, ArCH), 132.94 (+ve, ArCH), 132.58 (ab, C), 132.94 (ab, C), 133.58 (ab, C), 133.93 (ab, C), 142.31 (+ve, CH-6), 151.49 (ab, C), 162.63 (ab, C); ν_{max} (KBr)/cm^{-1}: 3100, 1708, 1670, 1658, 742, 798; (Found: C, 59.6; H, 4.0; N, 7.9. $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.85; H, 3.91; N, 7.76%).

4.2.3. 1-(2,4-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (4b). <1%; White solid, mp 140 °C (lit.[7] mp 140 °C).

4.2.4. 1,3-Bis(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6b). 82%; White solid, mp 72 °C (CH_3CN); FAB mass *m/z* 429, 431, 433, 435 (78:100:50:12) (M^+); ^1H NMR ($CDCl_3$): δ 5.01 (2H, s, CH_2), 5.21 (2H, s, CH_2), 5.85 (1H, d, *J*=7.8 Hz, C-5H), 6.91 (1H, d, *J*=8.0 Hz, ArH), 7.15 (1H, d, *J*=8.0 Hz, ArH), 7.24–7.51 (5H, m, 4×ArH, C-6H). The decoupling of C-5H signal at δ 5.85 gives a singlet at δ 7.37; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.88 (−ve, CH_2), 49.71 (−ve, CH_2), 101.97 (+ve, 5-CH), 127.07 (+ve, ArCH), 127.80 (+ve, ArCH), 127.99 (+ve, ArCH), 129.41 (+ve, ArCH), 129.82 (+ve, ArCH), 131.11 (ab, C), 131.71 (+ve, ArCH), 132.31 (ab, C), 133.46 (ab, C), 133.73 (ab, C), 134.28 (ab, C), 135.39 (ab, C), 142.40 (+ve, 6-CH), 151.41 (ab, C), 162.49 (ab, C); ν_{max} (KBr)/cm^{-1}: 3200, 1708, 1654, 727, 813; (Found: C, 50.3; H, 2.6; N, 6.2. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.26; H, 2.81; N, 6.51%).

4.2.5. 1-(2,6-Dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (4c). <1%; White solid, mp 256 °C (CH_3CN); FAB mass *m/z* 270, 272, 274 (100:60:10) (M^+); ^1H NMR ($CDCl_3$+TFA): δ 5.34 (2H, s, CH_2), 6.00 (1H, d, *J*=8.0 Hz, C5-H), 7.19 (1H, d, *J*=8.0 Hz, C6-H), 7.39–7.49 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 46.83 (−ve, CH_2), 102.38 (+ve, 5-CH), 128.56 (ab, C), 129.24 (+ve, ArCH), 131.83 (+ve, ArCH), 137.14 (ab, C), 144.80 (+ve, 6-CH), 151.78 (ab, C), 166.45 (ab, C); ν_{max} (KBr)/cm^{-1}: 3029, 1691,1658, 781, 767; (Found: C, 48.42; H, 2.89; N, 10.15. $C_{11}H_8Cl_2N_2O_2$ requires C, 48.7; H, 2.95; N, 10.33%).

4.2.6. 1,3-Bis(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (6c). 89%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 429, 431, 433, 435 (78:100:50:12) (M^+); ^1H NMR ($CDCl_3$): δ 5.20 (2H, s, CH_2), 5.42 (2H, s, CH_2), 5.63 (1H, d, *J*=8.0 Hz, C5-H), 6.78 (1H, d, *J*=8.0 Hz, C6-H), 7.12 (1H, t, *J*=8.0 Hz, ArH), 7.16–7.41 (5H, m,

ArH). The decoupling of the C-5H signal at δ 5.63 converts the doublet at δ 6.78 to a singlet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.16 (−ve, CH_2), 46.18 (−ve, CH_2), 101.79 (+ve, 5-CH), 128.48 (+ve, ArCH), 128.76 (+ve, ArCH), 128.91 (+ve, ArCH), 130.10 (ab, C), 130.20 (ab, C), 130.96 (+ve, ArCH), 131.88 (ab, C), 139.73 (+ve, 6-CH), 135.82 (ab, C), 137.05 (ab, C), 151.05 (ab, C), 162.49 (ab, C); ν_{max} (KBr)/cm^{-1}: 3100, 1716, 1668, 759, 777; (Found C, 49.9; H, 2.4; N, 6.8%. $C_{18}H_{12}Cl_4N_2O_2$ requires C, 50.26; H, 2.81; N, 6.51%).

4.2.7. 1-(2-Chlorobenzyl)-5-methyl-1H-pyrimidine-2,4-dione (5a). <1%; White solid, mp 130 °C (lit.[7] mp 132 °C).

4.2.8. 1,3-Bis[(2-chlorobenzyl]-5-methyl-1*H*-pyrimidine-2,4-dione (7a). 72%; White solid, mp 136 °C (CH_3CN); FAB mass *m/z* 375, 377, 379 (100:62:10) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.93 (3H, s, CH_3), 5.05 (2H, s, CH_2), 5.29 (2H, s, CH_2), 6.94–6.99 (1H, m, ArH), 7.13–7.27 (3H, m, ArH), 7.29–7.44 (5H, m, ArH, C6-H); ^{13}C (normal/DEPT) ($CDCl_3$): δ 13.12 (+ve, CH_3), 42.46 (−ve, CH_2), 49.54 (−ve, CH_2), 110.24 (ab, C-5), 126.73 (+ve, ArCH), 126.79 (+ve, ArCH), 127.40 (+ve, ArCH), 128.19 (+ve, ArCH), 129.54 (+ve, ArCH), 129.75 (+ve, ArCH), 129.91 (+ve, ArCH), 130.13 (+ve, ArCH), 133.01 (ab, C), 133.41 (ab, C), 133.85 (ab, C), 138.37 (+ve, C-6H), 151.58 (ab, C), 163.43 (ab, C); ν_{max} (KBr)/cm^{-1}: 3066, 2360, 2339, 1703, 1643, 748; (Found C, 60.88; H, 4.31; N, 7.26%. $C_{19}H_{16}Cl_2N_2O_2$ requires C, 60.88; H, 4.26; N, 7.46%).

4.2.9. 1-(2,4-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (5b). <1%; White solid, mp 138 °C (lit.[7] mp 140 °C).

4.2.10. 1,3-Bis(2,4-dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (7b). 76%; White solid, mp 152 °C (CH_3CN); FAB mass *m/z* 443, 445, 447, 449 (78:100:50:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.95 (3H, s, CH_3), 5.01 (2H, s, CH_2), 5.23 (2H, s, CH_2), 6.92 (1H, d, J=8.0 Hz, ArH), 7.12–7.17 (2H, m, ArH), 7.27–7.28 (2H, m, ArH), 7.38–7.45 (2H, m, ArH, C6-H); ^{13}C (normal/DEPT) ($CDCl_3$): δ 13.11 (+ve, CH_3), 42.07 (−ve, CH_2), 49.25 (−ve, CH_2), 110.45 (ab, C-5), 127.05 (+ve, ArCH), 127.76 (+ve, ArCH), 128.14 (+ve, ArCH), 129.37 (+ve, ArCH), 129,75 (+ve, ArCH), 131.24 (+ve, ArCH), 131.54 (ab, C), 132.57 (ab, C), 133.38 (ab, C), 133.76 (ab, C), 134.10 (ab, C), 135.12 (ab, C), 138.35 (+ve, C-6H), 151.46 (ab, C), 163.27 (ab, C); ν_{max} (KBr)/cm^{-1}: 2360, 2339, 1704, 1666, 1643, 775; (Found C, 51.12; H, 3.12; N, 6.11%. $C_{19}H_{14}Cl_4N_2O_2$ requires C, 51.3; H, 3.15; N, 6.30%).

4.2.11. 1-(2,6-Dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (5c). <1%; White solid, mp 240 °C (CH_3CN); ^{1}H NMR ($CDCl_3$+TFA): δ 1.93 (3H, s, CH_3), 5.30 (2H, s, CH_2), 6.93 (1H, s, C6-H), 7.31–7.47 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 12.02 (+ve, CH_3), 46.24 (−ve, CH_2), 129.07 (+ve, ArCH), 112.19 (ab, C-5), 128.88 (ab, C), 129.21 (+ve, ArCH), 131.65 (+ve, ArCH), 137.04 (ab, C), 140.32 (+ve, 6-CH), 151.95 (ab, C), 166.20 (ab, C). ν_{max} (KBr)/cm^{-1}: 3002, 2829, 1703, 1658, 784, 756; HRMS found 284.0119, $C_{12}H^{35}_{10}Cl_2N_2O_2$ requires 284.0119; found 286.0091, $C_{12}H^{35}_{10}Cl^{37}ClN_2O_2$ requires 286.0089; (Found: C, 50.23; H, 3.53; N, 9.69. $C_{12}H_{10}Cl_2N_2O_2$ requires C, 50.52; H, 3.50; N, 9.82%).

4.2.12. 1,3-Bis(2,6-dichlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (7c). 67%; White solid, mp 128 °C (CH_3CN); FAB mass *m/z* 443, 445, 447, 449 (76:100:48:12) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.81 (3H, s, CH_3), 5.22 (2H, s, CH_2), 5.45 (2H, s, CH_2), 6.65 (1H, s, C6-H), 7.07–7.15 (1H, m, ArH), 7.29–7.42 (5H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.26 (+ve, CH_3), 41.47 (−ve, CH_2), 110.08 (ab, C-5), 128.47 (+ve, ArCH), 128.74 (+ve, ArCH), 128.92 (+ve, ArCH), 130.43 (ab, C), 130.82 (+ve, ArCH), 132.04 (ab, C), 135.81 (ab, C), 135.88 (+ve, C6-H), 136.98 (ab, C), 151.91 (ab, C), 163.33 (ab, C); ν_{max} (KBr)/cm^{-1}: 1710, 1662, 1649, 775, 763; (Found C, 51.12; H, 3.13; N, 6.11%. $C_{19}H_{14}Cl_4N_2O_2$ requires C, 51.3; H, 3.15; N, 6.30%).

4.2.13. 1-(3-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (9a). 74%; White solid, mp 140 °C (lit.[7] mp 140 °C).

4.2.14. 1-(4-Chlorobenzyl)-1*H*-pyrimidine-2,4-dione (9b). 78%; white solid, mp 178 °C (lit.[7] mp 180 °C).

4.2.15. 1-(2-Nitrobenzyl)-1*H*-pyrimidine-2,4-dione (9c). 74%; white solid, mp 119 °C (lit.[7] mp 120 °C).

4.2.16. 1-(2,4,6-Trimethylbenzyl)-1H-pyrimidine-2,4-dione (9d). 68%; White solid, mp 230 °C (CH_3CN) (lit.[7] mp 230 °C).

4.2.17. 1-(3-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10a). 79%; White solid, mp 140 °C (CH_3CN); ^{1}H NMR ($CDCl_3$+TFA): δ 1.93 (3H, s, CH_3), 4.92 (2H, s, CH_2), 7.15–7.38 (6H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.80 (+ve, CH_3), 51.64 (−ve, CH_2), 112.90 (ab, C-5), 126.20 (+ve, ArCH), 128.13 (+ve, ArCH), 129.41 (+ve, ArCH), 130.75 (+ve, ArCH), 135.38 (ab, C), 135.78 (ab, C), 142.25 (+ve, C-6), 152.38 (ab, C), 166.58 (ab, C); ν_{max} (KBr)/cm^{-1}: 3022, 2999, 1685, 1656, 775; HRMS found: 250.0513, $C_{12}H^{35}_{11}ClN_2O_2$ requires 250.0509; found: 252.0488, $C_{12}H^{37}_{11}ClN_2O_2$ requires 252.0479; (Found: C, 57.1; H, 4.29; N, 11.20. $C_{12}H_{11}ClN_2O_2$ requires C, 57.4; H, 4.39; N, 11.2%).

4.2.18. 1-(4-Chlorobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10b). 82%; White solid, mp 160 °C (CH_3CN); FAB mass *m/z* 251, 253 (3:1) (M^+); ^{1}H NMR ($CDCl_3$+TFA): δ 1.95 (3H, s, CH_3), 4.95 (2H, s, CH_2), 7.23–7.25 (3H, m, ArH+C6-H), 7.37–7.40 (2H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.89 (+ve, CH_3), 51.56 (−ve, CH_2), 112.80 (ab, C5-H), 129.51 (+ve, ArCH), 129.65 (+ve, ArCH), 132.26 (ab, C), 135.37 (ab, C), 142.00 (+ve, C6-H), 152.32 (ab, C), 166.43 (ab, C); ν_{max} (KBr)/cm^{-1}: 3170, 2358, 1702, 1656, 746, 692; (Found: C, 56.68; H, 4.23; N, 11.4. $C_{12}H_{11}ClN_2O_2$ requires C, 57.4; H, 4.39; N, 11.2%).

4.2.19. 1-(2-Nitrobenzyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10c). 82%; White solid, mp 242 °C (CH_3CN); FAB mass *m/z* 262 (M^++1); ^{1}H NMR ($CDCl_3$+TFA): δ 1.99 (3H, s, CH_3), 5.40 (2H, s, CH_2), 7.35 (1H, d, J=9.0 Hz, ArH), 7.40 (1H, s, C6-H), 7.60 (1H, t, J=9.0 Hz, ArH), 7.72 (1H, t, J=9.0 Hz, ArH), 8.18 (1H, d, J=9.0 Hz, ArH);

^{13}C (normal/DEPT-135) ($CDCl_3$+TFA): δ 11.75 (+ve, CH_3), 49.83 (−ve, CH_2), 112.58 (ab, C-5), 125.89 (+ve, ArCH), 129.56 (+ve, ArCH), 129.62 (+ve, ArCH), 129.93 (ab, C), 134.74 (+ve, ArCH), 142.85 (+ve, 6-CH), 147.72 (ab, C), 152.42 (ab, C), 166.58 (ab, C); ν_{max} (KBr)/cm^{-1}: 3039, 1691, 1517, 1353, 727; (Found: C, 54.97; H, 4.18; N, 15.83. $C_{12}H_{11}N_3O_4$ requires C, 55.2; H, 4.21; N, 16.09%).

4.2.20. 1-(2,4,6-Trimethyl)-5-methyl-1*H*-pyrimidine-2,4-dione (10d). 87%; White solid, mp 210 °C (CH_3CN); FAB mass *m*/*z* 259 (M^++1); ^{1}H NMR ($CDCl_3$): δ 1.77 (3H, s, CH_3), 2.25 (6H, s, 2×CH_3), 2.33 (3H, s, CH_3), 4.93 (2H, s, CH_2), 6.48 (1H, s, C6-H), 6.94 (2H, s, ArH), 8.91 (1H, br s, NH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 12.51 (+ve, CH_3), 19.76 (+ve, CH_3), 20.99 (+ve, CH_3), 44.38 (−ve, CH_2), 110.52 (ab, C5), 126.82 (ab, ArCH), 129.75 (+ve, ArCH), 137.16 (+ve, 6-CH), 138.16 (ab, C), 138.92 (ab, C), 151.24 (ab, C), 163.90 (ab, C); ν_{max} (KBr)/cm^{-1}: 3033, 2385, 1701, 1676, 864; (Found: C, 69.56; H, 6.84; N, 10.83. $C_{15}H_{18}N_2O_2$ requires C, 69.7; H, 6.97; N, 10.85%).

4.3. N_3-(*o*-Chlorobenzylation) of 4a–4c

Procedure **B**: **4a** (2.36 g, 1 mmol) was heated with *N*,*O*-bis-(trimethylsilyl)acetamide (BSA) at 110 °C in an oil bath and a clear solution was obtained in 3–4 h. **3a** (2 equiv) and 1,2-DCE (10 ml) were added to the above solution and refluxing was continued for 48 h. The reaction mixture was treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel column using hexane–ethyl acetate mixture as eluent to isolate mixture of **6a**, **11a** and **12a**. Similarly, **4b** and **4c** on silylation with BSA followed by reactions with **3b** and **3c** gave respective mixtures of **6b+11b+12b** and **6c+11c+12c**.

4.4. General procedure for the synthesis of 1-allyl/alkyl/ethoxycarbonylmethyl 3-(2-Cl/2,4-diCl/2,6-diCl-benzyl-2,4-1*H*,3*H*-pyrimidine-2,4-dione derivatives

Procedure **C**: A solution of 2,4-bis-(trimethylsilyloxy)pyrimidine (**1**) (0.01 mol), alkyl/allyl halide (0.15 mol) and I_2 (127 mg, 0.001 mol) in 1,2-DCE (20 ml) was refluxed for 24–48 h. Then appropriately substituted *o*-chlorobenzyl chloride (0.02 mol) was added and the refluxing was continued. After completion of the reaction (TLC), it was cooled and treated with ethanol (10 ml). The solvent was distilled off under vacuum and the residue was column chromatographed over silica-gel column using hexane–ethyl acetate as eluents to isolate the pure compounds.

4.4.1. 1-Allyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15a). 73%; Pale yellow liquid, FAB mass *m*/*z* 277, 279 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.30 (2H, d, *J*=6.2 Hz, CH_2), 5.24 (2H, s, CH_2), 5.29–5.35 (2H, m, =CH_2), 5.88 (1H, d, *J*=8.0 Hz, C5-H), 5.91–5.95 (1H, m, =CH), 6.96–7.11 (1H, m, ArH), 7.15–7.35 (4H, m, ArH+C6-H). The decoupling of 5-H doublet at δ 5.88 gives a sharp singlet at δ 7.24 embedded into a multiplet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.76 (−ve, CH_2), 50.95 (−ve, CH_2), 101.45 (+ve, 5-CH), 117.53 (−ve, CH_2), 126.46 (+ve, ArCH), 126.62 (+ve, ArCH), 127.89 (+ve, ArCH), 129.42 (+ve, ArCH), 131.52 (+ve, CH), 133.27 (ab, C), 135.45 (ab, C), 143.98 (+ve, 6-CH), 150.85 (ab, C), 162.48 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3104, 1712, 1643, 752, 810; (Found C, 60.9; H, 4.76; N, 9.97%. $C_{14}H_{13}ClN_2O_2$ requires C, 60.7; H, 4.70; N, 10.12%).

4.4.2. 1-Cinnamyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15b). 72%; Light yellow solid, mp 110 °C (CH_3CN); FAB mass *m*/*z* 353, 355 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 4.53 (2H, d, *J*=6.0 Hz, CH_2), 5.17 (2H, s, CH_2), 5.84 (1H, d, *J*=7.8 Hz, C5-H), 6.22 (1H, dt, J_1=16.0 Hz, J_2=6.0 Hz, =CH), 6.87 (1H, d, *J*=16.0 Hz, =CH), 7.15–7.51 (10H, m, ArH+C6-H); ^{13}C (normal, DEPT-135) ($CDCl_3$): δ 42.14 (−ve, CH_2), 50.78 (−ve, CH_2), 101.75 (+ve, 5-CH), 122.14 (+ve, ArCH), 126.54 (+ve, ArCH), 126.74 (+ve, ArCH), 126.77 (+ve, ArCH), 128.22 (+ve, ArCH), 128.37 (+ve, ArCH), 128.62 (+ve, ArCH), 129.51 (+ve, CH), 132.94 (ab, C), 133.68 (ab, C), 135.04 (+ve, CH), 135.47 (ab, C), 141.93 (+ve, 6-CH), 151.22 (ab, C), 162.78 (ab, C); ν_{max} (KBr)/cm^{-1}: 3050, 1706, 1643, 752; (Found C, 67.9; H, 5.0; N, 8.2%. $C_{20}H_{17}ClN_2O_2$ requires C, 68.09; H, 4.86; N, 7.94%).

4.4.3. 1-Ethyl-3-[(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15c). 63%; Transparent liquid, FAB mass *m*/*z* 265, 267 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 1.27 (3H, t, *J*=7.8 Hz, CH_3), 3.82 (2H, q, *J*=7.8 Hz, CH_2), 5.25 (2H, s, CH_2), 5.82 (1H, d, *J*=7.8 Hz, C-5H), 6.94–6.98 (1H, m, ArH), 7.12–7.46 (4H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.24 (+ve, CH_3), 41.86 (−ve, CH_2), 44.89 (−ve, CH_2), 101.51 (+ve, 5-CH), 126.59 (+ve, ArH), 126.74 (+ve, ArH), 128.17 (+ve, ArH), 129.47 (+ve, ArH), 131.63 (ab, C), 133.48 (ab, C), 142.31 (+ve, 6-CH), 150.99 (ab, C), 162.88 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3050, 2900, 2950, 1710, 1618, 810; (Found: C, 58.92; H, 5.02; N, 9.86. $C_{13}H_{13}ClN_2O_2$ requires C, 58.97; H, 4.95; N, 10.59%).

4.4.4. 1-Butyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15d). 78%; Transparent liquid, FAB mass *m*/*z* 293, 295 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 0.98 (3H, t, *J*=7.2 Hz, CH_3), 1.32 (2H, hextet, *J*=7.2 Hz, CH_2), 1.68 (2H, quintet, *J*=7.2 Hz, CH_2), 3.74 (2H, t, *J*=7.2 Hz, CH_2), 5.28 (2H, s, CH_2), 5.84 (1H, d, *J*=8.0 Hz, C5-H), 6.97–7.01 (1H, m, ArH), 7.13–7.48 (4H, m, ArH+C6-H); The decoupling of the C5-H signal at δ 5.84 gives a singlet at δ 7.19 embedded into a multiplet; ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.56 (+ve, CH_3), 19.61 (−ve, CH_2), 30.97 (−ve, CH_2), 42.04 (−ve, CH_2), 49.63 (−ve, CH_2), 101.32 (+ve, 5-CH), 126.61 (+ve, ArH), 126.72 (+ve, ArH), 128.16 (+ve, ArH), 129.51 (+ve, ArH), 132.97 (ab, C), 133.76 (ab, C), 142.62 (+ve, 6-CH), 151.23 (ab, C), 162.96 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3050, 2958, 1708, 1662, 810 cm^{-1}; (Found C, 61.5; H, 5.68; N, 9.38%. $C_{15}H_{17}ClN_2O_2$ requires C, 61.5; H, 5.81; N, 9.57%).

4.4.5. 1-Octyl-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15e). 67%; Transparent liquid, FAB mass *m*/*z* 349, 351 (3:1) (M^+); ^{1}H NMR ($CDCl_3$): δ 0.87 (3H, t, *J*=7.2 Hz, CH_3), 1.27–1.29 (8H, m, 4×CH_2), 1.64–1.68 (4H, m, 2×CH_2), 3.74 (2H, t, *J*=7.2 Hz, CH_2), 5.25 (2H, s, CH_2), 5.80 (1H, d, *J*=8.0 Hz, C5-H), 6.93–6.98 (1H, m, ArH), 7.24 (1H, d, *J*=8.0 Hz, C6-H), 7.26–7.38 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.99 (+ve, CH_3), 22.52 (−ve, CH_2), 26.43 (−ve, CH_2), 29.03 (−ve,

CH_2), 31.65 (−ve, CH_2), 49.89 (−ve, CH_2), 101.31 (+ve, 5-CH), 126.62 (+ve, ArH), 126.91 (+ve, ArH), 128.15 (+ve, ArH), 129.35 (+ve, ArH), 132.99 (ab, C), 133.80 (ab, C), 142.6 (+ve, 6-CH), 150.99 (ab, C), 162.87 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3043, 2923, 1689, 1641, 813; (Found: C, 65.48; H, 7.23; N, 7.87. $C_{19}H_{25}ClN_2O_4$ requires C, 65.41; H, 7.22; N, 8.03).

4.4.6. 1-(Ethoxycarbonylmethyl)-3-(2-chlorobenzyl)-1*H*-pyrimidine-2,4-dione (15f). 64%; Transparent liquid, FAB mass *m/z* 323, 325 (3:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.29 (3H, t, J=7.2 Hz, CH_3), 4.22 (2H, q, J=7.2 Hz, CH_2), 4.46 (2H, s, CH_2), 5.24 (2H, s, CH_2), 5.85 (1H, d, J=7.8 Hz, C5-H), 6.95–7.51 (5H, m, ArH+C6-H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.98 (+ve, CH_3), 42.11 (−ve, CH_2), 49.87 (−ve, CH_2), 62.09 (−ve, CH_2), 102.13 (+ve, CH-5), 126.65 (+ve, ArH), 127.50 (+ve, ArH), 129.44 (+ve, ArH), 129.64 (+ve, ArH), 132.92 (ab, C), 133.43 (ab, C), 142.52 (+ve, CH-6), 151.34 (ab, C), 162.62 (ab, C), 167.29 (ab, C); ν_{max} ($CHCl_3$)/cm^{-1}: 3064, 2987, 1747, 1704, 1658, 1207, 811; (Found: C, 55.79; H, 4.77; N, 8.60. $C_{15}H_{15}ClN_2O_4$ requires C, 55.80; H, 4.65; N, 8.60).

4.4.7. 1-Allyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16a). 62%; Solid, mp 94 °C (CH_3CN); FAB mass *m/z* 311, 313, 315 (100:62:1) (M^+); ^1H NMR ($CDCl_3$): δ 4.36 (2H, d, J=8 Hz, CH_2), 5.21 (2H, s, CH_2), 5.25–5.35 (2H, m, =CH_2), 5.72 (1H, d, J=8.0 Hz, C5-H), 5.79–5.90 (1H, m, =CH), 6.96 (1H, d, J=8.0 Hz, Ar-6′H), 7.12 (1H, dd, J_1=8.0 Hz, J_2=1.2 Hz, Ar-5′H) 7.21 (1H, d, J=8.0 Hz, C6-H), 7.78 (1H, d, J=1.2 Hz, Ar-3′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 41.75 (−ve, CH_2), 51.09 (−ve, CH_2), 101.63 (+ve, 5-CH), 119.58 (−ve, =CH_2), 127.06 (+ve, ArCH), 128.02 (+ve, ArCH), 129.32 (+ve, ArCH), 131.27 (+ve, CH), 131.43 (ab, C), 132.40 (ab, C), 133.37 (ab, C), 142.27 (+ve, 6-CH), 151.06 (ab, C), 162.97 (ab, C); ν_{max} (KBr)/cm^{-1}: 3089, 1708, 1658, 808; (Found: C, 53.9; H, 3.9; N, 9.3. $C_{14}H_{12}Cl_2N_2O_2$ requires C, 54.04; H, 3.89; N, 9.00%).

4.4.8. 1-Ethyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16b). 70%; White solid, mp 98 °C (CH_3CN); FAB mass *m/z* 299, 301 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.27 (3H, t, J=7.2 Hz, CH_3), 3.81 (2H, q, J=7.2 Hz, CH_2), 5.19 (2H, s, CH_2), 5.83 (1H, s, J=7.8 Hz, C5-H), 6.92 (1H, d, J=8.4 Hz, Ar6′-H); 7.14 (1H, dd, J_1=8.4 Hz, J_2=1.8 Hz, Ar-5′H), 7.23 (1H, d, J=7.8 Hz, C6-H), 7.37 (1H, d, J=1.8 Hz, Ar-3′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.25 (+ve, CH_3), 41.68 (−ve, CH_2), 45.03 (−ve, CH_2), 101.42 (+ve, 5-CH), 127.05 (+ve, ArCH), 128.09 (+ve, ArCH), 129.31 (+ve, ArCH), 132.45 (ab, C), 133.39 (ab, C), 133.76 (ab, C), 142.51 (+ve, 6-CH), 150.94 (ab, C), 163.28 (ab, C); ν_{max} (KBr)/cm^{-1}: 3087, 3060, 2897, 1708, 1656, 808 cm^{-1}; (Found: C, 51.9; H, 3.8; N, 9.5. $C_{13}H_{12}Cl_2N_2O_2$ requires C, 52.19; H, 4.04; N, 9.36%).

4.4.9. 1-Butyl-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16c). 63%; White solid, mp 60 °C (CH_3CN); FAB mass *m/z* 327, 329, 331 (100:62:1) (M^+); ^1H NMR ($CDCl_3$): δ 0.98 (3H, t, CH_3), 1.25–1.42 (2H, m, CH_2), 1.62–1.72 (2H, m, CH_2), 3.76 (2H, t, CH_2), 5.17 (2H, s, CH_2), 5.83 (1H, d, J=8.0 Hz, C5-H), 6.94 (1H, d, J=8.0 Hz, C6-H), 7.13–7.48 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.59 (+ve, CH_3), 19.63 (−ve, CH_2), 30.90 (−ve, CH_2), 41.64 (−ve, CH_2), 49.67 (−ve, CH_2), 101.32 (+ve, 5-CH), 127.02 (+ve, ArH), 127.96 (+ve, ArH), 131.38 (+ve, ArH), 131.75 (absent, C), 133.38 (absent, C), 133.78 (absent, C), 142.8 (+ve, 6-CH), 151.18 (absent, C), 163.04 (absent, C); ν_{max} (KBr)/cm^{-1}: 3056, 2960, 1703, 1672, 811; HRMS found: 327.0662, $C_{15}H_{17}^{35}Cl_2N_2O_2$ requires 327.0659.

4.4.10. 1-(Ethoxycarbonylmethyl)-3-(2,4-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (16d). 64%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 357, 359, 361 (100:70:10) (M^+); ^1H NMR ($CDCl_3$): δ 1.28 (3H, t, J=7.2 Hz, CH_3), 4.23 (2H, q, J=7.2 Hz, OCH_2), 4.64 (2H, s, NCH_2), 5.20 (2H, s, CH_2), 5.83 (1H, d, J=8.0 Hz, C-5H), 6.93 (1H, d, J=8.0 Hz, C-6H), 7.07–7.38 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.04 (+ve, CH_3), 41.62 (−ve, CH_2), 49.76 (−ve, CH_2), 62.05 (−ve, CH_2), 102.03 (+ve, 5-CH), 127.03 (+ve, ArCH), 127.90 (+ve, ArCH), 129.28 (+ve, ArCH), 132.40 (ab, C), 133.57 (ab, C), 133.86 (ab, C), 142.32 (+ve, 6-CH), 151.26 (ab, C), 162.28 (ab, C), 167.10 (ab, C); ν_{max} (KBr)/cm^{-1}: 3074, 2995, 2958, 1743, 1720, 1683, 1236, 779; (Found: C, 50.3; H, 3.9; N, 7.8. $C_{15}H_{14}Cl_2N_2O_4$ requires C, 50.44; H, 3.95; N, 7.84%).

4.4.11. 1-Allyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17a). 65%; White solid, mp 110 °C (CH_3CN); FAB mass *m/z* 311, 313, 315 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 4.30 (2H, d, J=6.0 Hz, CH_2), 5.13–5.23 (2H, m, =CH_2), 5.41 (2H, s, CH_2), 5.72–5.87 (1H, m, =CH), 5.88 (1H, d, J=8.0 Hz, C5-H), 7.12 (1H, d, J=8.0 Hz, C6-H), 7.17 (1H, t, J=8.0 Hz, Ar-4′H), 7.37 (2H, d, J=8.0 Hz, Ar-3′/5′H); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 40.93 (−ve, CH_2), 50.77 (−ve, CH_2), 101.73 (+ve, 5-CH), 118.99 (−ve, CH_2), 128.53 (+ve, ArCH), 128.79 (+ve, ArCH), 131.61 (+ve, =CH), 131.87 (ab, C), 135.73 (ab, C), 141.74 (+ve, CH), 150.99 (ab, C), 162.73 (ab, C); ν_{max} (KBr)/cm^{-1}: 3050, 1708, 1656, 736; (Found: C, 53.9; H, 3.7; N, 9.1. $C_{14}H_{12}Cl_2N_2O_2$ requires C, 54.04; H, 3.89; N, 9.00%).

4.4.12. 1-Butyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17b). 62%; Solid, mp 140 °C (CH_3CN); FAB mass *m/z* 327, 329, 331 (100: 72:1) (M^+); ^1H NMR ($CDCl_3$): δ 0.98 (3H, t, J=7.2 Hz, CH_3), 1.25–1.37 (2H, m, CH_2), 1.40–1.72 (2H, m, CH_2), 3.73 (2H, t, J=7.2 Hz, CH_2), 5.18 (2H, s, CH_2), 5.80 (1H, d, J=9.0 Hz, C5-H), 6.92 (1H, d, J=9.0 Hz, C6-H), 7.09–7.45 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 13.56 (+ve, CH_3), 19.54 (−ve, CH_2), 30.93 (−ve, CH_2), 40.87 (−ve, CH_2), 49.46 (−ve, CH_2), 101.23 (+ve, 5-CH), 128.50 (+ve, ArCH), 128.68 (+ve, ArCH), 131.94 (ab, C), 135.65 (ab, C), 142.35 (+ve, 6-CH), 151.03 (ab, C), 162.87 (ab, C); ν_{max} (KBr)/cm^{-1}: 3070, 2952, 1712, 1656, 800; (Found: C, 55.36; H, 4.60; N, 8.19. $C_{15}H_{16}Cl_2N_2O_2$ requires C, 55.04; H, 4.89; N, 8.56%).

4.4.13. 1-Ethoxycarbonylmethyl-3-(2,6-dichlorobenzyl)-1*H*-pyrimidine-2,4-dione (17c). 62%; White solid, mp 120 °C (CH_3CN); FAB mass *m/z* 357, 359, 361 (100: 62:1) (M^+); ^1H NMR ($CDCl_3$): δ 1.29 (3H, t, J=7.2 Hz, CH_3),

4.14 (2H, q, J=7.2 Hz, OCH_2), 4.39 (2H, s, CH_2), 5.38 (2H, s, CH_2), 5.78 (1H, d, J=7.8 Hz, C5-H), 7.06 (1H, d, J=7.8 Hz, C6-H), 7.08–7.27 (3H, m, ArH); ^{13}C (normal/DEPT-135) ($CDCl_3$): δ 14.00 (+ve, CH_3), 40.88 (−ve, CH_2), 49.55 (−ve, CH_2), 61.86 (−ve, CH_2), 101.98 (+ve, 5-CH), 128.37 (+ve, ArCH), 128.60 (+ve, ArCH), 131.89 (ab, C), 136.00 (ab, C), 141.90 (+ve, 6-CH), 151.05 (ab, C), 162.31 (ab, C), 167.13 (ab, C); ν_{max} (KBr)/cm^{-1}: 3083, 2985, 2958, 1743, 1720, 1683, 1236, 779 (Found: C, 49.8; H, 3.8; N, 7.8. $C_{15}H_{14}Cl_2N_2O_4$ requires C, 50.04; H, 3.95; H, 7.84%).

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[6+3] Cycloaddition of pentafulvenes with 3-oxidopyrylium betaine: a novel methodology toward the synthesis of 5–8 fused oxabridged cyclooctanoids

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Abstract—Pentafulvenes undergo a facile [6+3] cycloaddition with 3-oxidopyrylium betaine, generated from the corresponding pyranulose acetate, leading to the formation of 5–8 fused oxabridged cyclooctanoids. The product is formed by a [6+3] cycloaddition, followed by a 1,5-hydrogen shift of the initially formed [6+3] adduct. The reaction was found to be general and a number of fulvenes with a wide range of substituents at the exocyclic double bond, that is, at the C6 position followed a similar reactivity pattern. The [6+3] adduct, a 5–8 fused oxabridged cyclooctanoid, is potentially amenable to a number of synthetic transformations due to the presence of an α,β-unsaturated ketone and cyclopentadiene part. By selecting appropriately substituted fulvene and pyranulose acetates, it is possible to use this methodology for the synthesis of a wide range of 5–8 fused cyclooctanoids. The experimental results have been rationalized on the basis of theoretical calculations.

1. Introduction

The synthesis of cyclooctanoids is of great importance in organic chemistry due to their wide occurrence in many biologically active natural products and synthetic compounds.[1] The interesting biological activities combined with the synthetic challenges have served to make them target molecules in a number of synthetic studies.[2] Some of the interesting cyclooctanoids are shown in Figure 1. Designing efficient, short routes for the stereoselective construction of cyclooctanoids is an interesting challenge in synthetic organic chemistry. Among the various strategies for the synthesis of eight-membered rings,[3] higher order cycloadditions that directly form eight-membered rings[4] are attractive because of their ability to produce complex molecules with extensive functionality in a single step, with good control over the creation of new stereocentres.

Eight-membered rings are notoriously difficult to prepare because of unfavorable entropic and enthalpic effects as well as the propensity for transannular interactions.[5]

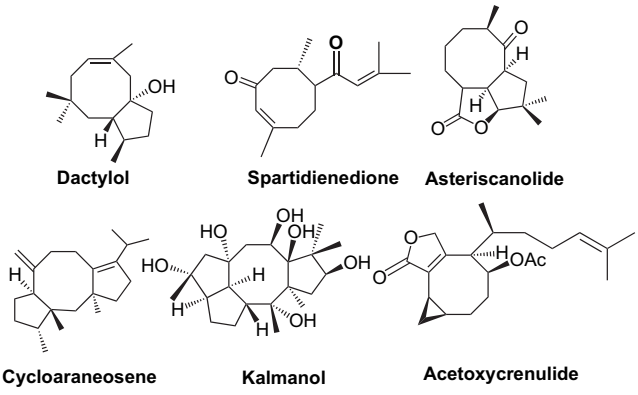

Figure 1. Some of the biologically active cyclooctanoids.

Fragmentation of complex bicyclic systems, metal mediated metathesis, and acyclic ring closures are the commonly used methodologies.[6] [3,3]-Sigmatropic rearrangements of smaller rings to such skeletons have gained popularity because of the high stereoselectivity observed.[6] Transition metal mediated cycloadditions provide another interesting route to cyclooctanoids.[7]

Fulvenes, cyclic molecules with an odd number of carbon atoms in the ring, belong to the category of non-functionalized

Keywords: Fulvenes; Oxidopyrylium betaine; [6+3] Cycloaddition; Oxabridged cyclooctanoids.
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carbon–carbon double bonds.[8] Among various fulvenes, pentafulvenes represent a very attractive structural unit, not only as a model for theoretical studies but also as a valuable building block to access polycyclic cyclopentanoids through a diverse array of cyclizations.[9] The development of efficient and short routes for the stereoselective construction of polycyclic molecules is currently one of the main challenges in synthetic organic chemistry. Pentafulvenes have been the subject of great interest both from synthetic and theoretical points because they exhibit different modes of cycloadditions. In cycloadditions, pentafulvenes can participate as a 2π, 4π, or 6π component[10] and have served as excellent synthons for the synthesis of triquinanes, pyrindines, etc. Investigations from our own laboratory have unraveled the interesting reactivity profile of fulvenes in cycloaddition reactions.[11] Barluenga and co-workers have reported a [6+3] cycloaddition of Fischer carbene complexes[10l] with fulvenes. Recent reports from Hong and co-workers have shown that fulvenes can undergo [6+3] cycloaddition with azomethine ylides leading to the formation of [2]pyrindines [12] and other molecules of biological importance.

3-Oxidopyrylium betaines[13] have been well utilized in the synthesis of cycloheptanoids.[13,14] Hendrickson has reported the generation and cycloaddition of oxidopyrylium betaine with a few electrophilic alkenes leading to oxabicyclo[3.2.1] systems.[14] Later Sammes has demonstrated the utility of oxidopyrylium betaines for the synthesis of oxabicyclic systems by cycloaddition with electron rich and electron deficient alkenes.[13] Wender has exploited the intermolecular cycloaddition of 4-methoxy and 4-silyloxy-3-oxidopyrylium betaines in the construction of phorbol framework.[15] To the best of our knowledge, there is no report on the cycloaddition of pentafulvenes with 3-oxidopyrylium betaines.

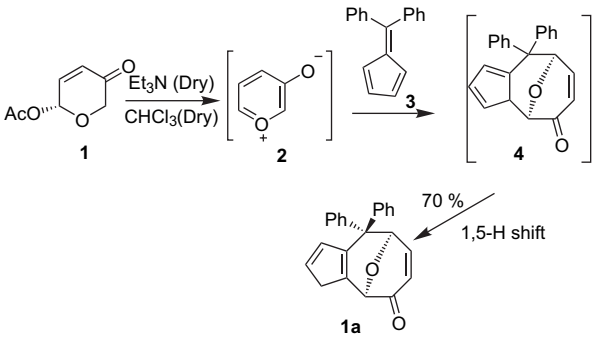
Recently, we have reported a [6+3] cycloaddition of pentafulvenes with 3-oxidopyrylium betaines.[16] We have carried out detailed investigation of the reported reaction with a number of pentafulvenes having wide range of substituents at the exocyclic double bond, that is, at the C6 position. The theoretical calculations were carried out to rationalize the results obtained. The details of our studies are presented in the following section.

2. Results and discussion

2.1. [6+3] Cycloaddition of 6,6-diaryl fulvenes with 3-oxidopyrylium betaine

The fulvenes selected for our studies were synthesized from the corresponding ketone or aldehyde following Little's procedure.[17] The pyranulose acetates,[18] precursors for 3-oxidopyrylium betaines, were synthesized from corresponding furfuryl alcohol by oxidation with *N*-bromosuccinimide followed by protection with acetic anhydride in the presence of pyridine and DMAP.

Our initial experiments involved the reaction of 6,6-diarylfulvene **3** with 3-oxidopyrylium betaine **2**. The reaction proceeded smoothly affording the [6+3] adduct **1a** in 70% yield (Scheme 1).



Scheme 1.

The product **1a** was characterized on the basis of spectroscopic data. The IR spectrum showed characteristic absorptions at 1691 cm^{-1}, indicating the presence of an α,β-unsaturated carbonyl, and at 1077 cm^{-1} indicative of the ether linkage. In the ^1H NMR spectrum, the two protons at C1 appeared as a singlet at δ 3.06 ppm. Two bridgehead protons resonated as a singlet and doublet at δ 4.88 and 5.36 ppm, respectively. The protons at C5 and C6 appeared as a doublet and double doublet at δ 5.76 and 5.99 ppm, respectively. ^{13}C NMR spectroscopy showed a characteristic signal for a carbonyl group at δ 194.5 ppm. The bridgehead carbons appeared at δ 76.6 and 74.9 ppm. Unambiguous evidence for the structure and stereochemistry of the product was obtained by single crystal X-ray analysis[16] (Fig. 2). The product **1a** is formed by a [6+3] cycloaddition followed by a 1,5-hydrogen shift.

Similar reactivity was observed with different 6,6-diaryl fulvenes and the results are summarized in Table 1. 6,6-Diaryl fulvenes afforded [6+3] adducts on reaction with 3-oxidopyrylium betaines in good to excellent yield.

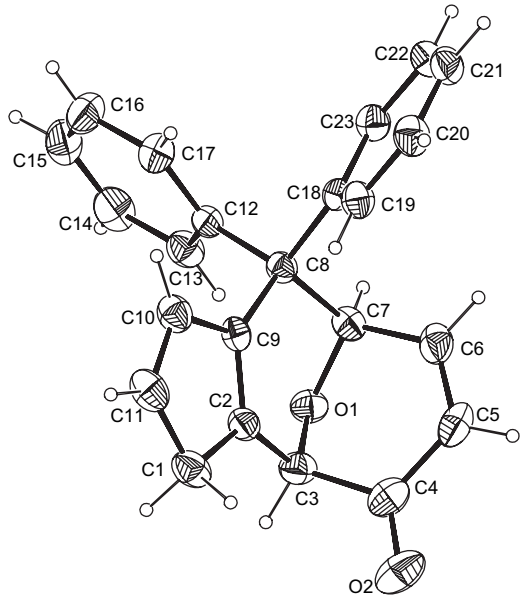
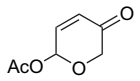
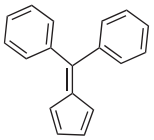
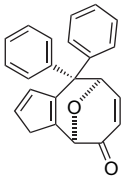
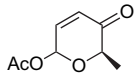
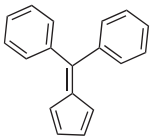
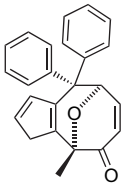
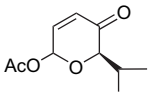
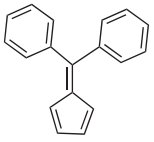
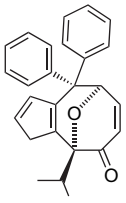
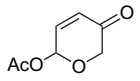
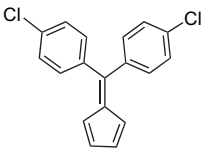
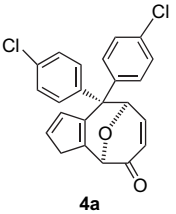


Figure 2. ORTEP plot for X-ray crystal structure of **1a**.

Table 1. [6+3] Cycloaddition of 6,6-diaryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1a**	70
2			 **2a**	62
3			 **3a**	53
4			 **4a**	57

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

2.2. [6+3] Cycloaddition of 6,6-dimethyl fulvene with 3-oxidopyrylium betaines

6,6-Dimethyl fulvene showed a similar reactivity pattern and the results are summarized in Table 2. The unsubstituted 3-oxidopyrylium betaine **2** on reaction with 6,6-dimethyl fulvene afforded [6+3] adduct in 83% yield. 2-Methyl and 2-isopropyl substituted 3-oxidopyrylium betaine also afforded [6+3] adducts in good yield.

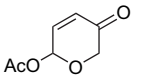
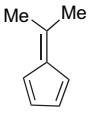
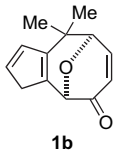
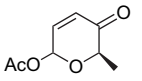
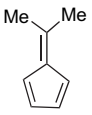
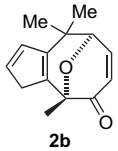
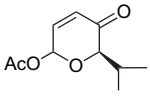
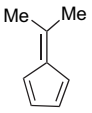
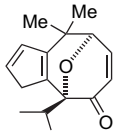
2.3. [6+3] Cycloaddition of cycloalkyl fulvenes with 3-oxidopyrylium betaines

Cycloalkyl fulvenes (6,6-pentamethylene, hexamethylene, and heptamethylene fulvenes), prepared from the corresponding cyclic ketones, also followed a similar reaction pathway and the results obtained with various substituted betaines are summarized in Table 3.

2.4. [6+3] Cycloaddition of 6-alkyl,6-aryl fulvenes and 6-aryl fulvenes with 3-oxidopyrylium betaines

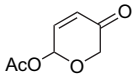
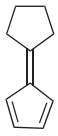
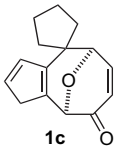
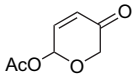
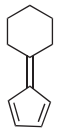
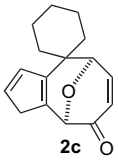
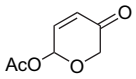
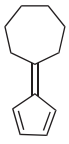
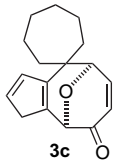
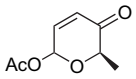
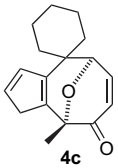
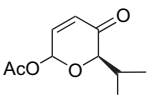
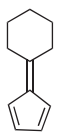
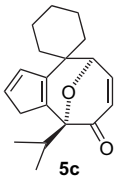
6-Alkyl,6-aryl fulvenes and 6-aryl fulvenes also underwent smooth [6+3] cycloaddition leading to the functionalized 5–8 fused cyclooctanoids in good to excellent yield. The results are summarized in Tables 4 and 5.

Table 2. [6+3] Cycloaddition of 6,6-dimethyl fulvene with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1b**	83
2			 **2b**	79
3			 **3b**	68

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

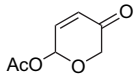
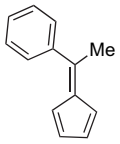
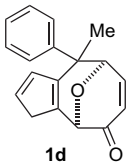
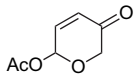
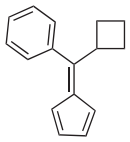
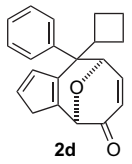
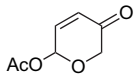
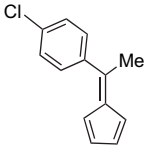
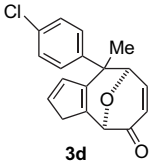
Table 3. [6+3] Cycloaddition of cycloalkyl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1c**	70
2			 **2c**	60
3			 **3c**	58
4			 **4c**	59
5			 **5c**	52

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

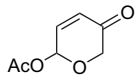
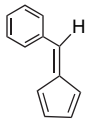
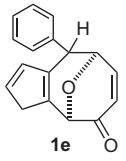
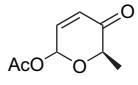
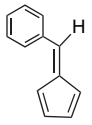
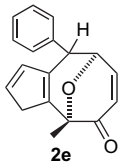
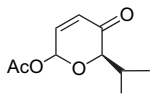
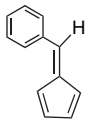
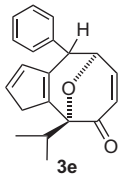
From the results summarized in Tables 1–5, it is clear that pentafulvenes undergo facile [6+3] cycloaddition with 3-oxidopyrylium betaines leading to the regioselective formation of 5–8 fused cyclooctanoids in good to excellent

Table 4. [6+3] Cycloaddition of 6-alkyl,6-aryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1d**	67
2			 **2d**	54
3			 **3d**	50

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

Table 5. [6+3] Cycloaddition of 6-aryl fulvenes with 3-oxidopyrylium betaines

Entry	Pyranulose acetate	Fulvene	Product	Yield [%]
1			 **1e**	65
2			 **2e**	50
3			 **3e**	45

Reaction conditions: fulvene (1.0 equiv), pyranulose acetate (1.2 equiv), Et_3N (1.2 equiv), $CHCl_3$, 50 °C, 6 h.

yield. The reaction is applicable to a wide range of fulvenes with substituents at C6 position, i.e., at the exocyclic double bond.

The adducts obtained may be transformed to fused eight-membered rings, which is the main structural skeleton of a number of natural products such as dactylol, asteriscanolide, cycloaraneosene, kalmanol, etc (Fig. 1). A survey of the literature showed that some of the naturally occurring oxabridged cyclooctanoids possess interesting biological activity such as cytotoxicity and anti-HIV activity (Fig. 3).[19] The presence of an α,β-unsaturated ketone, an oxabridge and the cyclopentadiene functionality makes these adducts

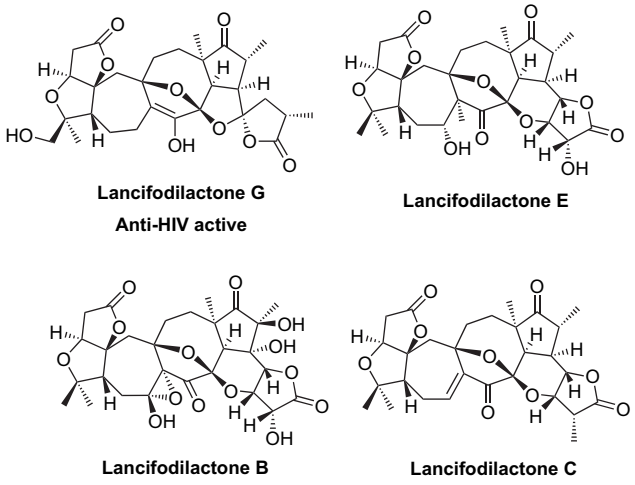


Figure 3. Examples of oxabridged cyclooctanoid natural products.

amenable to a number of synthetic transformations. It is presumed that by using appropriately functionalized fulvenes and oxidopyrylium betaines, the present methodology can be utilized in the synthesis of fused oxabridged cyclooctanoid natural products.

We have carried out theoretical calculations to rationalize the results obtained and are discussed in the following section.

3. Theoretical calculations

All the molecular geometries were optimized at the DFT level by using the Becke's three-parameter exchange functional (B3)[20,21] in conjunction with the Lee–Yang–Parr correlation functional (LYP)[22] as implemented in the Gaussian 03 suite of programs.[23] For H, C, and O, 6-31G(d) basis functions were selected.[24] Normal coordinate analysis has been performed for all stationary points to characterize the transition states and minimum structures. The calculated Gibbs' free energy changes were used throughout the text for discussing the energetics.

Several modes of cycloaddition reactions between fulvene and 3-oxidopyrylium betaine can be envisioned. At first, using unsubstituted fulvene and the 3-oxidopyrylium betaine shown in Figure 4, we have investigated the 18 different possible cycloaddition products. The structure and energetics of these cycloadducts are depicted in Figure 5.

The optimized geometry of fulvene shows two localized double bonds of length 1.353 Å each in the ring and another one of 1.344 Å in the *exo* position (Fig. 4a). The *exo* double bond is more localized than the ring double bonds, which is consistent with the experimental geometry.[25] In the case of 3-oxidopyrylium betaine, the C2–C3 and C3–C4 bonds are significantly longer than other bonds (Fig. 4b) as well as a typical C–C aromatic bond (1.400 Å), which means that the schematic structure given in Figure 4c is quite suitable for this molecule. The dotted lines represent a 6π electron conjugation, which includes two electrons from ring oxygen as in the case of furan molecule. However, compared to furan where the C–O bond lengths are 1.369 Å,[26] the bonding around the ring oxygen in the oxidopyrylium betaine

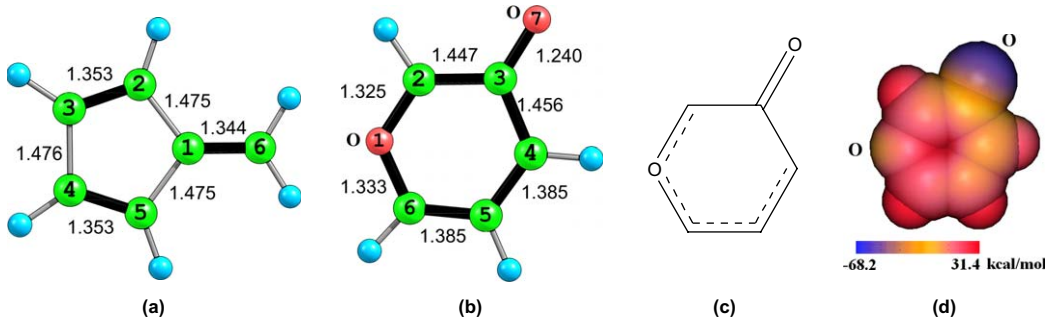


Figure 4. Optimized structure of (a) fulvene and (b) 3-oxidopyrylium betaine. (c) Schematic structure of 3-oxidopyrylium betaine and (d) MESP painted on the van der Waals' surface of betaine. Bond lengths in Å. See text for details.

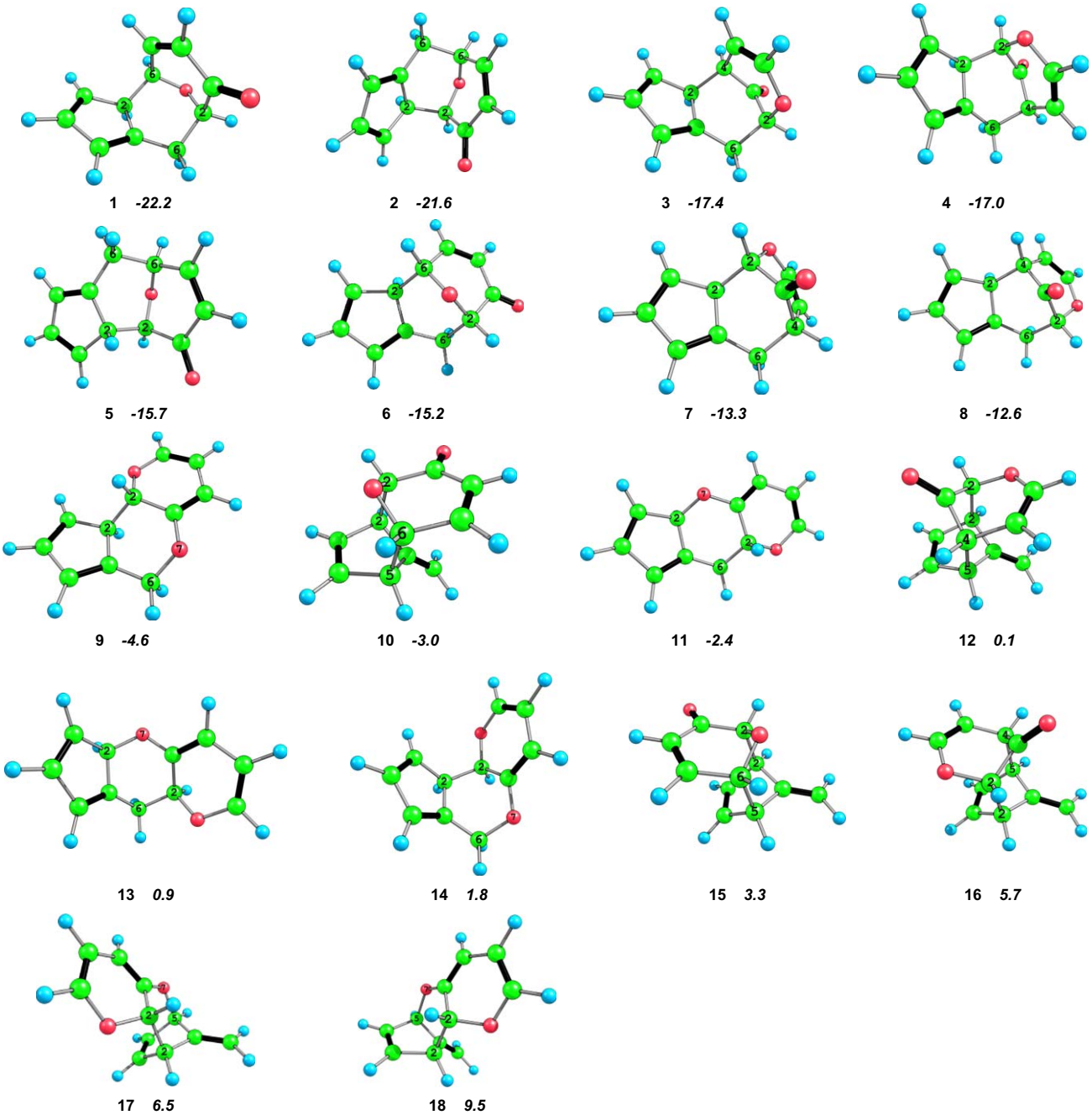


Figure 5. Optimized geometries of various cycloadducts (values in italics are relative free energy in kcal/mol). The sum of the free energies of fulvene and 3-oxidopyrylium betaine is taken as 0.0 kcal/mol.

is stronger. The molecular electrostatic potential (MESP) analysis was carried out on the oxidopyrylium betaine to understand its π-electron distribution.[27] It is found that the negative MESP is centered around the carbonyl oxygen and no negative MESP is observed over the ring region (Fig. 4d). This suggests a zwitterionic structure for this molecule wherein the carbonyl oxygen and the ring oxygen would bear the negative and positive charges, respectively.

Among the 18 cycloadducts given in Figure 5, the structures **1**, **2**, **5**, and **6** are formed as a result of [6+3] cycloaddition in which the atoms C2 and C6 of both fulvene and 3-oxidopyrylium betaine are reacted. Compound **1** is formed from *endo*-cycloaddition giving rise to $C2_{(fulvene)}$–$C6_{(betaine)}$ and $C6_{(fulvene)}$–$C2_{(betaine)}$ bond formations while **2**, also an *endo*-cycloaddition product is formed by the $C2_{(fulvene)}$–$C2_{(betaine)}$ and $C6_{(fulvene)}$–$C6_{(betaine)}$ bond formations. Similarly, **5** and **6** are obtained by the *exo*-cycloadditions. Clearly, the *endo*-cycloaddition products are more stable than *exo*- and all other cycloaddition products. The transition states (TSs) **TS1** and **TS2** are also located for the cycloaddition corresponding to the formation of **1** and **2**, respectively (Fig. 6). A relative free energy of 19.1 kcal/mol is obtained for **TS1** while it is 7.4 kcal/mol for **TS2**. This suggests that compound **2** is the most favored product in cycloaddition step of the reaction. It may be noted that in the experiment, predominantly only one product is formed and in the case of the reaction of 6,6-diphenyl fulvene, the X-ray structure of the product is also available (Fig. 2). This product can be considered as formed from **2** (except for the substituent phenyl groups) when it undergoes a 1,5-hydrogen shift of the H atom, which was originally bonded to the C2 atom of fulvene. For the 1,5-hydrogen shift starting from **2**, a TS **TS3** is also located which gives an activation barrier of 16.7 kcal/mol for it (Fig. 6). Thus, the theoretical study using the unsubstituted systems strongly support the stereoselective formation of the product shown in Figure 2. Since in the calculation **1** is 0.6 kcal/mol more stable than **2**, we expect that in the experiment the stereoelectronic effect exerted by the phenyl groups may give additional stability to the cycloadduct **2** than **1**. In order to understand this substituent effect, further modeling study is carried out for the reaction of 6,6-diphenyl fulvene and the 3-oxidopyrylium betaine.

The optimized geometry of the cycloadducts **19** and **20** which are similar to **1** and **2**, respectively, are presented in Figure 7. Interestingly, **20** is more stable than **19** by 1.9 kcal/mol and as noted in the previous paragraph, this can be attributed to the stereoelectronic effect of the phenyl groups. The TSs **TS4** and **TS5** are also located for the formation of **19** and **20**, respectively. **TS5** is 11.7 kcal/mol lower in energy than **TS4**, which further confirms the stereoselective formation of **20**. Moreover, the activation barrier of 22.2 kcal/mol obtained from **TS5** for the [6+3] cycloaddition is quite reasonable for a feasible reaction as compared to a higher activation barrier of 33.9 kcal/mol obtained from **TS4**. It may be noted that the steric effect is in favor of the less stable TS **TS4** because a closer approach of the reactants is found in this TS as compared to **TS5**. Therefore, the higher stability of **TS5** and the corresponding product **20** can be attributed mainly to the electronic effect. The same conclusion can be obtained even from the unsubstituted systems as one can see a higher stability of 11.7 kcal/mol for **TS2** than **TS1**. This difference should come mainly from the electronic effect because the steric effect is nearly the same or negligible in both the TSs. Also obtained is a TS **TS6** for the 1,5-hydrogen shift starting from **20** and the corresponding product **21** (Fig. 7). The activation energy of 26.6 kcal/mol is predicted for this step of the reaction.

4. Conclusion

In conclusion, we have unraveled a novel reactivity pattern of pentafulvenes with 3-oxidopyrylium betaines. It offers a useful methodology for the synthesis of 5–8 fused cyclooctanoids. The theoretical studies have confirmed a highly stereospecific *endo*-cycloaddition giving rise to $C2_{(fulvene)}$–$C2_{(betaine)}$ and $C6_{(fulvene)}$–$C6_{(betaine)}$ bond formations. The intermediate product thus formed (**20**) undergoes a facile 1,5-hydrogen shift at the five-membered ring of fulvene unit to yield the cyclooctanoid system **21** (Fig. 6), which is in complete agreement with the X-ray structure of the product reported in Figure 2. The reaction was found to be general and a number of fulvenes with a wide range of substituents at the exocyclic double bond, that is, at the C6 position followed similar reactivity pattern. The [6+3] adduct, a 5–8 fused oxabridged cyclooctanoid, is potentially amenable to a number of synthetic transformations due to the presence of an α,β-unsaturated ketone and cyclopentadiene part. By selecting appropriately substituted fulvene and pyranulose acetate, it is possible to use this methodology for the synthesis of a wide range of 5–8 fused cyclooctanoids.

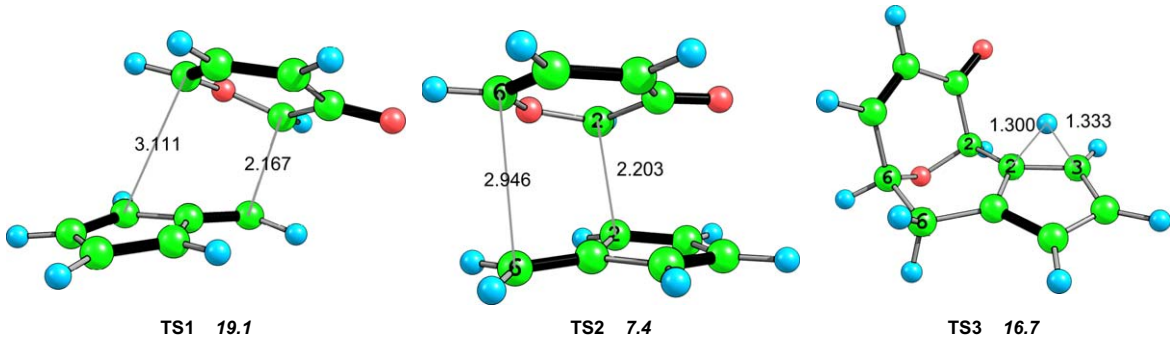


Figure 6. Optimized geometries of transition states. **TS1** and **TS2** are for the formation of **1** and **2**, respectively, and **TS3** for the 1,5-hydrogen shift. The sum of the free energies of fulvene and oxidopyrylium betaine is taken as 0.0 kcal/mol.

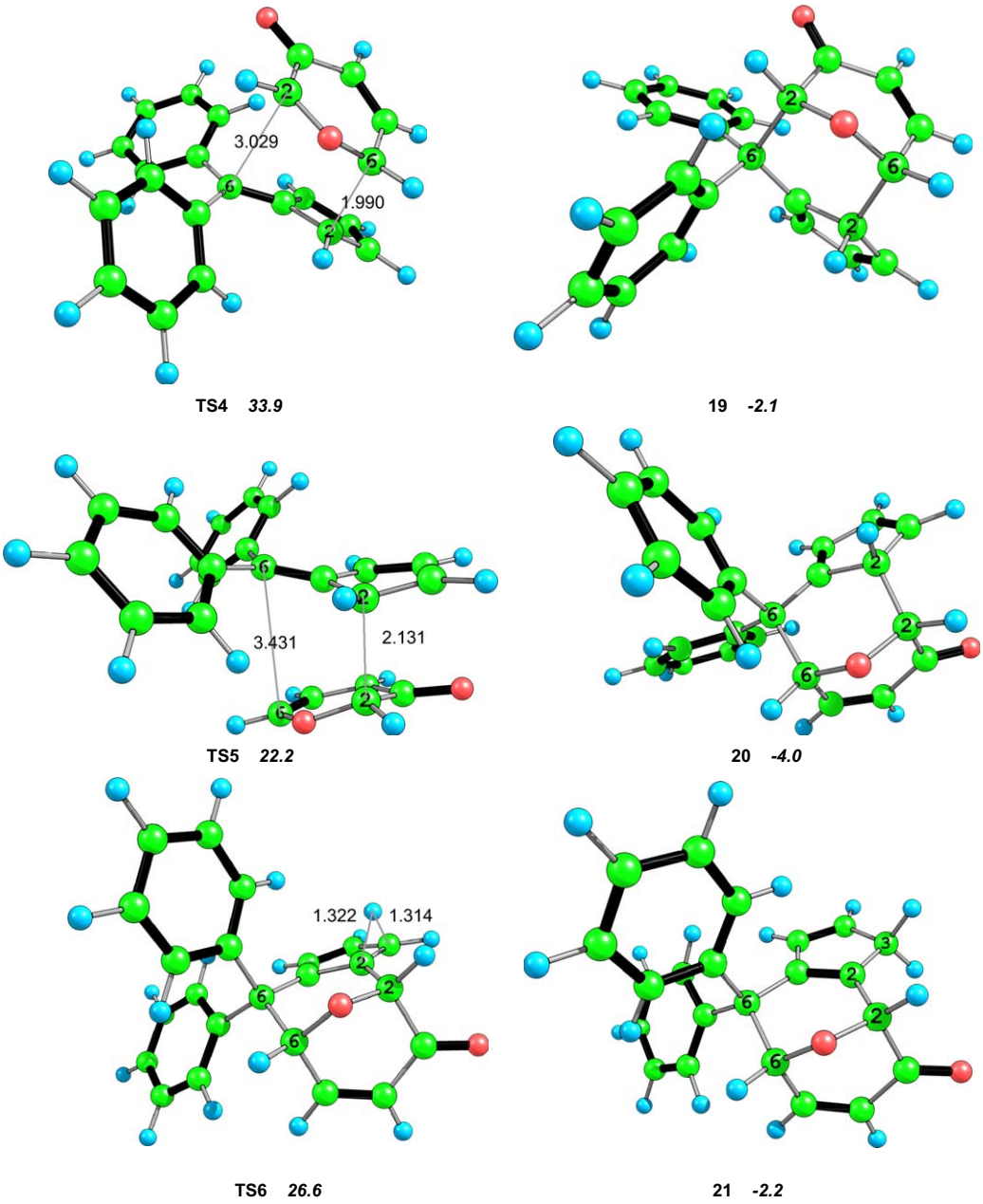


Figure 7. Optimized geometries of the TSs (**TS4** and **TS5**) and products (**19** and **20**) for [6+3] cycloaddition as well as the TS (**TS6**) and product (**21**) for 1,5-hydrogen shift. Relative free energy values with respect to the sum of the free energies of 6,6-diphenyl fulvene and 3-oxidopyrylium betaine are given in italics.

Further work to utilize this methodology toward the synthesis of biologically active oxabridged cyclooctanoids is in progress and will be reported in due course.

5. Experimental

5.1. General

All reactions were carried out in oven-dried glasswares under an atmosphere of argon. Progress of reactions was monitored by thin layer chromatography (Silica gel 60 F_{254}, 0.25 mm, Merck) and purification was effected using silica gel column chromatography. NMR spectra were recorded at 300 (^{1}H) and 75 (^{13}C) MHz on a Brücker DPX-300 MHz spectrometer. Chemical shifts (δ) were reported relative to TMS (^{1}H) and $CDCl_3$ (^{13}C) as the internal standards. Coupling constants (J) are reported in Hertz (Hz). IR spectra were recorded on a Bomem MB Series FTIR spectrophotometer. Melting points were recorded on a Buchi melting point apparatus and are uncorrected. Fulvenes were prepared according to the literature procedure.[17] Pyranulose acetates,[18] precursors for 3-oxidopyrylium betaines, were prepared from corresponding furfuryl alcohol by oxidation with *N*-bromosuccinimide followed by protection with acetic anhydride in presence of pyridine and DMAP. Commercial grade solvents were distilled prior

to use. Triethylamine, chloroform and diethyl ether were dried as per the standard procedures.

5.1.1. Details of a typical experiment are as follows. Diphenyl fulvene (100 mg, 0.43 mmol), pyranulose acetate (81 mg, 0.52 mmol) and dry triethylamine (52 mg, 0.52 mmol) were taken in anhydrous chloroform and stirred at 50 °C in a Schlenk tube for 6 h under nitrogen. The solvent was removed under reduced pressure and the residue was subjected to chromatography on a silica gel (60–120 mesh) column using 5% ethyl acetate/hexane mixture as eluent to afford the product as a pale yellow crystalline solid (98 mg, 70%). The product **1a** was recrystallized from dichloromethane/hexane mixture.

5.2. Spectroscopic data for new compounds

5.2.1. Compound 1a. Yield 70%, pale yellow crystalline solid. Mp 173–175 °C. R_f 0.50 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3062, 2928, 1691, 1598, 1443, 1376, 1247, 1160, 1077, 1036, 943 cm^{-1}. ^1H NMR: δ 3.06 (s, 2H), 4.88 (s, 1H), 5.36 (d, 1H, J=4.3 Hz), 5.76 (d, 1H, J=10.4 Hz), 5.99 (dd, 1H, J_1=4.3, J_2=10.4 Hz), 6.44 (d, 1H, J=5.3 Hz), 6.56 (d, 1H, J=5.3 Hz), 7.00–7.54 (m, 10H). ^{13}C NMR: δ 194.5, 148.5, 145.8, 142.3, 141.4, 133.9, 132.9, 132.3, 129.3, 129.0, 128.6, 128.4, 128.3, 128.2, 127.3, 126.4, 123.2, 76.6, 74.9, 52.7, 40.7. HRMS (EI): m/z calcd for $C_{23}H_{18}O_2$: 326.1307. Found: (M^+) 326.1323. Anal. Calcd for $C_{23}H_{18}O_2$: C, 84.64; H, 5.56. Found: C, 84.37; H, 5.41.

5.2.2. Compound 2a. Yield 62%, pale yellow crystalline solid. Mp 213–215 °C. R_f 0.48 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3061, 2929, 1692, 1596, 1491, 1446, 1262, 1157, 1069, 1024, 947 cm^{-1}. ^1H NMR: δ 1.56 (s, 3H), 2.98 (s, 2H), 5.35 (d, 1H, J=4.2 Hz), 5.73 (d, 1H, J=10.3 Hz), 5.94 (dd, 1H, J_1=4.2, J_2=10.3 Hz), 6.42 (d, 1H, J=5.1 Hz), 6.55 (d, 1H, J=5.2 Hz), 7.00–7.57 (m, 10H). ^{13}C NMR: δ 196.1, 148.3, 146.2, 142.5, 141.4, 137.9, 132.9, 132.5, 129.5, 129.2, 128.8, 128.5, 128.3, 128.3, 128.2, 127.2, 126.4, 123.3, 79.6, 75.8, 52.6, 39.9, 20.4. HRMS (EI): m/z calcd for $C_{24}H_{20}O_2$: 340.1463. Found: (M^+) 340.1490.

5.2.3. Compound 3a. Yield 53%, pale yellow solid. Mp 193–195 °C. R_f 0.43 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2918, 2851, 1687, 1460, 1383, 1209, 1176, 1069, 900, 760 cm^{-1}. ^1H NMR: δ 0.70 (d, 3H, J=6.8 Hz), 0.99 (d, 3H, J=6.6 Hz), 2.58–2.68 (m, 1H), 2.95 (s, 2H), 5.38 (d, 1H, J=4.3 Hz), 5.75 (d, 1H, J=10.3 Hz), 5.95 (dd, 1H, J_1=4.3, J_2=10.3 Hz), 6.43 (d, 1H, J=5.3 Hz), 6.52 (d, 1H, J=5.3 Hz), 6.96–7.56 (m, 10H). ^{13}C NMR: δ 196.2, 147.8, 146.1, 142.7, 142.1, 137.1, 132.9, 132.3, 129.0, 128.4, 128.3, 128.1, 128.0, 127.9, 126.9, 126.1, 124.3, 84.8, 75.2, 39.4, 30.8, 16.3, 16.1. HRMS (EI): m/z calcd for $C_{26}H_{24}O_2$: 368.1776. Found: (M^+) 368.1773.

5.2.4. Compound 4a. Yield 57%, pale yellow viscous liquid. R_f 0.71 (7:3 hexane/EtOAc) IR (KBr) ν_{max}: 2956, 2927, 1691, 1495, 1379, 1252, 1098, 1074, 1015, 906 cm^{-1}. ^1H NMR: δ 3.07 (s, 2H), 4.88 (s, 1H), 5.28 (d, 1H, J=4.3 Hz), 5.79 (d, 1H, J=10.4 Hz), 6.02 (dd, 1H, J_1=4.3 Hz, J_2=10.4 Hz), 6.47 (s, 2H), 6.89–7.47 (m, 8H). ^{13}C NMR: δ 193.9, 147.6, 143.9, 140.5, 140.3, 134.4, 133.8, 133.6, 132.7, 131.5, 130.5, 130.3, 129.7, 128.9, 128.7, 128.6, 123.5, 74.7, 51.8, 40.8. HRMS (EI): m/z calcd for $C_{23}H_{16}O_2Cl_2$: 394.0527. Found: (M^+) 394.0509.

5.2.5. Compound 1b. Yield 83%, pale yellow solid. Mp 110–112 °C. R_f 0.45 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2917, 1702, 1468, 1379, 1243, 1159, 1069, 896, 769 cm^{-1}. ^1H NMR: δ 1.13 (s, 3H), 1.43 (s, 3H), 2.79–3.07 (m, 2H), 4.29 (d, 1H, J=4.1 Hz), 4.74 (s, 1H), 5.92 (d, 1H, J=10.2 Hz), 6.32 (d, 1H, J=4.2 Hz), 6.41 (s, 1H), 6.97 (dd, 1H, J_1=4.1 Hz, J_2=10.2 Hz). ^{13}C NMR: δ 193.0, 147.4, 133.9, 131.5, 129.9, 129.7, 123.9, 77.0, 76.5, 40.5, 39.2, 29.3, 22.7. HRMS (EI): m/z calcd for $C_{13}H_{14}O_2$: 202.0994. Found: (M^+) 202.0999. Anal. Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.18; H, 7.35.

5.2.6. Compound 2b. Yield 79%, pale yellow solid. Mp 124–126 °C. R_f 0.51 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.13 (s, 3H), 1.39 (s, 3H), 1.48 (s, 3H), 2.75–3.04 (m, 2H), 4.31 (d, 1H, J=4.2 Hz), 5.88 (d, 1H, J=10.3 Hz), 6.28 (s, 1H), 6.39 (d, 1H, J=10.7 Hz), 6.91 (dd, 1H, J_1=4.2 Hz, J_2=10.3 Hz). ^{13}C NMR: δ 196.4, 147.1, 133.9, 130.1, 124.1, 123.9, 123.7, 76.9, 76.1, 39.7, 38.4, 29.7, 22.7, 19.2. HRMS (EI): m/z calcd for $C_{14}H_{16}O_2$: 216.1150. Found: (M^+) 216.1122.

5.2.7. Compound 3b. Yield 68%, pale yellow solid. Mp 178–180 °C. R_f 0.56 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 0.78 (d, 3H, J=6.6 Hz), 0.88 (d, 3H, J=6.6 Hz), 1.22 (s, 3H), 1.41 (s, 3H), 2.64–2.97 (m, 3H), 4.25 (d, 1H, J=4.2 Hz), 5.81 (d, 1H, J=10.3 Hz), 6.21 (s, 1H), 6.29–6.36 (m, 1H), 6.80–6.85 (dd, 1H, J_1=4.2, J_2=10.3 Hz). ^{13}C NMR: δ 196.4, 146.8, 134.0, 131.4, 129.9, 125.3, 125.0, 85.1, 76.6, 39.5, 37.7, 30.9, 29.8, 23.6, 16.4, 16.3. HRMS (EI): m/z calcd for $C_{16}H_{20}O_2$: 244.1463. Found: (M^+) 244.1469.

5.2.8. Compound 1c. Yield 70%, pale yellow viscous liquid. R_f 0.53 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3067, 2953, 1702, 1620, 1455, 1377, 1157, 1128, 1067, 980, 940 cm^{-1}. ^1H NMR: δ 0.88–1.26 (m, 8H), 2.89–2.99 (m, 2H), 4.34 (d, 1H, J=4.1 Hz), 4.73 (s, 1H), 5.91 (d, 1H, J=10.4 Hz), 6.36 (d, 1H, J=5.2 Hz), 6.42 (d, 1H, J=5.2 Hz), 6.93 (dd, 1H, J_1=4.1, J_2=10.4 Hz). ^{13}C NMR: δ 194.9, 146.8, 133.9, 130.5, 129.7, 123.8, 77.2, 74.5, 40.7, 32.9, 31.6, 26.0, 24.5. HRMS (EI): m/z calcd for $C_{15}H_{16}O_2$: 228.1150. Found: (M^+) 228.1133.

5.2.9. Compound 2c. Yield 60%, pale yellow solid. Mp 125–127 °C. R_f 0.50 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3070, 2933, 1691, 1612, 1454, 1378, 1245, 1157, 1067, 996, 943 cm^{-1}. ^1H NMR: δ 1.25–1.79 (m, 10H), 2.81–3.07 (m, 2H), 4.71 (s, 1H), 4.84–4.87 (m, 1H), 5.94 (d, 1H, J=10.5 Hz), 6.29–6.34 (m, 1H), 6.39–6.47 (m, 1H), 6.96–7.06 (m, 1H). ^{13}C NMR: δ 194.9, 147.2, 133.8, 130.2, 129.5, 123.8, 123.7, 76.5, 70.4, 40.6, 39.7, 36.4, 31.7, 25.7, 22.2, 22.1. HRMS (EI): m/z calcd for $C_{16}H_{18}O_2$: 242.1307. Found: (M^+) 242.1321. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49; O, 13.21. Found: C, 79.69; H, 4.08.

5.2.10. Compound 3c. Yield 58%, pale yellow viscous liquid. R_f 0.69 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2928, 2856, 1697, 1459, 1377, 1248, 1161, 1068, 924, 733 cm^{-1}. ^1H NMR: δ 1.29–1.81 (m, 12H), 2.89–3.07 (m, 2H), 4.71 (s, 1H), 4.84–4.87 (m, 1H), 5.94 (d, 1H, J=10.5 Hz), 6.28–6.34 (m, 1H), 6.39–6.48 (m, 1H), 6.97–7.07 (m, 1H). ^{13}C NMR: δ 193.4, 147.7, 133.9, 131.2, 130.7, 124.0, 123.8, 77.3, 76.3, 43.7, 40.1, 38.7, 34.2, 31.3, 30.5, 23.9, 23.6. HRMS (EI): m/z calcd for $C_{17}H_{20}O_2$: 256.1463. Found: (M^+) 256.1451.

5.2.11. Compound 4c. Yield 59%, pale yellow viscous liquid. R_f 0.59 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3066, 2932, 2859, 1691, 1621, 1453, 1370, 1257, 1174, 1057, 938, 900 cm^{-1}. ^1H NMR: δ 1.35–1.70 (m, 13H), 2.84–3.05 (m, 2H), 4.89 (d, 1H, J=4.3 Hz), 5.90 (d, 1H, J=10.3 Hz), 6.40–6.46 (m, 2H), 6.97 (dd, 1H, J_1=4.3, J_2=10.3 Hz). ^{13}C NMR: δ 196.2, 148.0, 146.9, 133.6, 130.9, 130.4, 124.1, 76.5, 71.9, 40.3, 35.1, 33.2, 31.7, 26.3, 22.6, 22.3, 21.8. HRMS (EI): m/z calcd for $C_{17}H_{20}O_2$: 256.1463. Found: (M^+) 256.1467.

5.2.12. Compound 5c. Yield 52%, pale yellow viscous liquid. R_f 0.61 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2933, 2861, 1681, 1537, 1454, 1259, 1259, 1184, 1069, 749 cm^{-1}. ^1H NMR: δ 0.79 (d, 3H, J=6.8 Hz), 0.93 (d, 3H, J=6.6 Hz), 1.25–1.59 (m, 10H), 2.55–2.59 (m, 1H), 2.86–3.07 (m, 2H), 4.87–4.90 (m, 1H), 5.89 (d, 1H, J=10.3 Hz), 6.27 (s, 1H), 6.40–6.42 (m, 1H), 6.91–6.95 (m, 1H). ^{13}C NMR: δ 196.9, 146.5, 133.6, 131.4, 130.2, 129.1, 125.2, 70.5, 39.5, 35.1, 32.9, 31.4, 25.6, 22.2, 21.9, 16.3, 15.9. HRMS (EI): m/z calcd for $C_{19}H_{24}O_2$: 284.1776. Found: (M^+) 284.1776.

5.2.13. Compound 1d. Yield 67%, pale yellow viscous liquid. R_f 0.51 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3063, 2927, 1693, 1602, 1490, 1370, 1240, 1116, 1072, 991, 940 cm^{-1}. ^1H NMR: δ 1.84 (s, 3H), 3.12 (s, 2H), 4.51 (dd, 1H, J_1=0.9, J_2=4.3 Hz), 4.83 (s, 1H), 5.78 (d, 1H, J=10.5 Hz), 6.08 (dd, 1H, J_1=4.3, J_2=10.5 Hz), 6.27 (d, 1H, J=5.3 Hz), 6.46 (d, 1H, J=5.3 Hz), 7.17–7.33 (m, 5H). ^{13}C NMR: δ 194.5, 148.6, 143.9, 140.9, 133.4, 133.0, 131.8, 128.7, 128.4, 127.9, 127.5, 127.2, 122.9, 77.4, 76.6, 44.5, 40.9, 26.5. HRMS (EI): m/z calcd for $C_{18}H_{16}O_2$: 264.1150. Found: (M^+) 264.1156.

5.2.14. Compound 2d. Yield 54%, pale yellow solid. Mp 55–57 °C. R_f 0.56 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.11–1.41 (m, 7H), 3.07–3.27 (m, 2H), 4.58 (d, 1H, J=4.1 Hz), 4.78 (s, 1H), 5.73 (d, 1H, J=10.3 Hz), 6.00 (dd, 1H, J_1=4.1, J_2=10.3 Hz), 6.38 (d, 1H, J=4.9 Hz), 6.49 (d, 1H, J=4.9 Hz), 7.13–7.28 (m, 5H). ^{13}C NMR: δ 194.4, 148.8, 139.6, 139.5, 133.5, 131.9, 128.5, 127.9, 126.9, 122.8, 77.8, 76.4, 59.5, 45.3, 38.1, 31.2, 29.6, 26.6. HRMS (EI): m/z calcd for $C_{21}H_{20}O_2$: 304.1463. Found: (M^+) 304.1487.

5.2.15. Compound 3d. Yield 50%, pale yellow viscous liquid. R_f 0.37 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2963, 2937, 1687, 1442, 1370, 1206, 1172, 1059, 902, 770 cm^{-1}. ^1H NMR: δ 1.82 (s, 3H), 3.12 (s, 2H), 4.47 (d, 1H, J=4.2 Hz), 4.83 (s, 1H), 5.80 (d, 1H, J=10.3 Hz), 6.11 (dd, 1H, J_1=4.2, J_2=10.3 Hz), 6.20 (d, 1H, J=5.3 Hz), 6.47 (d, 1H, J=4.9 Hz), 7.10–7.29 (m, 4H). ^{13}C NMR: δ 194.0, 148.7, 134.3, 132.2, 129.8, 129.7, 124.0, 123.7, 121.4, 121.1, 78.3, 76.4, 41.7, 30.6, 27.3. HRMS (EI): m/z calcd for $C_{18}H_{15}ClO_2$: 298.0761. Found: (M^+) 298.0788.

5.2.16. Compound 1e. Yield 65%, pale yellow crystalline solid. Mp. 99–101 °C. R_f 0.49 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 3065, 2928, 1692, 1605, 1492, 1377, 1248, 1154, 1069, 995, 944 cm^{-1}. ^1H NMR: δ 2.82–3.21 (m, 2H), 3.57 (d, 1H, J=8.7 Hz), 4.69 (d, 1H, J=4.0 Hz), 4.93 (s, 1H), 5.96 (d, 1H, J=10.4 Hz), 6.19 (d, 1H, J=5.2 Hz), 6.42 (d, 1H, J=4.8 Hz), 7.06 (dd, 1H, J_1=4.0, J_2=10.4 Hz), 7.14–7.30 (m, 5H). ^{13}C NMR: δ 194.9, 146.9, 133.8, 132.6, 129.6, 128.9, 128.8, 127.9, 127.2, 123.9, 123.7, 76.6, 73.7, 42.9, 40.6. HRMS (EI): m/z calcd for $C_{17}H_{14}O_2$: 250.0994. Found: (M^+) 250.0991.

5.2.17. Compound 2e. Yield 50%, pale yellow viscous liquid. R_f 0.52 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2928, 2851, 1694, 1460, 1388, 1249, 1176, 1072, 909, 749 cm^{-1}. ^1H NMR: δ 1.26 (s, 3H), 2.86–3.03 (m, 2H), 4.28–4.34 (m, 1H), 4.90–4.95 (m, 1H), 5.92 (d, 1H, J=10.3 Hz), 6.12 (d, 1H, J=5.3 Hz), 6.34–6.40 (m, 1H), 6.39–6.43 (m, 1H), 7.00–7.28 (m, 5H). ^{13}C NMR: δ 196.9, 146.9, 134.2, 132.8, 132.6, 129.6, 128.9, 128.8, 127.9, 127.2, 123.8, 123.7, 76.3, 74.0, 44.9, 40.5, 20.6. HRMS (EI): m/z calcd for $C_{18}H_{16}O_2$: 264.1150. Found: (M^+) 264.1164.

5.2.18. Compound 3e. Yield 45%, pale yellow viscous liquid. R_f 0.47 (7:3 hexane/EtOAc). IR (KBr) ν_{max}: 2969, 2928, 1692, 1460, 1388, 1249, 1176, 1074, 909, 749 cm^{-1}. ^1H NMR: δ 0.86 (d, 3H, J=7.0 Hz), 0.96 (d, 3H, J=6.6 Hz), 2.66–2.73 (m, 1H), 2.97–3.05 (m, 2H), 4.35–4.38 (m, 1H), 4.94–4.98 (m, 1H), 5.93 (d, 1H, J=10.3 Hz), 6.14 (d, 1H, J_1=5.3 Hz), 6.31–6.36 (m, 1H), 6.39–6.43 (m, 1H), 7.05–7.33 (m, 5H). ^{13}C NMR: δ 196.2, 147.8, 146.1, 142.7, 137.1, 132.9, 132.3, 129.0, 128.4, 128.3, 128.1 127.9, 126.9, 126.1, 124.3, 84.8, 75.2, 39.4, 30.8. HRMS (EI): m/z calcd for $C_{20}H_{20}O_2$: 292.1463. Found: (M^+) 292.1464.

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Conformationally restricted triplex-forming oligonucleotides (TFOs). Binding properties of α-L-LNA and introduction of the N^7-glycosylated LNA-guanosine

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Abstract—The method for scaled-up production of α-L-LNA phosphoramidite building blocks containing thymine and 5-methylcytosine nucleobases is described. Binding properties of pyrimidine TFOs modified with α-L-LNA are reported. In contrast to LNA TFOs, the fully modified α-L-LNA forms a stable triplex with a model DNA duplex. Pyrimidine DNA/LNA/α-L-LNA chimeras also efficiently hybridize with a model DNA duplex in the parallel mode. LNA nucleoside containing unnatural N^7-glycosylated guanine (LNA-^{7}G) was synthesized by a convergent method and incorporated into LNA oligonucleotides. The triplex-forming alternating DNA/LNA oligonucleotides containing a single LNA-^{7}G modification instead of internal LNA-mC demonstrate improved pH-dependent properties. The single LNA-^{7}G modification can also discriminatively reduce competitive binding of TFOs to natural nucleic acids in the antiparallel duplex mode.

1. Introduction

The design of molecules that can specifically recognize the DNA double helix would provide a means to interfere with gene expression at an early stage, thus giving tools for a wide range of applications in gene-based biotechnology and therapeutics. One approach for specific recognition of predetermined DNA sequences is based on triple helix formation, which is the phenomenon of third oligonucleotide strand (triplex-forming oligonucleotide, TFO) binding to a specific target site in duplex DNA.[1–3] It has been found that TFOs bind in the major groove of oligopyrimidine–oligopurine sequences in duplex DNA by hydrogen bonding with purine bases to produce base triplets in a sequence-specific manner.[4] Two main structural motifs have been established in which a TFO binds either in a parallel or antiparallel fashion respective to the target purine strand. Parallel triplexes contain C^+·GC and T·AT triplets[5] and have attracted much attention due to their comparatively high stability under physiological conditions. The fact that TFOs can only bind to oligopurine–oligopyrimidine target strands results in a major limitation to the application of TFOs. However, the recent in silico analysis of the human genome[6] has revealed that regions likely to form triplexes are more common than predicted by random models. The population of TFO target sequences is large in all the genome, without major differences between chromosomes. Moreover, the largest concentration of such sequences has been found in regulatory regions, especially in promoter regions, suggesting a tremendous potential for triplex technology.[6]

Much research on exploiting TFO binding in vivo has been reviewed recently.[7–9] However, there are still limitations to the use of TFOs. These concern binding affinity and specificity, uptake into cells and tissues, and in vivo stability. Major efforts have been devoted to improving TFO characteristics through chemical modifications. Thus, large variety of modifications to the TFO backbone has been attempted in order to increase the general affinity of the TFO to duplex DNA and its stability in vivo. The structures of the most promising TFO analogues with modified backbone are depicted in Figure 1. In the case of peptide nucleic acids (PNA), the whole phosphodiester backbone is replaced by an uncharged polyamide backbone.[10,11] The triplex-forming feature of PNAs has been described to lie in recognition of the DNA duplex via a strand invasion mechanism.[12,13] Cellular uptake of PNAs, however, still raises major problems and needs to be improved in order to fully exploit their properties.[14]

N3′–P5′ phosphoramidate TFOs (Fig. 1) have been demonstrated to bind strongly to double-stranded DNA.[15,16] It appears that this class of modified oligonucleotides has a favorable intracellular and tissue distribution, which makes them good candidates for in vivo applications.[16,17] The replacement of the 3′-oxygen atom by nitrogen, made in N3′–P5′ phosphoramidates in comparison to DNA, results in a substantial change of the sugar conformation. The

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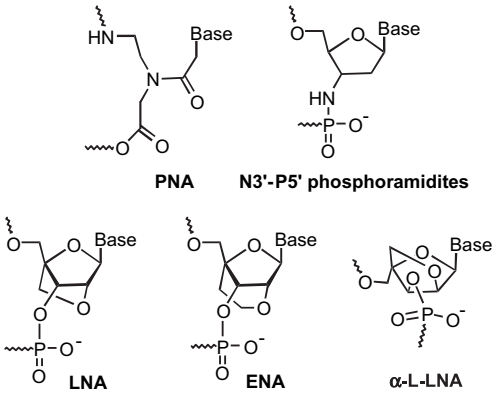


Figure 1. Molecular structures of selected TFOs with modified backbone.

resulting N-type conformation[18] may give an explanation for enhanced triplex-forming ability.

Modifications made to the ribose moiety in TFOs have also been able to generate derivatives with advantageous properties. Thus, locked nucleic acid (LNA) and 2′-*O*,4′-*C*-ethylene-briged nucleic acid (ENA) are RNA derivatives in which the ribose unit is constrained by a methylene or an ethylene linkage between the 2′-oxygen and the 4′-carbon (Fig. 1). This bridge reduces the conformational flexibility of the ribose and thus results in a locked 3′-*endo* (N-type) sugar puckering.[19–21] Along with N3′–P5′ phosphoramidates, the outstanding results on binding properties of LNA and ENA have clearly demonstrated that such restriction of the sugar conformation is a very promising approach for TFOs design.[21,22] Accordingly, TFOs consisting of alternating LNA and DNA residues have demonstrated significantly enhanced affinity to dsDNA with respect to the isosequential DNA TFOs.[21] The NMR structure of an LNA·dsDNA triplex has been determined recently.[23] The triplex has a regular seamless structure despite the fact that the TFO strand is composed of DNA and LNA monomers with different sugar puckers. The structure of the DNA duplex is changed to fit TFO accommodation, and it adopts a geometry intermediate between A and B types.

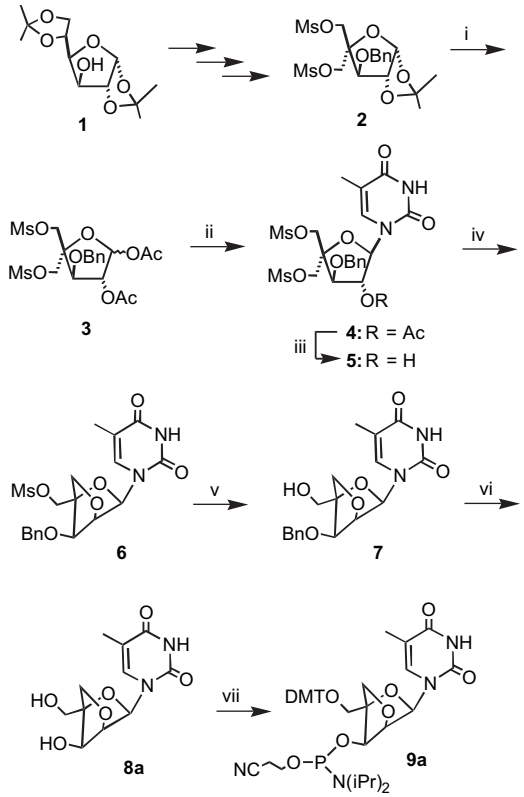
It has been found that ENA TFOs (Fig. 1) form stable triplexes with dsDNA similar to those partially modified with LNA nucleosides.[22] Furthermore, in contrast to LNA, fully modified ENA oligonucleotides have high triplex formation ability. Additionally, ENAs are generally more nuclease resistant than LNAs and, as a result, have greater potential for in vivo applications.[20,22] However, the availability of ENA is still comparatively limited as its synthesis, reported hitherto,[20] is significantly more resource consuming than that for LNA.[24]

Bearing in mind the achievements in constructing conformationally constrained TFOs, we report herein the results of our investigations into the binding properties of TFOs modified with α-L-*ribo*-configured locked nucleic acid (α-L-LNA; Fig. 1). The first synthesis and some properties of α-L-LNA have been recently reported.[25,26] The binding studies have demonstrated high affinity Watson–Crick hybridization between α-L-LNA and single stranded DNA oligonucleotides.[25] Interestingly, NMR studies have revealed that, in general, α-L-LNA nucleosides do not perturb native B-like dsDNA geometry.[27] In other words, when incorporated into the DNA duplex, they acted in a similar way to the fixed *S*-type sugar conformers despite their unnatural stereochemistry. Based on these findings, we anticipated that TFOs modified with α-L-LNA would form, if any, very structurally distinctive triplexes with dsDNA. The knowledge of particular properties of α-L-LNA TFOs can provide insights that are useful for further progress in rational design of molecules capable of specifically recognizing the dsDNA helix.

To improve the binding properties of LNA TFOs at higher pH, we additionally introduce herein a new LNA nucleoside containing N^7-glycosylated guanine as a nucleobase. It has been shown that N^7-deoxyguanosine (d^7G) mimics protonated cytosine and specifically binds GC base pairs within a parallel triple helix motif.[28] The stabilities of d^7G-containing triplexes are independent of pH but strongly dependent on the sequence context. The TFOs containing d^7G are particularly useful for targeting continuous GC base pairs.[29]

2. Results and discussion

The first synthesis of α-L-LNA 3′-*O*-phosphoramidites containing thymine, 5-methylcytosine, and adenine nucleobases was reported by Wengel.[25,26] However, to make α-L-LNA practically available, a significantly improved and more efficient route to α-L-LNA monomers has been developed (Scheme 1). Analogous to commercially available LNA



Scheme 1. *Reagents and conditions*: (i) Ac_2O, concd H_2SO_4, AcOH, 91%; (ii) thymine, BSA, trimethylsilyl triflate, MeCN, quant.; (iii) HCl, MeOH, 99%; (iv) (a) MsCl, pyridine; (b) NaOH, H_2O, quant.; (v) (a) NaOBz, DMSO; (b) NaOH, H_2O, 74%; (vi) 20% $Pd(OH)_2$/C, HCO_2NH_4, MeOH, 1,4-dioxane, reflux, 93%; (vii) (a) DMT-Cl, pyridine; (b) 2-cyanoethyl-*N*,*N*,*N*′,*N*′ -tetraisopropylphosphordiamidite, 4,5-dicyanoimidazole, CH_2Cl_2, 92%, Ref. 31.

nucleosides,[24] a convergent strategy was chosen for the production of α-L-LNA. A starting material for the synthesis of α-L-LNA-T phosphoramidite **9a** (Scheme 1), the known 4-C-branched furanose **2**,[25] was obtained from commercial 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **1** as described earlier. However, NMR data reported by Wengel[25] for compound **2** was significantly different from that reported here. Coupling sugar **3** was subsequently obtained in 91% yield after one-pot acetolysis and acetylation of **2**. The anomeric mixture **3** was then used as a glycosyl donor for Vorbrügen-type[30] coupling reaction with silylated thymine to give a 4′-C-branched nucleoside **4** after standard aqueous work-up. Transformation of compound **4** into α-L-*ribo*-configured LNA-T derivative **6** required epimerization at the 2′-position. To make this inversion, the 2′-*O*-acetyl group was first replaced with mesyl and the resulting compound was then treated with aqueous sodium hydroxide. Accordingly, treatment of **4** with methanolic hydrochloride resulted in quantitative removal of the acetyl group to give intermediate **5**. In the same flask, the solvents were replaced by anhydrous pyridine and **5** was consecutively treated with mesyl chloride and sodium hydroxide to give protected α-L-LNA-T nucleoside **6**. Apparently, the transformation of **5** into **6** proceeded via the 2,2′-anhydro intermediate, which could be consecutively formed, hydrolyzed, and subjected to ring-closure reaction in the same reaction mixture.[26] Indeed, corresponding intermediates were detected by RP-HPLC analyses of the reaction mixture (data not shown). This reaction cascade proceeded very smoothly and was completed overnight in nearly quantitative yield. The purity of nucleoside **6** was about 96% (RP-HPLC, integration at 260 nm) after aqueous work-up and the compound was used further without additional purification. Instead, **6** was converted to crystalline compound **7** after deprotection of the 5′-hydroxy group. Thus, nucleoside **6** was reacted with sodium benzoate in hot DMSO and the obtained 5′-benzoate was hydrolyzed by the excess of alkali to give **7** in 67% yield (from **2**) after crystallization from ethyl acetate. As expected, catalytic removal of the 3′-*O*-benzyl group from **7** easily afforded diol **8a** in 93% yield after crystallization from water. Finally, α-L-LNA-T phosphoramidite building block **9a** was derived from **8a** by means of the standard methods.[26,31] The synthetic route to phosphoramidite **9a** described above is significantly superior to the earlier reported procedure,[25,26] which makes the commercial production of α-L-LNA-T nucleoside very feasible.

An important limitation of the triplex technology is that parallel triplexes require conditions of low pH, which are necessary for protonation of the nitrogen at position 3 of cytosines in TFOs (Fig. 2). To address this problem, several derivations of cytosine analogues have been introduced that provide less pH-dependent triplex formation. Thus, 5-methylcytosine (mC) replacement for cytosine in the DNA TFOs gave more stable triplexes at neutral pH, because of the increase in pK_a for 5-methylcytosine (4.3) compared with cytosine (4.15).[32] A similar effect has recently been demonstrated for LNA and ENA modified TFOs.[22,33] For this reason, we concentrated on studying α-L-LNA-modified TFOs containing thymine and 5-methylcytosine nucleobases.

It has already been reported[25,34] that both α-L-LNA-mC and LNA-mC phosphoramidites **13a**,**b** (Scheme 2) could be

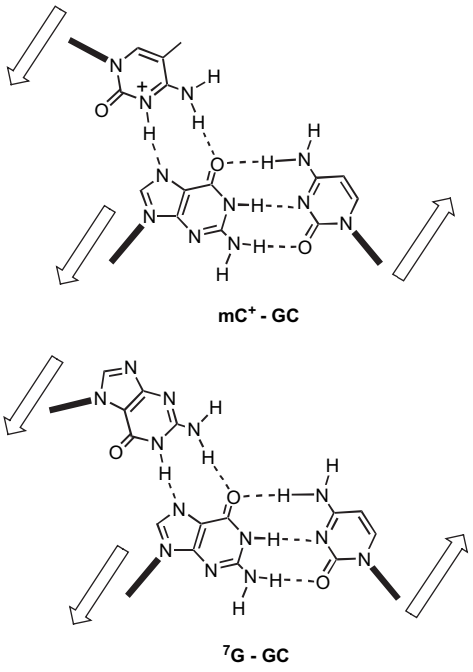
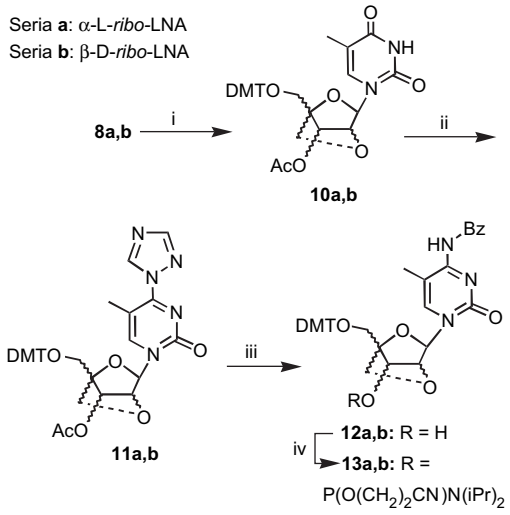


Figure 2. Schematic comparison of the base triplets involving 5-methylcytosine (mC) and N^7-glycosylated guanine (^{7}G).[28,29]

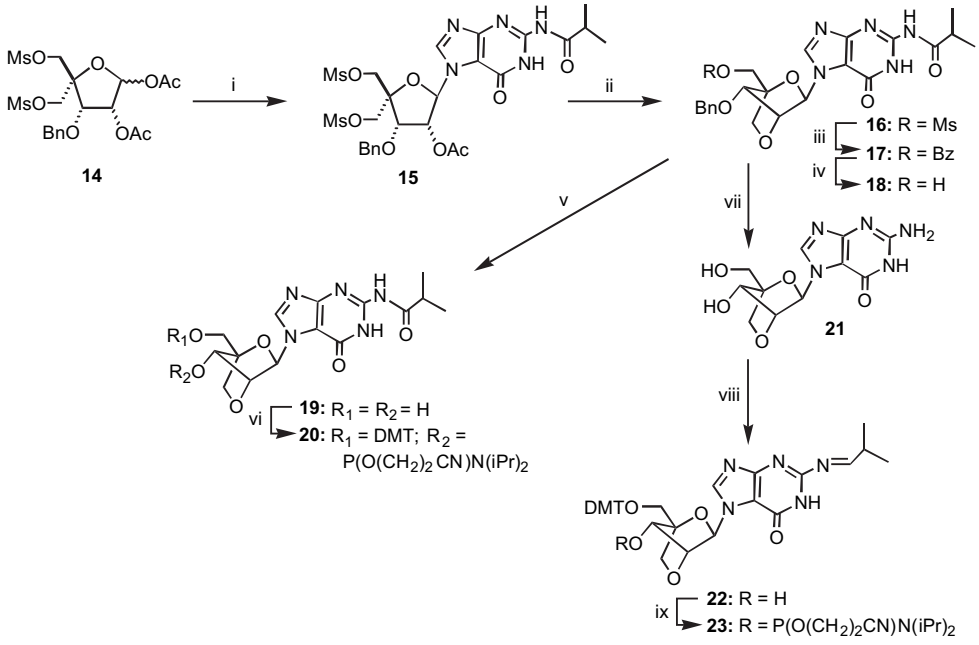
derived by different methods from the corresponding thymin-1-yl diols **8a**,**b**. The recent developments for a universal (both for LNA and α-L-LNA) scale-up synthesis of **13a**,**b** are depicted in Scheme 2. The method has several advanced points, which make it considerably more useful in comparison to already reported procedures. Thus, starting with α-L-LNA-T diol **8a**, fully carbohydride protected thymin-1-yl derivative **10a** was easily produced after one-pot consecutive treatment of **8a** with DMT-chloride and acetic anhydride in anhydrous pyridine. The introduction of a hydrophobic DMT group at this stage significantly facilitated handling of nucleosides in later steps of the synthesis. The 3′-*O*-acetyl



Scheme 2. *Reagents and conditions*: (i) (a) DMT-Cl, pyridine; (b) Ac_2O, pyridine, 90% (**10a**) and 89% (**10b**); (ii) 1,2,4-triazole, $POCl_3$, DIPEA, MeCN, 97% (**11a**) and 90% (**11b**); (iii) (a) concd NH_4OH, MeCN; (b) Bz_2O, pyridine; (c) NaOH, pyridine, MeOH, H_2O, 81% (**12a**) and 76% (**12b**); (iv) 2-cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite, 4,5-dicyanoimidazole, CH_2Cl_2, 95%, Ref. 31.

protection group was selected due to the simplicity of its introduction and removal, avoiding undesired side reactions. Second, nucleoside **10a** was almost quantitatively converted to a stable 4-(1,2,4-triazol-1-yl) derivative **11a** by the method of Reese.[35] Accordingly, **10a** was treated with freshly distilled phosphoryl chloride in the presence of 1,2,4-triazole and excess of a base to give **11a** after aqueous work-up. Compound **11a** can serve as a valuable intermediate in the synthesis of different 4-substituted α-L-LNA-pyrimidine nucleosides as it can be easily handled and stored. Thus, a simple procedure was applied to convert **11a** to 4-*N*-benzoyl-cytosine-1-yl derivative **12a** (Scheme 2). After compound **11a** was allowed to react with ammonia overnight, the solvents were thoroughly removed and the residue was treated with benzoic anhydride in anhydrous pyridine to give a mixture of mono- and di-benzoylated (MALDI-MS analysis) nucleosides. Addition of aqueous sodium hydroxide to the same reaction mixture led to very selective hydrolysis of undesired 3′-benzoate leaving the intact nucleoside **12a**. The nucleoside **12a** was isolated in 81% yield by column chromatography and phosphitylated using the method used for the production of **9a**.[31] The above synthetic procedures were also successfully applied for the preparation of phosphoramidite **13b** (Scheme 2), which established them as a reliable universal method for the production of both LNA and α-L-LNA monomers **13a**,**b**.

The unnatural N^7-glycosylated deoxyguanosine was introduced as another promising replacement for cytosine in TFOs[28] (Fig. 2). To investigate compatibility of this approach with LNA technology, TFOs modified with LNA-^{7}G were synthesized. The synthesis of phosphoramidite monomers **20** and **23** was first attempted (Scheme 3). The coupling of silylated 2-*N*-isobutyrylguanine with glycosyl donor **14** was already reported.[24] In the reaction conditions (trimethylsilyl triflate as a catalyst in 1,2-dichloromethane; reflux), N^7-glycosylated compound **15** was formed as a minor product in approximately 10% yield along with N^9-isomeric counterpart. However, when conditions favoring the formation of N^7-isomer[28,29] were applied, **15** was produced as the sole product after chromatographic purification albeit in moderate 34% yield (Scheme 3). The correct structure of the obtained isomer was confirmed by comparison of NMR data for **15** with that published for N^7- and N^9-glycosylated guanines.[36,37] Thus, the most characteristic signal corresponding to C5 positioned at 110.2 ppm in the ^{13}C NMR spectrum of **15**. The conversion of nucleoside **15** to diol **19** was performed generally following the synthetic route developed for N^9-glycosylated LNA-G.[24] Accordingly, the ring-closure reaction promoted in **15** by sodium hydroxide afforded protected LNA-^{7}G nucleoside **16**. The 5′-methylsulfonate of **16** was displaced by benzoate to give **17**, which in turn was hydrolyzed to furnish nucleoside **18**. To keep 2-*N*-isobutyryl intact, debenzylation of **18** was carried out on Pd/C using formic acid as a hydrogen supply[24] to give diol **19**. Monomeric unit **20**, finally derived from **19**, was successfully applied for automated oligonucleotide synthesis using the phosphoramidite method.[38] However, the 2-*N*-isobutyryl group of the LNA-^{7}G mononucleotide turned out to be considerably more stable in comparison to all the other commonly used protections. Therefore, modifications of deprotection procedure were required for LNA-^{7}G containing oligonucleotide after the synthesis (vide infra). To facilitate the synthesis of oligonucleotides containing multiple LNA-^{7}G modifications, (dimethylamino)methylidene[39] protected phosphoramidite **23** was ultimately produced. Thus, the fully deprotected nucleoside **21** was furnished in 86% yield after consecutive catalytic hydrogenation and treatment with ammonium hydroxide of **18**. 2-*N*-(Dimethylamino)methylidene and 5′-*O*-DMT groups were introduced into **21** by conventional



Scheme 3. *Reagents and conditions*: (i) 2-*N*-isobutyrylguanine, BSA, $SnCl_4$, MeCN, 34%; (ii) NaOH,1,4-dioxane, H_2O, 89%; (iii) NaOBz, DMF, 93%; (iv) NaOH, pyridine, EtOH, H_2O, 85%; (v) 10% Pd/C, HCO_2H, MeOH, 81%; (vi) (a) DMT-Cl, pyridine; (b) 2-cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite, 4,5-dicyanoimidazole, CH_2Cl_2, 82%; (vii) (a) 10 % Pd/C, HCO_2NH_4, MeOH; (b) NH_3, MeOH, 86%; (viii) (a) *N*,*N*-dimethylformamide dimethyl acetal, DMF; (b) DMT-Cl, pyridine, 89%; (ix) 2-cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropylphosphordiamidite, 4,5-dicyanoimidazole, CH_2Cl_2, MeCN, 92%.

methods[36] and compound **22** was isolated in 89% yield after column chromatography. Phosphoramidite **23** was derived from **22** in 92% yield generally following the procedure developed for other LNA nucleosides.[31]

Along with commercially available DNA and LNA phosphoramidites, the phosphoramidite building blocks **9a**, **13a**, and **23** were used for automated oligonucleotide synthesis to produce the LNA oligonucleotides depicted in Tables 1 and 2. The standard protocols of DNA synthesis were applied for all LNA and α-L-LNA amidites, except for coupling (extended to 500 s) and oxidation cycles (extended to 30 s). After synthesis, the oligonucleotides were deprotected by treatment with concentrated ammonium hydroxide for 6 h at 60 °C and purified by RP-HPLC. To synthesize LNA-^{7}G modified oligonucleotide **46** (Table 2), phosphoramidite **20** was used instead of **23**. The above conditions for the automated synthesis were also successfully applied in this case. However, the deprotection procedure was modified in order to complete the removal of the 2-*N*-isobutyryl group from LNA-^{7}G mononucleotide. Thus, ammonium hydroxide treatment used during the synthesis of all the other oligonucleotides was first applied. MALDI-MS analysis of the mixture, however, revealed the presence of a product (a signal of approximately equal intensity as for the target product) containing intact isobutyryl protection group. This signal completely disappeared after additional treatment of the reaction mixture with aqueous methylamine for 2 h at 60 °C. Analogous data demonstrating the increased stability of the 2-*N*-isobutyryl group on N^7-glycosylated guanine have been previously reported by Dervan.[29]

Triplex-forming properties of α-L-LNA-modified oligonucleotides were assessed against target DNA duplex containing an oligopurine–oligopyrimidine sequence of 14 bp in the central core and presented in Table 1 as melting temperatures of the corresponding triplexes. The recently reported results on binding properties of LNA and ENA TFOs[22,33] have been obtained by studying the same oligonucleotide model and can be directly compared with the data reported herein. Thus, in good agreement with the data reported by Imanishi,[33] the sequences of alternating LNA and DNA nucleotides **24** and **25** (Table 1, entries 1 and 2) formed stable triplexes with the complementary duplex **40**·**41** in the pH range 6.5–7.5. It was found that stability of triplex **25**:**40**·**41** slightly exceeds stability of **24**:**40**·**41** at pH 6.5. This observation clearly parallels the rules derived recently for designing LNA-modified TFOs.[40] Accordingly, the sequence effect and the differential stabilization by LNA-T and LNA-mC nucleotides have been pointed out.[40] For LNA-modified TFOs, maximizing the number of LNA5′–3′DNA steps (e.g., by the use of an LNA nucleotide

Table 1. Melting temperatures[a] of the perfectly matched triplexes (±1 °C) and duplexes (±0.5 °C) containing β-D- and α-L-LNA nucleotides

Entry	Oligo structure (5′–3′) (compound number)	Parallel triplex[b] at diff. pH			Antiparallel duplex[c]
		pH 6.5	pH 7.0	pH 7.5	
1	tCtCtCtCcCtTtT (**24**)	56.5	43.0	32.0	71.8
2	TcTcTcTcCcTtTt (**25**)	58.5	41.5	27.5	71.7
3	t*X*t*X*t*X*c*X*t*Y*t*Y* (**26**)	45.0	30.5	nt[d]	68.4
4	*YXYXYXYXXXYYYY* (**27**)	36.0	25.5	nt	90.5
5	*YCYCYCYCXCYTYT* (**28**)	20.0	nt	nt	83.4
6	tCtCtCt*X*cCtTtT (**29**)	57.5	43.0	31.5	70.6
7	TcTcTc*Y*cCcTtTt (**30**)	47.0	29.0	nt	68.4
8	Tc*Y*cTc*Y*cCc*Y*tTt (**31**)	37.0	21.0	nt	66.5
9	tCt*X*tCt*X*cCt*Y*tT (**32**)	52.0	38.0	27.0	69.3
10	t^{7}Gt^{7}Gt^{7}Gt^{7}Gc^{7}GtTtT (**33**)	nt	nt	nt	nt
11	t^{7}GtCt^{7}GtCc^{7}GtTtT (**34**)	nt	nt	nt	45.7
12	t^{7}GtCt^{7}Gtc^{7}GctTtT (**35**)	41.5	34.0	nt	41.5
13	t^{7}Gtct^{7}Gtc^{7}GcttTt (**36**)	38.0	28.0	nt	36.6
14	tCtCtCt^{7}GcCtTtT (**37**)	57.0	44.5	34.5	59.6
15	TcTcTcTc^{7}GcTtTt (**38**)	>60	45.5	31.0	59.5
16	Tc*Y*cTc*Y*c^{7}Gc*Y*tTt (**39**)	41.5	27.5	nt	56.5

[a] The melting temperatures (T_m values) were obtained as maxima of the first derivatives of the corresponding melting curves (optical density at 260 nm versus temperature). Presented as the mean of three measurements. LNA residues are capitalized. ^{7}G=β-D-LNA-G (N^7-isomer); *X*=α-L-LNA-mC; *Y*=α-L-LNA-T. C, c=5-methyl-cytosines.

[b] The model complementary duplex (1 μM) was obtained by mixing purine strand **40**: 5′-gaacaaacagagagagggaaaatcccccta and pyrimidine strand **41**: 5′-tagggggattttccctctctctgtttgttc in 0.01 M Na-phosphate buffer (pH 6.5, 7.0, or 7.5) containing 0.1 M NaCl and 1 mM EDTA. Concentration of TFOs: 1 μM.

[c] T_ms of the antiparallel duplexes were measured against complementary tetradecadeoxynucleotide **42**: 5′-aaaagggagagaga. Concentration of duplexes: 1 μM; the same buffer as for triplex study (pH 7.4).

[d] nt—No cooperative transition observed over 20 °C.

Table 2. Melting temperatures (±1 °C) of the perfectly matched and singly mismatched LNA·DNA duplexes[a]

Entry	Oligonucleotide structure (5′–3′)	T_ms (±1 °C) of the duplexes with complementary deoxynucleotides			
		3′-ctg*a*atcc (**47**)	3′-ctg*t*atcc (**48**)	3′-ctg*g*atcc (**49**)	3′-ctg*c*atcc (**50**)
1	GAC*T*TAGG (**43**)	**61**	28	36	24
2	GAC*A*TAGG (**44**)	38	**62**	43	41
3	GAC*G*TAGG (**45**)	32	55	41	**71**
4	GAC^7*G*TAGG (**46**)	nt	32	37	31

[a] Concentration of duplexes: 2.5 μM. All other experimental conditions and abbreviations as in Table 1.

at 5′-end as for **25**) and maximizing the use of LNA-T is thermodynamically preferable for triplex formation. On the other hand, it has been reported[41] that triplex formation in the pyrimidine motif proceeds from the 5′-end to the 3′-end according to the nucleation–zipping mechanism. Association rate is thus governed by the composition of base triplets on the 5′-end of the triplex, which are significantly different for **24** and **25**. According to this model, oligonucleotide **25** containing two LNA-T nucleotides at the 5′-end might presumably bind to duplex **40**·**41** slightly faster than its counterpart **24**.

The thermostability of triplex **24**:**40**·**41**, however, demonstrated a notably lower pH dependence than stability of **25**:**40**·**41** (Table 1, entries 1 and 2). The higher apparent pK_a of the LNA-modified 5-methylcytidines in the dsDNA:LNA triplex has been attributed to lowered base-pair dissociation rates.[23] Therefore, due to the increased number of LNA-mC nucleotides in **24** compared with isosequential **25**, the stability of triplex **24**:**40**·**41** at pH 7.5 is already 4.5 °C higher.

The triplex-forming ability of α-L-LNA-modified TFOs turned out to be significantly reduced in comparison to LNA TFOs. Thus, replacement of LNA nucleotides in **24** by analogous α-L-LNA monomers resulted in a T_m decrease of the corresponding triplex by 11.5 °C at pH 6.5 (triplex **26**:**40**·**41**; entry 3). The fully modified α-L-LNA oligonucleotide **27** (Table 1, entry 4) was able to bind the complementary DNA duplex **40**·**41** at pH 6.5 and 7.0, albeit with reduced affinity. These data are particularly interesting, considering the fact that no stable triplexes have been detected for fully modified LNA TFOs.[33]

The attempt to construct a potent TFO consisting of altering LNA and α-L-LNA units failed as oligonucleotide **28** (Table 1, entry 5) did not form a stable triplex with **40**·**41**. However, LNA TFO **24** could tolerate a single α-L-LNA replacement for LNA-mC monomer. Thus, a DNA/LNA/α-L-LNA chimera **29** demonstrated the same binding properties as the parent **24** (compare entries 1 and 6). In sharp contrast to **29**, a single α-L-LNA-T replacement made for LNA-T in **25** resulted in significant destabilization of the triplex demonstrating differential pairing abilities of α-L-LNA-T and α-L-LNA-mC units in TFOs. This phenomenon was additionally confirmed by triple α-L-LNA-T replacements for LNA-T. The T_m value for the triplex formed by chimera **31** (entry 8) containing three α-L-LNA-T units is already 21.5 °C lower than T_m of **25**:**40**·**41**. At the same time, oligonucleotide **32** containing two α-L-LNA-mC and only a single α-L-LNA-T modification bound to the model duplex with significantly higher potency (compare entries 8 and 9; Table 1).

Binding properties of TFOs modified with LNA-^{7}G are presented in entries 10–16 (Table 1). Thus, TFOs **33** and **34** containing five or three LNA-^{7}G residues instead of LNA-mC did not bind to **40**·**41** at any pH. However, a further experiment demonstrated that DNA/LNA chimeras modified with three LNA-^{7}G could form triplexes when LNA-^{7}G units were separated by two DNA mononucleotides (TFOs **35** and **36**; entries 12 and 13). Importantly, the improved pH dependence observed for triplex stability in this case indicates that LNA-^{7}G units were involved in triplex formation by pairing mode as suggested by Dervan[28,29] (Fig. 2). The most stable triplexes were detected for TFOs **37** and **38** (entries 14 and 15) containing a single LNA-^{7}G replacement for LNA-mC (entries 14 and 15). Accordingly, at pH 6.5, **37** bound to the model duplex with the same efficacy as parent **24**. However, the melting temperature of **37**:**40**·**41** was detectably higher than T_m of **24**:**40**·**41** at pH 7.5 (compare entries 1 and 14). The melting temperature of the triplex formed by **38** (entry 15) at pH 6.5 was close to T_m of duplex **40**·**41** and could not be measured by the used method. Nevertheless, remarkable T_ms=45.5 and 31.0 °C were measured for **38**:**40**·**41** at pH 7.0 and 7.5, respectively. Noteworthy, a lower pH sensitivity of T_m for triplex formed by **37** in comparison to **38** (Table 1, entries 14 and 15) can be explained by the higher content of LNA-mC nucleotides as was already pointed out for TFOs **24** and **25** (vide supra). The stabilizing effect of the single LNA-^{7}G modification was also shown in the case of DNA/LNA/α-L-LNA chimera **39** (compare entries 8 and 16).

Binding properties of LNA-^{7}G were further studied in the antiparallel duplex context. It was shown that single LNA-^{7}G replacement for the internal LNA-mC nucleotide resulted in significant destabilization (by 10–12 °C) of the antiparallel duplex with complementary oligodeoxynucleotide **42** (Table 1, entries 14–16). Furthermore, an additive destabilizing effect of multiple LNA-^{7}G modifications was shown for the complementary duplexes involving DNA/LNA chimerical oligonucleotides **33**–**36** (entries 10–13). Incompatibility of LNA-^{7}G with Watson–Crick duplex geometry was also demonstrated for a fully modified LNA oligonucleotide of random sequence. When incorporated into LNA octanucleotide **46**, LNA-^{7}G was unable to efficiently pair with any natural DNA base (Table 2, entry 4). The melting temperatures measured for duplexes formed by **46** against **47**–**50** were very low, close to the T_ms of the most unstable mismatched duplexes formed by unmodified **43**–**45** (entries 1–3). Thus, replacement of LNA-G with unnatural LNA-^{7}G led to destabilization of the complementary duplex against **50** by 40 °C (compare duplexes **45**·**50** and **46**·**50**). The discriminating pairing properties of the single LNA-^{7}G modification can be very useful for in vivo application of alternating DNA/LNA TFOs in order to minimize undesired competitive biding to nucleic acids in the antiparallel duplex mode.

3. Conclusions

In conclusion, we developed an improved method for scaled-up synthesis of the building blocks for oligonucleotides containing α-L-LNA thymine and 5-methylcytosine units as well as a method for synthesis of the novel N^7-glycosylated LNA-guanosine monomer. The compounds were successfully incorporated into triplex-forming oligonucleotides and their binding properties were systematically studied. Pyrimidine DNA/α-L-LNA chimeras demonstrate a reduced binding ability compared with the analogous DNA/LNA TFOs. However, in contrast to LNA TFOs, the fully modified α-L-LNA form a stable triplex with the model DNA duplex. The alternating DNA/LNA TFOs containing a single LNA-^{7}G replacement for internal LNA-mC demonstrate improved pH-dependent properties and can also be used to discriminatively reduce competitive binding of TFOs to

nucleic acids in the antiparallel duplex mode. Our findings may be useful for further developments in the field of triplex technology.

4. Experimental

4.1. General

All chemicals were obtained from commercial suppliers and were used without additional purification. An atmosphere of nitrogen was applied when reactions were conducted in anhydrous solvents. Column chromatography was performed using Silica gel 60 (0.063–0.200 mm) from Merck and HPLC using a column Prep Nova-Pak HR Silica 60 (6 μm, 30×300 mm). Analytical reverse-phase chromatography (RP-HPLC) was performed on XTerra RP_{18} 5 μm (3.9×150 mm) column using Delivery System and Dual λ Absorbance Detector (all from Waters) in the following eluent system: linear gradient 20–100% v/v of MeCN in 0.05 M aqueous triethylammonium acetate (pH 7.2) during 15 min. Flow rate: 1 mL/min. R_t—retention time. $A_{290/260}$—the ratio between absorbance at 290 and 260 mn measured at maximum of the corresponding peak. All ^{1}H and ^{31}P NMR spectra were recorded at 400 and 161.9 MHz, respectively. ^{13}C NMR spectra for **10a**, **10b**, **16**, and **18** were recorded at 62.9 MHz and at 100.6 MHz for all other compounds. The values for chemical shifts are reported in parts per million relative to tetramethylsilane (TMS) as internal standard for ^{1}H and ^{13}C, and relative to 85% H_3PO_4 as external standard for ^{31}P. MALDI-TOF mass spectra of nucleosides were recorded on a Voyager-DE PRO spectrometer in positive ion mode using 2,5-dihydroxybenzoic acid as the matrix. Melting points were measured on a Büchi Melting Point B-540 apparatus and uncorrected. The mp values are reported for all crystalline compounds. All the other solid products were obtained as amorphous solid foam after chromatographic purification and generally demonstrated broad phase transitions.

4.1.1. 3-*O*-Benzyl-4-*C*-methanesulfonoxymethyl-5-*O*-methanesulfonyl-1,2-*O*-isopropylidene-β-L-*threo*-pentofuranose (2). Colorless viscous oil; obtained as described earlier.[25] ^{1}H NMR ($CDCl_3$): δ 7.40–7.31 (m, 5H), 5.98 (d, *J*=4.0 Hz, 1H), 4.71 (d, *J*=11.5 Hz, 1H), 4.70 (d, *J*=3.9 Hz, 1H), 4.55 (d, *J*=11.5 Hz, 1H), 4.39 (d, *J*=10.4 Hz, 1H), 4.38 (d, *J*=10.8 Hz, 1H), 4.33 (d, *J*=10.6 Hz, 2H), 4.10 (s, 1H), 3.02 (s, 3H), 3.00 (s, 3H), 1.57 (s, 3H), 1.33 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 136.1, 128.5, 128.3, 127.9, 113.2, 105.7, 85.9, 84.0, 82.8, 72.7, 67.3, 67.0, 37.5, 37.3, 26.4, 25.8. MALDI-TOF MS: *m*/*z* 489.0 ($M+Na^+$).

4.1.2. 1,2-Di-*O*-acetyl-3-*O*-benzyl-4-*C*-methanesulfonoxymethyl-5-*O*-methanesulfonyl-α,β-L-*threo*-pentofuranose (3). To a solution of furanose **2** (73.4 g, 0.157 mol) in AcOH (250 mL) were added Ac_2O (40 mL, 0.424 mol) and concd H_2SO_4 (1.1 mL). The solution was stirred overnight, cooled in an ice bath, and 2 M NaOH (400 mL) was added under intensive stirring. The mixture was washed with CH_2Cl_2 (3×200 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×400 mL) and brine (400 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give **3** (72.6 g, 91%) as a brownish viscous oil.[25]

4.1.3. 1-(2-*O*-Acetyl-3-*O*-benzyl-4-*C*-methanesulfonoxymethyl-5-*O*-methanesulfonyl-α-L-*threo*-pentofuranosyl)thymine (4). A mixture of furanose **3** (72.4 g, 0.14 mol) and thymine (22.5 g, 0.18 mol) was suspended in anhydrous MeCN (300 mL) and *N*,*O*-bis(trimethylsilyl)acetamide (68 mL, 0.27 mol) was added. After refluxing for 1.5 h, a clear solution was obtained and the mixture was cooled to room temperature. Trimethylsilyl trifluoromethanesulfonate (50 mL, 0.28 mol) was added and refluxing was continued for 6 h. The reaction mixture was cooled to room temperature, neutralized with saturated $NaHCO_3$ (400 mL), and washed with CH_2Cl_2 (2×300 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2×300 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give compound **4** (84.0 g, 103%) as a brownish solid residue, which was used for the next step without additional purification. RP-HPLC: R_t=9.85 min, $A_{290/260}$=0.12, purity 97% (integration at 260 nm). Analytical sample was obtained after silica gel column chromatography (1–3% v/v MeOH/CH_2Cl_2) as a white solid foam. ^{1}H NMR ($CDCl_3$): δ 9.34 (br s, 1H), 7.31–7.42 (m, 6H), 6.28 (d, *J*=3.5 Hz, 1H), 5.36 (dd, *J*=3.5 and 2.8 Hz, 1H), 4.78 (d, *J*=11.4 Hz, 1H), 4.66 (d, *J*=11.4 Hz, 1H), 4.55 (d, *J*=11.2 Hz, 1H), 4.42 (d, *J*=11.2 Hz, 1H), 4.35 (d, *J*=10.8 Hz, 1H), 4.26 (d, *J*=10.8 Hz, 1H), 4.25 (d, *J*=2.8 Hz, 1H), 3.05 (s, 3H), 3.02 (s, 3H), 2.14 (s, 3H), 1.80 (d, *J*=1.1 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 169.6, 163.3, 150.3, 135.8, 134.9, 128.6, 128.5, 128.3, 112.3, 87.5, 84.6, 81.1, 79.3, 73.0, 66.9, 65.4, 37.6, 20.5, 12.2. MALDI-TOF MS: *m*/*z* 599.1 ($M+Na^+$). Anal. Calcd for $C_{22}H_{28}N_2O_{12}S_2$: C, 45.83; H, 4.89; N, 4.86. Found: C, 45.97; H, 4.86; N, 4.80.

4.1.4. 1-(3-*O*-Benzyl-5-*O*-methanesulfonyl-2-*O*,4-*C*-methylene-α-L-ribofuranosyl)thymine (6). Compound **4** (83.7 g, 0.145 mol) was dissolved in 1 M HCl in MeOH (450 mL) and stirred for 24 h. The solvents were removed under reduced pressure to give a solid residue. The residue was co-evaporated with anhydrous MeCN (250 mL) and dried in vacuo overnight to give intermediate **5** (77.2 g, 99.6 %). RP-HPLC: R_t=8.82 min, $A_{290/260}$=0.155. The intermediate was dissolved in anhydrous pyridine (200 mL), cooled in an ice bath, and MsCl (14.5 mL, 0.183 mol) was added under intensive stirring. The mixture was allowed to warm to room temperature and stirred overnight, whereupon 1 M NaOH (1.5 L) was added. After stirring for 18 h, AcOH (90 mL) was added and the mixture was washed with CH_2Cl_2 (2×400 mL). The combined organic layers were washed with saturated $NaHCO_3$, dried (Na_2SO_4), and concentrated under reduced pressure to give an oily residue. The residue was co-evaporated with anhydrous toluene (2×300 mL) and dried in vacuo to give compound **6** (64.8 g, 102%) as a brown solid material. RP-HPLC: R_t=8.75 min, $A_{290/260}$=0.28, purity 96% (integration at 260 nm). Analytical sample was obtained after silica gel column chromatography (1.5–3.5% v/v MeOH/CH_2Cl_2) as a white solid foam. ^{1}H NMR (DMSO-d_6): δ 11.40 (br s, 1H), 7.64 (d, J=1.1 Hz, 1H), 7.40–7.30 (m, 5H), 5.96 (s, 1H), 4.71 (d, *J*=12.1 Hz, 1H), 4.68 (d, *J*=12.1 Hz, 1H), 4.60 (m, 3H), 4.50 (s, 1H), 4.12 (d, *J*=8.6 Hz, 1H), 4.00 (d, *J*=8.5 Hz, 1H), 3.25 (s, 3H), 1.84 (d, *J*=1.1 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 163.8, 150.3, 137.7, 135.8, 128.4, 127.8, 127.6, 108.3, 86.8, 86.5, 79.2, 76.5, 72.0, 71.3, 65.3, 37.0, 12.3. MALDI-TOF MS: *m*/*z* 460.8 ($M+Na^+$).

4.1.5. 1-(3-*O*-Benzyl-2-*O*,4-*C*-methylene-α-L-ribofuranosyl)thymine (7). A mixture of **6** (64.0 g, 0.146 mol) and NaOBz (41 g, 0.285 mol) suspended in anhydrous DMSO (450 mL) was stirred for 3 h at 120 °C. The mixture was cooled to room temperature and 1 M NaOH (500 mL) was added under intensive stirring. The obtained clear solution was stirred for 1 h, neutralized with AcOH (30 mL), and washed with CH_2Cl_2 (3×300 mL). The combined organic layers were filtered through a silica gel pad (300 cm^3); silica gel was washed with 4% MeOH/CH_2Cl_2 (v/v, 500 mL). The combined filtrates were dried (Na_2SO_4) and concentrated under reduced pressure at 70 °C until complete removal of DMSO. The solid residue was crystallized from EtOAc to give nucleoside **7** (30.5 g) as a white powder. The mother liquor was concentrated to a solid residue and applied to silica gel column chromatography (1–4% v/v MeOH/CH_2Cl_2). The fractions containing **7** were pooled, concentrated under reduced pressure, and the residue was crystallized from EtOAc to give another 8.4 g of **7** (total yield 74%). Mp 169–170 °C. MALDI-TOF MS: *m/z* 382.7 ($M+Na^+$). Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 55.99; H, 5.59; N, 7.77. Found: C, 60.02; H, 5.47; N, 7.79. NMR data were identical with those reported earlier.[26]

4.1.6. 1-(2-*O*,4-*C*-Methylene-α-L-ribofuranosyl)thymine (8a). To a solution of compound **7** (30.4 g, 84 mmol) in MeOH/1,4-dioxane (1:1 v/v, 200 mL) were added $Pd(OH)_2$/C (6 g) and HCO_2NH_4 (15 g). The mixture was stirred under reflux for 1 h. More HCO_2NH_4 was added in portions of 5 g at an interval of 30 min (total amount 25 g). The mixture was cooled to room temperature, diluted with 30% aqueous NH_4OH (50 mL), and filtered through a Celite pad. The Celite was washed with 30% aqueous NH_4OH (75 mL). The filtrates were combined, concentrated under reduced pressure to ca. half of its volume and kept at 4 °C overnight. The precipitate formed was collected by filtration, washed with cold H_2O, and dried in vacuo to give compound **8a** (21.1 g, 93%) as a white crystalline powder. Mp 239–242 °C (dec.); starts sintering at 234 °C. MALDI-TOF MS: *m/z* 292.9 ($M+Na^+$). Anal. Calcd for $C_{11}H_{14}N_2O_6 \cdot 1/5H_2O$: C, 48.25; H, 5.30; N, 10.23. Found: C, 48.18; H, 5.16; N, 10.23. NMR data were identical with those reported earlier.[26]

4.1.7. 1-[3-*O*-Acetyl-5-*O*-(4,4′-dimethoxytrityl)-2-*O*,4-*C*-methylene-α-L-ribofuranosyl]thymine (10a). To a solution of compound **8a** (9.13 g, 33.8 mmol) in anhydrous pyridine (60 mL) was added DMT-Cl (14.2 g, 42.2 mmol). The mixture was stirred for 4 h and Ac_2O (4.5 mL, 43.9 mmol) was added. After stirring overnight, the mixture was diluted with EtOAc (250 mL), washed with saturated $NaHCO_3$ (2×300 mL), dried (Na_2SO_4), and concentrated under reduced pressure to an oily residue. The residue was co-evaporated with toluene (2×200 mL) and purified by silica gel column chromatography (0.5–2% v/v MeOH/CH_2Cl_2, containing 1% of Et_3N) to give compound **10a** (18.7 g, 90%) as a white solid foam. ^1H NMR (DMSO-d_6): δ 11.46 (br s, 1H), 7.62 (d, *J*=1.1 Hz, 1H), 7.41–7.24 (m, 9H), 6.91 (m, 4H), 6.12 (s, 1H), 5.45 (s, 1H), 4.55 (s, 1H), 4.18 (d, *J*=8.8 Hz, 1H), 3.86 (d, *J*=8.8 Hz, 1H), 3.74 (s, 6H), 3.32 (m, 2H; overlaps with H_2O), 2.04 (s, 3H), 1.84 (d, *J*=1.1 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 169.5, 163.9, 158.3, 150.4, 144.6, 135.6, 135.2, 135.1, 129.9, 128.0, 127.7, 126.9, 113.4, 108.4, 88.0, 86.6, 85.7, 77.1, 73.6, 72.5, 58.8, 55.1, 20.6, 12.4. MALDI-TOF MS: *m/z* 636.5 ($M+Na^+$).

4.1.8. Compound 10b. White solid foam; prepared by the method described for **10a** (yield 89%). ^1H NMR (DMSO-d_6): δ 11.50 (br s, 1H), 7.59 (s, 1H), 7.43–7.23 (m, 9H), 6.93–6.90 (m, 4H), 5.56 (s, 1H), 5.15 (s, 1H), 4.51 (s, 1H), 3.81 (d, *J*=8.4 Hz, 1H), 3.75 (d, *J*=8.4 Hz, 1H), 3.74 (s, 6H), 3.46 (d, *J*=11.5 Hz, 1H), 3.38 (d, *J*=11.5 Hz, 1H), 2.02 (s, 3H), 1.63 (d, *J*=0.9 Hz, 3H). ^{13}C NMR (DMSO-d_6): δ 169.4, 163.8, 158.3, 150.0, 144.5, 135.1, 135.0, 133.8, 129.8, 129.7, 128.1, 127.6, 127.0, 113.4, 109.2, 86.6, 86.5, 86.0, 77.4, 71.7, 70.6, 57.8, 55.1, 20.5, 12.5. MALDI-TOF MS: *m/z* 635.9 ($M+Na^+$). Anal. Calcd for $C_{34}H_{34}N_2O_9 \cdot 1/4H_2O$: C, 65.96; H, 5.62; N, 4.52. Found: C, 65.89; H, 5.55; N, 4.47.

4.1.9. 1-[3-*O*-Acetyl-5-*O*-(4,4′-dimethoxytrityl)-2-*O*,4-*C*-methylene-α-L-ribofuranosyl]-5-methyl-4-(1,2,4-triazol-1-yl)-2-oxypyrimidine (11a). A mixture of compound **10a** (18.5 g, 29.2 mmol) and 1,2,4-triazole (18.6 g, 263 mmol) was suspended in anhydrous acetonitrile (300 mL) and freshly distilled phosphoryl chloride (4.1 mL, 50 mmol) was added. The mixture was cooled in an ice bath and diisopropylethylamine (51 mL, 292.3 mmol) was slowly added under intensive stirring. The mixture was stirred for 2 h at room temperature, diluted with ethyl acetate (300 mL), washed with saturated $NaHCO_3$ (3×300 mL) and brine (250 mL), dried (Na_2SO_4), and concentrated under reduced pressure to give after drying compound **11a** (18.9 g, 97%) as a brownish solid material. RP-HPLC: R_t=12.76 min, $A_{290/260}$=0.235, purity 98% (integration at 260 nm). Analytical sample was obtained after silica gel column chromatography (50–80% v/v EtOAc/hexane, containing 1% of Et_3N) as a white solid foam. ^1H NMR ($CDCl_3$): δ 9.29 (s, 1H), 8.12 (s, 1H), 8.10 (s, 1H), 7.45–7.41 (m, 2H), 7.34–7.24 (m, 7H), 6.88–6.83 (m, 4H), 6.18 (s, 1H), 5.34 (s, 1H), 4.95 (1H, s), 4.07 (d, *J*=9.0 Hz, 1H), 4.01 (d, *J*=9.0 Hz, 1H), 3.80 (s, 6H), 3.57 (d, *J*=11.0 Hz, 1H), 3.46 (d, *J*=11.0 Hz, 1H), 2.55 (s, 3H), 2.05 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 169.1, 158.5, 158.2, 153.5, 153.3, 146.1, 144.9, 144.0, 135.0, 129.8, 127.8, 127.6, 126.9, 113.1, 105.0, 89.05, 88.98, 86.3, 76.8, 73.7, 73.3, 59.1, 55.1, 20.5, 17.4. MALDI-TOF MS: *m/z* 686.7 ($M+Na^+$).

4.1.10. Compound 11b. White solid foam; prepared in 90% yield as described for **11a**. ^1H NMR ($CDCl_3$): δ 9.29 (s, 1H), 8.27 (s, 1H), 8.12 (s, 1H), 7.46–7.24 (m, 9H), 6.89–6.84 (m, 4H), 5.85 (s, 1H), 5.15 (s, 1H), 4.82 (1H, s), 3.91 (d, *J*=8.2 Hz, 1H,), 3.88 (d, *J*=8.2 Hz, 1H), 3.80 (s, 6H), 3.64 (d, *J*=11.2 Hz, 1H), 3.38 (d, *J*=11.2 Hz, 1H), 2.22 (s, 3H), 2.03 (s, 3H,). ^{13}C NMR ($CDCl_3$): δ 169.1, 158.6, 158.4, 153.3, 153.2, 145.4, 145.0, 143.9, 134.8, 129.9, 129.8, 127.9, 127.8, 127.0, 113.2, 106.1, 88.3, 87.4, 86.7, 77.1, 72.1, 70.2, 57.4, 55.1, 20.5, 17.2. MALDI-TOF MS: *m/z* 687.5 ($M+Ma^+$). Anal. Calcd for $C_{36}H_{35}N_5O_8$: C, 64.95; H, 5.30; N, 10.52. Found: C, 64.69; H, 5.26; N, 10.45.

4.1.11. 4-*N*-Benzoyl-1-[5-*O*-(4,4′-dimethoxytrityl)-2-*O*,4-*C*-methylene-α-L-ribofuranosyl]-5-methylcytosine (12a). To a solution of compound **11a** (18.5 g, 27.8 mmol) in MeCN (250 mL) was added concentrated NH_4OH

(200 mL). The mixture was kept overnight at room temperature and the solvents were removed under reduced pressure to give a solid residue. The residue was co-evaporated with anhydrous pyridine (2×200 mL), dissolved in anhydrous pyridine (250 mL), and Bz_2O (19.0 g, 84.0 mmol) was added. After stirring overnight, to the mixture were added MeOH (150 mL) and 2 M NaOH (150 mL). The obtained clear solution was stirred for 1 h and washed with CH_2Cl_2 (2×300 mL). The combined organic phases were excessively washed with saturated $NaHCO_3$ and brine, dried (Na_2SO_4), and concentrated under reduced pressure to a solid residue. Purification by silica gel column chromatography (5–15% v/v EtOAc/CH_2Cl_2, containing 1% of Et_3N) gave compound **12a** (15.2 g, 81%) as a white solid foam.[25]

4.1.12. Compound 12b. White solid foam; prepared as described for **10a** (yield 76%). ^{1}H NMR (DMSO-d_6): δ 13.14 (br s, 1H), 8.20 (m, 2H), 7.79 (s, 1H), 7.57–7.24 (m, 12H), 6.93 (m, 4H), 5.87 (d, J=3.9 Hz, 1H), 5.54 (s, 1H), 4.31 (s, 1H), 4.22 (d, J=4.4 Hz, 1H), 3.81 (d, J=7.9 Hz, 1H), 3.75 (s, 7H), 3.51 (d, J=11.0 Hz, 1H), 3.39 (d, J=11.0 Hz, 1H), 1.80 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 178.3, 159.3, 158.3, 147.0, 144.8, 137.0, 135.4, 135.4, 135.2, 132.6, 129.9, 129.5, 128.3, 128.1, 127.8, 126.9, 113.4, 109.6, 87.8, 87.1, 85.9, 78.7, 71.5, 69.3, 58.6, 55.2, 13.3. MALDI-TOF MS: m/z 697.3 (M+Na$^+$).

4.1.13. 7-(2-*O*-Acetyl-3-*O*-benzyl-4-*C*-methanesulfoxymethyl-5-*O*-methanesulfonyl-β-D-*erythro*-pentofuranosyl)-2-*N*-isobutyrylguanine (15). A mixture of furanose **14**[24] (6.0 g, 11.7 mmol) and 2-*N*-isobutyrylguanine (3.1 g, 14.1 mmol) was suspended in anhydrous MeCN (60 mL) and *N*,*O*-bis(trimethylsilyl)acetamide (5.7 mL, 23.1 mmol) was added. The mixture was stirred overnight whereupon the presence of insoluble residue was still observed. The solvents were removed under reduced pressure and the residue was co-evaporated with anhydrous MeCN (2×50 mL) and suspended in anhydrous MeCN (50 mL). To the mixture was added *N*,*O*-bis(trimethylsilyl)acetamide (2.8 mL, 11.3 mmol). After stirring for 1 h, a clear solution was obtained and $SnCl_4$ (1.5 mL, 12.8 mmol) was added. After stirring for 20 h, the mixture was diluted with EtOAc (100 mL) and saturated $NaHCO_3$ (50 mL). The mixture was filtrated through Celite pad and the Celite was additionally washed with 10% v/v MeOH/EtOAc (50 mL). Organic layer was separated, washed with saturated $NaHCO_3$ (2×100 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated to a solid residue. Purification with silica gel HPLC (0–4% v/v MeOH/CH_2Cl_2) gave compound **15** (2.7 g, 34%) as a white solid foam. ^{1}H NMR ($CDCl_3$): δ 12.07 (br s, 1H), 9.48 (br s, 1H), 7.97 (s, 1H), 7.30 (m, 5H), 6.62 (d, J=5.7 Hz, 1H), 6.32 (s, 1H), 5.33 (d, J=5.8 Hz, 1H), 4.76 (d, J=11.4 Hz, 1H), 4.74 (d, J=11.5 Hz, 1H), 4.68 (d, J=11.4 Hz, 1H), 4.57 (d, J=10.6 Hz, 1H), 4.46 (d, J=11.5 Hz, 1H), 4.44 (d, J=10.5 Hz, 1H), 3.05 (s, 3H), 3.00 (s, 3H), 2.77 (m, 1H), 2.27 (s, 3H), 1.39 (d, J=7.0 Hz, 3H), 1.30 (d, J=6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 179.7, 170.3, 157.4, 152.2, 147.4, 141.0, 137.1, 128.4, 128.3, 128.1, 110.2, 90.8, 84.7, (77.2, 76.9, 76.6 overlap with $CDCl_3$), 74.1, 68.0, 37.6, 36.7, 36.3, 21.0, 19.0, 18.6. MALDI-TOF MS: m/z 671.8 (M+H$^+$). Anal. Calcd for $C_{26}H_{33}N_5O_{12}S_2$: C, 46.49; H, 4.95; N, 10.43. Found: C, 46.45; H, 4.93; N, 9.90.

4.1.14. 7-(3-*O*-Benzyl-5-*O*-methanesulfonyl-2-*O*,4-*C*-methylene-β-D-ribofuranosyl)-2-*N*-isobutyrylguanine (16). White solid foam; prepared using the method described earlier[24] for the N^9-glycosylated counterpart (yield 89%). ^{1}H NMR ($CDCl_3$): δ 10.17 (br s, 1H), 8.12 (s, 1H), 7.28–7.20 (m, 5H), 6.20 (s, 1H), 4.82 (s, 1H), 4.67 (d, J=11.9 Hz, 1H), 4.60 (d, J=11.9 Hz, 1H), 4.58 (d, J=11.5 Hz, 1H), 4.53 (d, J=11.5 Hz, 1H), 4.21 (s, 1H), 4.15 (d, J=7.9 Hz, 1H), 3.97 (d, J=7.9 Hz, 1H), 3.11 (s, 3H), 2.90 (m, 1H), 1.28 (d, J=6.8 Hz, 3H), 1.22 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 179.7, 157.4, 152.8, 147.8, 140.0, 136.5, 128.4, 128.1, 127.7, 110.4, 88.3, 85.7, 78.0, 76.1, 72.3, 71.8, 64.2, 37.7, 35.9, 19.0, 18.8. MALDI-TOF MS: m/z 533.6 (M+H$^+$). Anal. Calcd for $C_{23}H_{27}N_5O_8S\cdot 1/6H_2O$: C, 51.49; H, 5.13; N, 13.05. Found: C, 51.46; H, 5.02; N, 12.64.

4.1.15. 7-(5-*O*-Benzoyl-3-*O*-benzyl-2-*O*,4-*C*-methylene-β-D-ribofuranosyl)-2-*N*-isobutyrylguanine (17). White solid foam; prepared using the method described earlier[24] for the N^9-glycosylated counterpart (yield 93%). ^{1}H NMR ($CDCl_3$): δ 10.39 (br s, 1H), 7.99–7.97 (m, 3H), 7.61–7.57 (m, 1H), 7.47–7.43 (m, 2H), 7.23–7.18 (m, 5H), 6.21 (s,1H), 4.84 (s, 1H), 4.80 (d, J=12.7 Hz, 1H), 4.70 (d, J=12.8 Hz, 1H), 4.62 (d, J=11.7 Hz, 1H), 4.48 (d, J=11.7 Hz, 1H), 4.25 (d, J=7.9 Hz, 1H), 4.15 (s, 1H), 4.07 (d, J=7.9 Hz, 1H), 2.96 (m, 1H), 1.25 (d, J=6.8 Hz, 3H), 1.21 (d, J=7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 179.8, 165.7, 157.5, 152.7, 148.0, 139.7, 136.5, 133.4, 129.4, 129.0, 128.5, 128.3, 128.0, 127.5, 110.5, 88.3, 86.1, 78.0, 76.2, 72.3, 72.1, 59.8, 35.9, 19.0, 18.9. MALDI-TOF MS: m/z 560.0 (M+H$^+$). Anal. Calcd for $C_{29}H_{29}N_5O_7\cdot 1/5H_2O$: C, 61.85; H, 5.26; N, 12.44. Found: C, 61.91; H, 5.25; N, 11.95.

4.1.16. 7-(3-*O*-Benzyl-2-*O*,4-*C*-methylene-β-D-ribofuranosyl)-2-*N*-isobutyrylguanine (18). White crystalline powder; synthesized using the method described earlier[24] for the N^9-glycosylated counterpart; crystallized from MeOH/H_2O (yield 85%). Mp 190–191.5 °C. ^{1}H NMR (DMSO-d_6): δ 12.19 (br s, 1H), 11.57 (br s, 1H), 8.29 (s, 1H), 7.31–7.22 (m, 5H), 6.11 (s,1H), 5.26 (t, J=5.8 Hz, 1H), 4.64 (s, 1H), 4.57 (s, 2H), 4.13 (s, 1H), 3.93 (d, J=7.9 Hz, 1H), 3.85 (d, J=5.8 Hz, 2H), 3.79 (d, J=7.9 Hz, 1H), 2.76 (m, 1H), 1.14–1.11 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 180.1, 157.7, 152.5, 147.4, 140.6, 137.9, 128.3, 127.6, 127.5, 110.5, 88.6, 87.3, 77.8, 76.0, 71.8, 71.3, 56.5, 34.8, 19.0, 18.9. MALDI-TOF MS: m/z 457.1 (M+H$^+$). Anal. Calcd for $C_{29}H_{29}N_5O_7\cdot H_2O$: C, 55.81; H, 5.75; N, 14.79. Found: C, 55.63; H, 5.59; N, 14.69.

4.1.17. 7-(2-*O*,4-*C*-Methylene-β-D-ribofuranosyl)guanine (21). To a solution of compound **18** (540 mg, 1.19 mmol) in MeOH (10 mL) were added Pd/C (10%, 250 mg) and HCO_2NH_4 (0.5 g). The mixture was refluxed until complete consumption of **18** had occurred whereupon formation of insoluble product(s) was observed. Saturated NH_3 in MeOH was added (20 mL) under intensive stirring and the catalyst was filtered off and washed with saturated NH_3 in MeOH (100 mL). The combined filtrates were stirred for 72 h and concentrated to a solid residue. The residue was suspended in MeOH/EtOAc (1:1 v/v, 100 mL) under reflux for 30 min. The mixture was concentrated to ca. half of its volume, and cooled in an ice bath. Insoluble material was filtered off,

washed with EtOAc and Et_2O, and dried in vacuo to give **21** (302 mg, 86%) as a white powder. ^{1}H NMR (DMSO-d_6; low solubility): δ 10.87 (br s, 1H), 8.08 (s, 1H), 6.18 (br s, 2H), 5.94 (s, 1H), 5.59 (br s, 1H), 5.03 (br s, 1H), 4.29 (s, 1H), 4.04 (s, 1H), 3.88 (d, J=7.8 Hz, 1H), 3.79 (m, 2H), 3.70 (d, J=7.7 Hz, 1H). ^{13}C NMR (DMSO-d_6; sugar part): δ 88.7, 87.0, 80.1, 71.1, 68.8, 56.4. MALDI-TOF MS: m/z 296.0 (M+H$^+$).

4.1.18. 7-[5-*O*-(4,4′-Dimethoxytrityl)-2-*O*,4-*C*-methylene-β-D-ribofuranosyl]-2-*N*-dimethylaminomethyleneguanine (22). Compound **21** (250 mg, 0.85 mmol) was dissolved in hot anhydrous DMF (8 mL) and *N*,*N*-dimethylformamide dimethyl acetal (300 μL, 2.26 mmol) was added. The mixture was stirred overnight and H_2O (1 mL) was added. The solvents were removed under reduced pressure to give an oily residue. The residue was co-evaporated with anhydrous pyridine (2×10 mL), dissolved in anhydrous pyridine (5 mL), and DMT-Cl (310 mg, 0.92 mmol) was added. The mixture was stirred for 4 h, diluted with EtOAc (20 mL), washed with saturated $NaHCO_3$ (2×20 mL), dried (Na_2SO_4), and concentrated to a solid residue. Purification by silica gel HPLC (1–4% v/v MeOH/CH_2Cl_2, containing 0.1% of pyridine) gave compound **22** (490 mg, 89%) as a white solid foam. ^{1}H NMR (DMSO-d_6): δ 11.51 (br s, 1H), 8.62, (s, 1H), 8.11 (s, 1H), 7.46–7.28 (m, 9H), 6.91 (m, 4H), 6.10 (s, 1H), 5.71 (d, J=4.4 Hz, 1H), 4.41 (s, 1H), 4.20 (d, J=4.4 Hz, 1H), 3.89 (d, J=7.9 Hz, 1H), 3.86 (d, J=7.9 Hz, 1H), 3.75 (s, 6H), 3.56 (d, J=11.0 Hz, 1H), 3.33 (d, J=11.0 Hz, 1H), 3.15 (s, 3H), 3.02 (s, 3H). ^{13}C NMR (DMSO-d_6): δ 159.5, 158.2, 157.9, 156.9, 155.2, 144.8, 139.6, 135.5, 135.3, 129.9, 129.8, 128.0, 127.8, 126.9, 113.4, 109.9, 87.3, 85.6, 80.2, 71.6, 69.5, 59.6, 55.2, 40.6, 34.7. MALDI-TOF MS: m/z 675.7 (M+Na$^+$).

4.1.19. 7-[3-*O*-Cyanoethoxy(diisopropylamino)phosphinoxy)-5-*O*-(4,4′-dimethoxytrityl)-2-*O*,4-*C*-methylene-β-D-ribofuranosyl]-2-*N*-dimethylaminomethyleneguanine (23). To a solution of compound **22** (415 mg, 0.64 mmol) in anhydrous CH_2Cl_2 (3 mL) were added 0.75 M solution of 4,5-dicyanoimidazole (700 μL, 0.53 mmol) in CH_3CN and 2-cyanoethyl-*N*,*N*,*N*′,*N*′-tetraisopropyl phosphordiamidite (230 μL, 0.72 mmol). The mixture was stirred overnight, diluted with EtOAc (25 mL), and washed with saturated $NaHCO_3$ (2×25 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4) and concentrated to a white solid residue. The residue was dissolved in anhydrous CH_2Cl_2 (5 mL) and pentane (100 mL) was added under intensive stirring. The precipitate formed was collected by filtration, washed with pentane, and dried in vacuo to give compound **23** (498 mg, 92%) as a white amorphous powder consisting of two stereoisomers. RP-HPLC: R_t=15.05 min, $A_{290/260}$=2.54. MALDI-TOF MS: m/z 791.2 (M−N^{i}Pr$_2$+OH+Na$^+$). ^{31}P NMR (DMSO-d_6): δ 149.20, 147.98.

Compound **20**. ^{31}P NMR (DMSO-d_6): δ 148.96, 148.70.

4.2. Oligonucleotide synthesis

All oligonucleotides were synthesized in 0.2 μmol scales on Expedite DNA synthesizer using the phosphoramidite method. Standard protocols recommended by the manufacturer were used for commercial DNA amidites. For all LNA amidites coupling times and times of oxidation were extended to 500 and 30 s, respectively. After oligomerization, the solid support bound oligonucleotides were transferred into 1.5 mL reaction tubes and treated with concentrated NH_4OH for 6 h at 60 °C. Oligonucleotide **46** (phosphoramidite **20** used) was subsequently treated with 30% $MeNH_2$ for 2 h at 60 °C. The solvents were removed under reduced pressure and target oligonucleotides were purified by RP-HPLC. Structures of the oligonucleotides were verified by MALDI-TOF mass spectra recorded in negative ion mode using picolinic acid as the matrix (results shown in Table 3).

Table 3. The results of MALDI-TOF analysis

Oligonucleotide	(M−H)$^-$	
	Calcd	Found
24	4385.8	4380.1
25	4385.8	4381.3
26	4385.8	4385.2
27	4581.8	4576.6
28	4581.8	4583.0
29	4385.8	4386.0
30	4385.8	4383.9
31	4385.8	4384.0
32	4385.8	4384.7
33	4515.7	4513.1
34	4463.7	4459.4
35	4435.7	4435.4
36	4379.7	4376.8
37	4411.8	4405.1
38	4411.8	4407.8
39	4411.8	4410.6
40	9259.0	9264.0
41	9150.8	9147.0
42	4417.7	4414.8
43	2672.7	2972.8
44	2681.8	2681.9
45	2697.5	2698.9
46	2697.5	2697.9

4.3. Thermal denaturation studies

The samples of model triplexes and duplexes were obtained after mixing the equal molar amounts of complementary oligonucleotides and buffers (final volumes 0.5 mL). The buffer and concentration conditions are described in the footnotes to Tables 1 and 2. To ensure triplex formation, the samples were kept for 12 h at 4 °C prior to melting experiments. Melting temperature measurements were carried out on a Perkin–Elmer UV-spectrometer equipped with a PTP-6 Peltier temperature controller. The optical density of samples was monitored at 260 nm while raising the temperature from 20 to 95 °C at a rate of 1 °C/min. The T_m values were determined as the maxima of the first derivatives of the melting curves obtained.

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α,α-Difluoro-α-phenylsulfanylmethyl carbanion equivalent: a novel *gem*-difluoromethylenation of carbonyl compounds

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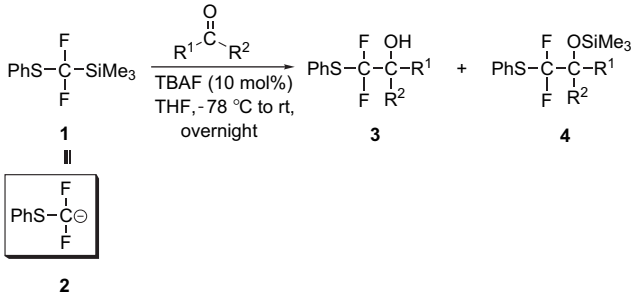
Abstract—α,α-Difluoro-α-phenylsulfanyl-α-trimethylsilylmethane ($PhSCF_2SiMe_3$) has been demonstrated as an α,α-difluoro-α-phenylsulfanylmethyl carbanion equivalent. *gem*-Difluorophenylsulfanylmethylation of carbonyl compounds has been successfully achieved by using $PhSCF_2SiMe_3$ in the presence of TBAF in THF. The adducts have been converted to the corresponding *gem*-difluoroalkenes by a novel pyrolytic and/or FVP elimination of the β-hydroxy-α-phenylsufinyl derivatives under reduced pressure.

1. Introduction

Organofluorine chemistry is receiving remarkable interest due to the enormous utility of organofluorine compounds in several fields, such as medicine, biology, agriculture and analytical chemistry.[1] The development of synthetic routes of such compounds and investigations for the use of new fluorinated compounds as building blocks are of great importance. Of particular interest is the introduction of a *gem*-difluoromethylene group into organic molecules, which have been the subject of recent reports by several prominent research groups such as those of Prakash et al.,[2] Hu[3] and Qing.[4] In continuation with our research on utilizing bromodifluorophenylsulfanylmethane as the *gem*-difluoromethylene building block,[5] we have investigated the utilization of α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane (**1**)[2b] as the synthetic equivalent of difluorinated carbanion **2** (Scheme 1).[6] In this paper, we wish to report our findings on the chemistry of the carbanion **2** and also provide novel examples of pyrolytic elimination of β-hydroxy-α-phenylsulfinyl derivatives to *gem*-difluoroalkenes.



Scheme 1.

2. Results and discussion

We first examined the nucleophilic difluorophenylsulfanylmethylation of benzaldehyde using compound **1** under the catalysis of fluoride ion (Scheme 1). It was found that the reaction of **1** (1.1 equiv) with benzaldehyde (1 equiv) took place between −78 °C and room temperature over 15 h in the presence of 10 mol % of anhydrous tetra-*n*-butylammonium fluoride (TBAF) in dry THF,[7] giving the desired **3a** and **4a** in 52 and 31% yields, respectively, after chromatography on silica gel. The reactions employing 20 or 50 mol % of TBAF afforded lower yields of the expected adducts **3a** and **4a**.[8] Thus, the standard conditions using 10 mol % of TBAF at −78 °C to room temperature overnight were used for the reactions of **1** with other carbonyl compounds. It was found that fluoride-catalyzed condensation of **1** with aromatic aldehydes gave mixtures of **3** and **4** in good yields (Table 1, entries 1–4 and 7–9), whereas

Keywords: Difluoro(phenylsulfanyl)trimethylsilane; *gem*-Difluoroalkene; *gem*-Difluoromethylenation; Fluoride-catalyzed reaction; Carbonyl compounds.
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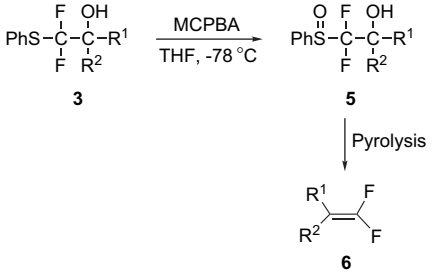
Table 1. Fluoride-catalyzed condensation of **1** with carbonyl compounds

Entry	Carbonyl compounds	**3** (%)[a]	**4** (%)[a]	**3+4** (%)[a]
1	Benzaldehyde	**3a** (52)	**4a** (31)	83
2	4-Methoxybenzaldehyde	**3b** (41)	**4b** (48)	89
3	2,4-Dimethoxybenzaldehyde	**3c** (28)	**4c** (60)	88
4	3,4-Dimethoxybenzaldehyde	**3d** (37)	**4d** (48)	85
5	Cinnamaldehyde	**3e** (50)	**4e** (18)	68
6	2-Methoxycinnamaldehyde	**3f** (53)	**4f** (37)	90
7	4-Methylbenzaldehyde	**3g** (35)	**4g** (51)	86
8	4-Bromobenzaldehyde	**3h** (61)	**4h** (31)	92
9	2-Furaldehyde	**3i** (73)	—	73
10	*n*-Butanal	**3j** (69)	—	69
11	Crotonaldehyde	**3k** (70)	—	70
12	1-Tetralone	**3l** (22)	**4l** (26)	48
13	6-Methoxy-1-tetralone	**3m** (21)	**4m** (29)	50
14	Acetophenone	**3n** (30)	**4n** (21)	51
15	Benzophenone	**3o** (33)	**4o** (6)	39
16	Cyclohexanone	**3p** (63)	—	63
17	Cyclopentanone	**3q** (45)	—	45
18	Acetone	**3r** (65)	—	65
19	2-Cyclohexenone	**3s** (60)	—	60

[a] Isolated yield.

aromatic ketones afforded moderate yields of **3** and **4** (entries 12–15). The reactions proceeded well with aliphatic aldehydes and ketones (Table 1, entries 10 and 16–18) to give the adduct **3** as the sole products. Interestingly, 1,2-addition products were obtained, when **1** was combined with α,β-unsaturated carbonyl compounds, indicating the nature of non-stabilized carbanion **2** (Table 1, entries 5, 6, 11 and 19).[9] The silyl ether **4b** could be converted into the corresponding adduct **3b** in quantitative yield by employing KF in acetonitrile/THF at room temperature overnight.

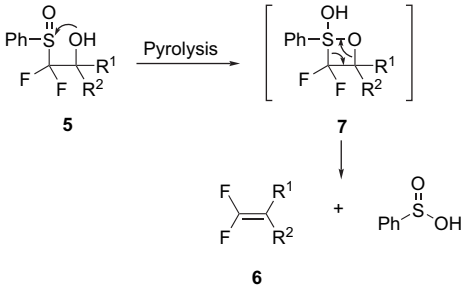
The synthetic utility of this reaction for the synthesis of *gem*-difluoromethylene compounds as described in Scheme 1 was further demonstrated by transformation of selected adduct **3** to *gem*-difluoroalkene **6**. Logically, we expected that the pyrolysis of the sulfoxide **5**, obtained from the oxidation of the aromatic aldehyde adduct **3** with MCPBA would lead to the corresponding α,α-difluoromethylketones (Scheme 2).[10] Thus, the oxidation of **3b** proceeded smoothly by using 1.1 equiv MCPBA in THF at −78 °C to room temperature overnight (15 h) to give the corresponding sulfoxide **5b** in 74% yield. To our surprise, neat pyrolysis of **3b** at 200 °C under reduced pressure (0.05 mmHg) furnished *gem*-difluoroalkene **6b** in 79% yield instead of the expected α,α-difluoromethyl 4-methoxyphenyl ketone. Similar result was observed when flash vacuum pyrolysis (FVP) of **5b** was performed. A good yield of **6b** (82%) resulted (Table 2, entries 1). Moreover, this novel synthetic conversion was extended to compounds **3c–f**, **3l** and **3n** to give *gem*-difluoroalkenes **6c–f**, **6l** and **6n** in moderate to good yields. It



Scheme 2.

should be mentioned here that the sulfoxide elimination of **5b–f** proceeded equally well under both neat pyrolysis and FVP, while **5l** and **5o** proceeded only under FVP conditions as summarized in Table 2 (entries 6 and 7). Our synthetic route thus provides a general entry to *gem*-difluoromethylenation of carbonyl compounds.[2d,2e,11]

The mechanism for the formation of *gem*-difluoroalkene **6** from the corresponding sulfoxide **5** is unclear but can be rationalized as proposed in Scheme 3. An intramolecular nucleophilic addition of the hydroxyl group to the electron deficient sulfur atom of **5** (due to the electronegativity of α,α-difluoro atoms) furnishes a cyclic intermediate **7**, which undergoes fragmentation to give *gem*-difluoroalkene **6**.



Scheme 3.

In conclusion, we have demonstrated that α,α-difluoro-α-phenylsulfanyl-α-trimethylsilylmethane (**1**) can serve as a practical and useful synthetic equivalent of α,α-difluoro-α-phenylsulfanylmethyl carbanion **2**, which is not easy to access. Both aldehydes and ketones undergo facile α,α-difluorophenylsulfanylmethylation with **1** in the presence of 10 mol % TBAF in THF, providing *gem*-difluoro substituted alcohols in moderate to good yields. We have also illustrated that these adducts can be used as useful precursors for preparing *gem*-difluoroalkenes through the β-hydroxy-α-phenylsulfinyl derivatives.

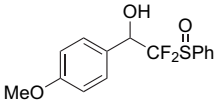
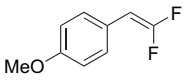
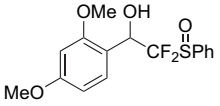
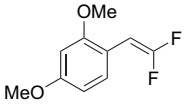
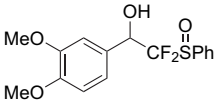
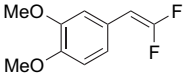
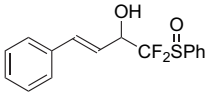
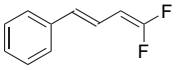
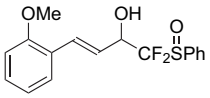
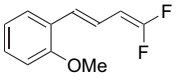
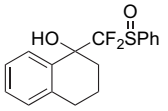
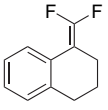
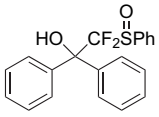
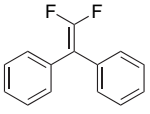
3. Experimental

3.1. General methods

The ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DPX-300 or a Bruker DPX-400 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The ^{19}F NMR spectra were recorded on a Bruker DPX-400 (376 MHz) spectrometer and chemical shifts (δ) were measured with fluorotrichloromethane (δ=0) as an internal standard. The IR spectra were recorded on either a Jasco A-302 or a Perkin Elmer 683 infrared spectrometer. The electron impact mass spectra were recorded by using Thermo Finnigan Polaris Q mass spectrometer. The high resolution mass spectra were recorded on HR-TOF-MS Micromass model VQ-TOF2. Elemental analyses were performed on a Perkin Elmer Elemental Analyzer 2400 CHN. Melting points were recorded on a Buchi 501 melting point apparatus and are uncorrected.

Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl. Dry dichloromethane (CH_2Cl_2) and dry

Table 2. Preparation of *gem*-difluoroalkene **6**

Entry	3	5[a]	6	Conditions, % yield of 6[b]	
				200 °C (0.05 mmHg)	FVP (temp, 0.05 mmHg)
1	**3b**	 **5b** (74%)	 **6b**	79%	82% (425 °C)
2	**3c**	 **5c** (69%)	 **6c**	74%	70% (425 °C)
3	**3d**	 **5d** (70%)	 **6d**	71%	68% (425 °C)
4	**3e**	 **5e** (50%)	 **6e**	70%	60% (425 °C)
5	**3f**	 **5f** (60%)	 **6f**	78%	70% (425 °C)
6	**3l**	 **5l** (68%)	 **6l**	—	41% (518 °C)
7	**3o**	 **5o** (71%)	 **6o**	—	80% (518 °C)

[a] Number in parenthesis is the isolated yield of **5** from **3** and obtained as a mixture of diastereomers.
[b] Isolated yield.

N,*N*-dimethylformamide (DMF) were obtained by distilling over phosphorus pentoxide and calcium hydride, respectively. Other common solvents (dichloromethane, hexane, ethyl acetate and acetone) were distilled before use.

The starting compound $PhSCF_2SiMe_3$ (**1**) was prepared according to the literature procedure.[2b]

The reactions of compound **1** with carbonyl compounds were run under an argon atmosphere. All glasswares and syringes were oven-dried and kept in a desiccator before use. Radial chromatography (chromatotron) and column chromatography were performed by using Merck silica gel 60 F_{254} (Art. 7749) and silica gel 60H (Art. 7736), respectively.

3.2. Preparation of compounds 3 and 4 by fluoride-catalyzed condensation of compound 1 with carbonyl compounds

3.2.1. 2,2-Difluoro-1-phenyl-2-phenylsulfanylethanol (3a) and 2,2-difluoro-1-phenyl-2-phenylsulfanyl-1-trimethylsiloxyethane (4a). *General procedure*: To a mixture of compound **1** (2.32 g, 10 mmol) and benzaldehyde (1.06 g, 10 mmol) in THF (25 mL), was added TBAF (1.0 mL, 1.0 mmol, 1 M solution in THF). The reaction mixture was stirred at −78 °C, followed by slow warming up to room temperature overnight. The solution was quenched with a saturated aqueous NH_4Cl solution and extracted with EtOAc (3×70 mL). The organic phase was washed

successively with brine, water and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by column chromatography (SiO_2, 5% EtOAc in hexanes) to give a pale yellow liquid of **3a** (1.373 g, 52% yield) and a white powder of **4a** (1.035 g, 31% yield, mp=45–46 °C). **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.58 (m, 2H, Ar*H*), 7.54–7.48 (m, 2H, Ar*H*), 7.49–7.35 (m, 6H, Ar*H*), 5.02 (dd, J=11.3, 7.9 Hz, 1H, C*H*OH), 2.62 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1 (2×CH), 135.9 (C), 130.6 (CH), 129.8 (CH), 129.7 (2×CH), 129.6 (t, J=283.1 Hz, CF_2), 129.0 (2×CH), 128.5 (2×CH), 126.5 (C), 76.8 (t, J=26.6 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.18 (dd, J=209.3, 11.2 Hz, 1F), −81.60 (dd, J=209.3, 7.5 Hz, 1F). IR (neat): ν_{max} 3419br s, 3065m, 3036m, 2901w, 1958w, 1889w, 1811w, 1604w, 1581w, 1496m, 1475s, 1455s, 1441s, 1394m, 1309m, 1201m, 1158s, 1059s, 1028s, 984s, 966s, 919w, 848m, 802m, 750s, 699s, 637s cm^{-1}. EIMS: *m*/*z* (% relative intensity) 266 (M^+, 68), 249 (40), 247 (9), 227 (7), 171 (36), 160 (77), 109 (23), 107 (51), 80 (100), 78 (51), 65 (6), 51 (14). Anal. Calcd for $C_{14}H_{12}F_2OS$: C, 63.14; H, 4.54. Found: C, 63.28; H, 4.44. **4a**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63–7.53 (m, 2H, Ar*H*), 7.53–7.43 (m, 2H, Ar*H*), 7.43–7.29 (m, 6H, Ar*H*), 5.10 (dd, J=10.9, 7.5 Hz, 1H, C*H*OSiMe$_3$), 0.15 (s, 9H, OSi(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9 (d, J=41.1 Hz, C), 136.3 (2×CH), 129.4 (CH), 128.9 (t, J=284.0 Hz, CF_2), 128.8 (2×CH), 128.7 (CH), 128.0 (3×CH), 126.9 (C), 77.6 (t, J=27.4 Hz, CH), −0.1 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.49 (dd, J=203.8, 11.1 Hz, 1F), −80.14 (dd, J=204.4, 7.0 Hz, 1F). IR (Nujol): ν_{max} 3062w, 3036w, 2924s, 2855s, 1952w, 1881w, 1658w, 1584w, 1455s, 1442s, 1417w, 1377m, 1358w, 1337w, 1309w, 1280w, 1250s, 1202m, 1173m, 1120s, 1108s, 1075s, 1060s, 1026m, 1003w, 983s, 925w, 878s, 847s, 803m, 748s, 728s, 699s, 690s, 662w, 634m, 612s, 505s, 439w, 419w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 338 (M^+, 0.18), 199 (16), 181 (5), 180 (16), 179 (100), 118 (5), 109 (10), 90 (5), 77 (4), 75 (5), 73 (63). HRMS Calcd for $C_{17}H_{20}F_2OSSi$ (M^+): 338.0972; found: 338.0972.

3.2.2. 2,2-Difluoro-1-(4-methoxyphenyl)-2-phenylsulfanylethanol (3b) and 2,2-difluoro-1-(4-methoxyphenyl)-2-phenylsulfanyl-1-trimethylsiloxyethane (4b). The reaction of **1** (1.86 g, 8 mmol) with 4-methoxybenzaldehyde (1.09 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3b** (0.970 g, 41% yield) and a white powder of **4b** (1.425 g, 48% yield, mp=39–40.5 °C). **3b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64–7.56 (m, 2H, Ar*H*), 7.47–7.33 (m, 5H, Ar*H*), 6.97–6.90 (m, 2H, Ar*H*), 4.97 (dd, J=10.9, 8.3 Hz, 1H, C*H*OH), 3.83 (s, 3H, OC*H*$_3$), 2.68 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9 (C), 137.0 (2×CH), 130.4 (CH), 129.7 (2×CH), 129.68 (2×CH), 129.62 (t, J=283.6 Hz, CF_2), 128.0 (C), 126.6 (C), 114.4 (2×CH), 76.5 (t, J=26.6 Hz, CH), 55.9 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.11 (dd, J=208.5, 11.1 Hz, 1F), −82.26 (dd, J=208.3, 8.1 Hz, 1F). IR (neat): ν_{max} 3446br s, 3062w, 3006w, 2960w, 2936w, 2910w, 2839w, 2028w, 1892w, 1772w, 1613s, 1586m, 1515s, 1474m, 1441s, 1306m, 1252s, 1177s, 1159s, 1056s, 1029s, 983s, 966s, 858m, 835m, 792s, 750s, 704m, 691s cm^{-1}. EIMS: *m*/*z* (% relative intensity) 296 (M^+, 1), 279 (4), 167 (15), 139 (15), 137(100), 109 (45), 94 (24), 77 (16). Anal. Calcd for $C_{15}H_{14}F_2O_2S$: C, 60.80; H, 4.76. Found: C, 60.73; H, 4.94. **4b**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.56 (m, 2H, Ar*H*), 7.42–7.30 (m, 5H, Ar*H*), 6.91 (m, 2H, Ar*H*), 4.96 (dd, J=10.8, 7.7 Hz, 1H, C*H*OSiMe$_3$), 3.80 (s, 3H, OC*H*$_3$), 0.13 (s, 9H, OSi(C*H*$_3$)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6 (C), 136.9 (2×CH), 130.0 (CH), 129.8 (2×CH), 129.6 (t, J=283.3 Hz, CF_2), 129.4 (2×CH), 127.4 (C), 126.8 (C), 114.1 (2×CH), 77.7 (t, J=27.0 Hz, CH), 55.8 (CH_3), 0.6 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.55 (dd, J=203.0, 11.2 Hz, 1F), −80.59 (dd, J=203.0, 7.4 Hz, 1F). IR (neat): ν_{max} 3063w, 2956s, 2924s, 2855s, 1644w, 1611s, 1586m, 1513s, 1463s, 1442s, 1421w, 1377m, 1330w, 1340m, 1288m, 1251s, 1205m, 1171s, 1121s, 1103s, 1065s, 1038s, 984s, 943w, 858s, 875s, 844s, 809m, 780m, 746s, 711w, 703w, 689m, 638w, 601m, 573m, 561m, 534m, 497m, 444m, 417m cm^{-1}. EIMS: *m*/*z* (% relative intensity) 278 (3), 244 (5), 229 (4), 211 (5), 210 (17), 209 (100), 167 (12), 139 (5), 135 (10), 75 (5), 73 (43). HRMS Calcd for $C_{18}H_{22}F_2O_2SSi$ (M^+): 368.1078; found: 368.1075.

3.2.3. 2,2-Difluoro-1-(2,4-dimethoxyphenyl)-2-phenylsulfanylethanol (3c) and 2,2-difluoro-1-(2,4-dimethoxyphenyl)-2-phenylsulfanyl-1-trimethylsiloxyethane (4c). The reaction of **1** (1.86 g, 8 mmol) with 2,4-dimethoxybenzaldehyde (1.33 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3c** (0.742 g, 28% yield) and a colourless liquid of **4c** (1.911 g, 60% yield). **3c**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70–7.59 (m, 2H, Ar*H*), 7.45–7.3 (m, 4H, Ar*H*), 6.55 (dd, J=8.5, 2.4 Hz, 1H, Ar*H*), 6.52 (d, J=2.4 Hz, 1H, Ar*H*), 5.36 (dd, J=12.6, 8.6 Hz, 1H, C*H*OH), 3.88 (s, 3H, OC*H*$_3$), 3.85 (s, 3H, OC*H*$_3$), 1.7 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.0 (C), 159.4 (C), 137.0 (2×CH), 131.1 (CH), 130.2 (CH), 130.0 (t, J=284.0 Hz, CF_2), 129.5 (2×CH), 127.1 (C), 116.5 (C), 105.4 (CH), 99.6 (CH), 73.7 (t, J=26.6 Hz, CH), 56.3 (CH_3), 56.0 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −84.90 (dd, J=204.0, 13.4 Hz, 1F), −81.98 (dd, J=204.4, 7.8 Hz, 1F). IR (neat): ν_{max} 3460br s, 3062w, 3005w, 2940m, 2839m, 1614s, 1589s, 1464s, 1509s, 1440s, 1421s, 1296s, 1268s, 1210s, 1160s, 1126s, 1035s, 981s, 965s, 936m, 921m, 835s, 781m, 751s, 704s, 692m, 642m, 593w, 570m, 502m cm^{-1}. EIMS: *m*/*z* (% relative intensity) 326 (M^+, 0.08), 242 (14), 167 (100), 139 (12), 137 (24), 109 (6), 91 (5), 77 (5). HRMS Calcd for $C_{16}H_{16}F_2O_3$ (M^+): 326.0788; found: 326.0788. **4c**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52–7.42 (m, 3H, Ar*H*), 7.39–7.25 (m, 3H, Ar*H*), 6.52 (dd, J=8.6, 2.2 Hz, 1H, Ar*H*), 6.41 (d, J=2.1 Hz, 1H, Ar*H*), 5.51 (dd, J=10.6, 8.4 Hz, 1H, C*H*OSiMe$_3$), 3.8 (s, 6H, OC*H*$_3$), 0.10 (s, 9H, OSi(C*H*$_3$)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.0 (C), 157.9 (C), 136.1 (2×CH), 130.3 (CH), 129.2 (t, J=284.8 Hz, CF_2), 129.1 (CH), 128.6 (2×CH), 127.1 (C), 118.0 (C), 104.6 (CH), 97.9 (CH), 69.6 (dd, J=28.4, 25.7 Hz, CH), 55.5 (CH_3), 55.2 (CH_3), 0.2 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −84.12 (dd, J=201.0, 10.8 Hz, 1F), −81.98 (dd, J=201.0, 8.1 Hz, 1F). IR (neat): ν_{max} 3062w, 3004m, 2959s, 2838m, 1614s, 1589s, 1507s, 1465s, 1440s, 1420m, 1361m, 1329w, 1305s, 1293s, 1264s, 1253s, 1209s, 1159s, 1126s, 1097s, 1035s, 982s, 937m, 922m, 879s, 844s, 793w, 775w, 750s, 704m, 691s, 637w, 610w, 568m, 519w, 502m, 478w cm^{-1}. EIMS: *m*/*z*

(% relative intensity) 398 (M^+, 0.06), 240 (18), 239 (100), 209 (4), 166 (6), 165 (22), 77 (5), 73 (33). HRMS Calcd for $C_{19}H_{24}F_2O_3SSi$ (M^+): 398.1183; found: 398.1182.

3.2.4. 2,2-Difluoro-1-(3,4-dimethoxyphenyl)-2-phenylsulfanylethanol (3d) and 2,2-difluoro-1-(3,4-dimethoxyphenyl)-2-phenylsulfanyl-1-trimethylsiloxyethane (4d). The reaction of **1** (1.86 g, 8 mmol) with 3,4-dimethoxybenzaldehyde (1.329 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a white powder of **3d** (0.967 g, 37% yield, mp=92–93 °C) and a white powder of **4d** (1.542 g, 48% yield, mp=61–62 °C). **3d**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.55 (m, 2H, Ar*H*), 7.45–7.33 (m, 3H, Ar*H*), 7.06–6.99 (m, 2H, Ar*H*), 6.87 (d, J=8.1 Hz, 1H, Ar*H*), 4.96 (dd, J=10.9, 8.2 Hz, 1H, C*H*OH), 3.90 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 2.35 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3 (C), 149.5 (C), 137.1 (2×CH), 130.5 (CH), 129.7 (2×CH), 129.6 (t, J=283.1 Hz, CF_2), 128.3 (C), 126.5 (C), 121.2 (CH), 111.3 (CH), 111.2 (d, J=1.2 Hz, CH), 76.6 (t, J=26.4 Hz, CH), 56.6 (CH_3), 56.5 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −84.72 (dd, J=208.4, 10.9 Hz, 1F), −82.17 (dd, J=208.4, 8.2 Hz, 1F). IR (neat): ν_{max} 3480s, 3082m, 3060m, 3011m, 2969m, 2943m, 2913m, 2842m, 2597w, 2031w, 1961w, 1733w, 1608s, 1594s, 1515s, 1471s, 1456s, 1442s, 1387m, 1346m, 1309m, 1256s, 1141s, 1096s, 1056s, 1019s, 990s, 930m, 869m, 821w, 785s, 764s, 745s, 690s, 663m cm^{-1}. EIMS: *m*/*z* (% relative intensity) 326 (M^+, 1), 167 (100), 139 (57), 124 (15), 109 (8), 108 (6), 95 (4), 79 (5), 77 (8), 65 (3). HRMS Calcd for $C_{16}H_{16}F_2O_3S$ (M^+): 326.0788; found: 326.0788. **4d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J=7.6 Hz, 2H, Ar*H*), 7.39–7.22 (m, 3H, Ar*H*), 7.02–6.90 (m, 2H, Ar*H*), 6.78 (d, J=8.2 Hz, 1H, Ar*H*), 4.91 (dd, J=11.0, 7.5 Hz, 1H, C*H*OSiMe$_3$), 3.85 (s, 6H, 2×OCH_3), 0.10 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (75 MHz $CDCl_3$): δ 149.3 (C), 148.6 (C), 136.3 (2×CH), 129.4 (CH), 129.2 (C), 128.9 (t, J=283.0 Hz, CF_2), 128.8 (2×CH), 126.7 (C), 120.5 (CH), 110.8 (CH), 110.3 (CH), 77.2 (t, J=27.2 Hz, CH), 55.9 (CH_3), 55.8 (CH_3), −0.1 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$) δ −83.44 (dd, J=203.0, 11.0 Hz, 1F), −80.69 (dd, J=203.0, 7.3 Hz, 1F). IR (neat): ν_{max} 3056w, 3015m, 2956s, 2925s, 2855s, 1605m, 1591m, 1519s, 1466s, 1442s, 1420m, 1377m, 1360m, 1337w, 1308w, 1264s, 1256s, 1233s, 1168m, 1152s, 1141s, 1102s, 1066s, 1037m, 1023s, 992s, 938s, 874s, 853s, 803m, 775m, 767m, 749s, 728m, 703w, 691m, 625m, 604w, 586m, 571w, 498m, 456w, 417w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 398 (M^+, 2), 274 (5), 240 (17), 239 (100), 165 (14), 109 (5), 77 (4), 73 (51). HRMS Calcd for $C_{19}H_{24}F_2O_3SSi$ (M^+): 398.1183; found: 398.1185.

3.2.5. 1,1-Difluoro-4-phenyl-1-phenylsulfanyl-3-buten-2-ol (3e) and 1,1-difluoro-4-phenyl-1-phenylsulfanyl-2-trimethylsiloxy-3-butene (4e). The reaction of **1** (2.32 g, 10 mmol) with cinnamaldehyde (1.29 g, 9.8 mmol) and TBAF (1.0 mL, 1.0 mmol, 1 M solution in THF) gave a pale yellow liquid of **3e** (1.420 g, 50% yield) and a white powder of **4e** (0.661 g, 18% yield, mp=39–40 °C). **3e**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.62 (m, 2H, Ar*H*), 7.48–7.26 (m, 8H, Ar*H*), 6.83 (d, J=15.9 Hz, 1H, PhC*H*=CH), 6.28 (dd, J=15.9, 6.3 Hz, 1H, PhCH=C*H*), 4.68–4.58 (m, 1H, C*H*OH), 2.12 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2 (2×CH), 136.5 (C), 135.9 (CH), 130.6 (CH), 129.8 (2×CH), 129.6 (t, J=286.0 Hz, CF_2), 129.3 (2×CH), 129.1 (CH), 127.5 (2×CH), 126.4 (C), 123.1 (CH), 75.7 (t, J=27.0 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.12 (dd, J=209.0, 9.1 Hz, 1F), −83.13 (dd, J=209.0, 8.4 Hz, 1F). IR (neat): ν_{max} 3392br m, 3061m, 3028w, 2911w, 1955w, 1885w, 1803w, 1654m, 1599w, 1579m, 1497m, 1475s, 1449m, 1441s, 1388m, 1309m, 1164s, 1058s, 966s, 861m, 748s, 704s, 691s cm^{-1}. EIMS: *m*/*z* (% relative intensity) 292 (M^+, 4), 275 (26), 235 (3), 165 (5), 162 (9), 160 (20), 133 (100), 116 (44), 103 (9), 92 (7), 77 (13), 65 (4), 55 (32). Anal. Calcd for $C_{16}H_{14}F_2OS$: C, 65.73; H, 4.83. Found: C, 65.97; H, 4.91. **4e**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (d, J=6.5 Hz, 2H, Ar*H*), 7.51–7.24 (m, 8H, Ar*H*), 6.75 (d, J=15.8 Hz, 1H, PhC*H*=CH), 6.30 (dd, J=15.8, 6.2 Hz, 1H, PhCH=C*H*), 4.64 (app. dd, J=15.4, 8.1 Hz, 1H, C*H*OSiMe$_3$), 0.22 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4 (2×CH), 136.1 (C), 134.0 (CH), 129.4 (CH), 128.9 (t, J=283.0 Hz, CF_2), 128.8 (2×CH), 128.5 (2×CH), 128.1 (CH), 126.8 (2×CH), 126.4 (t, J=2.0 Hz, C), 124.3 (CH), 76.3 (t, J=27.5 Hz, CH), 0.1 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.07 (dd, J=204.0, 7.9 Hz, 1F), −81.24 (dd, J=204.0, 8.5 Hz, 1F). IR (neat): ν_{max} 3066w, 3029w, 2958s, 2925s, 2863s, 1959w, 1890w, 1815w, 1474s, 1450s, 1441s, 1377m, 1357w, 1332s, 1305w, 1251s, 1205w, 1164m, 1117s, 1085s, 1067s, 1042s, 1022s, 974s, 917w, 878s, 844s, 779m, 750s, 705m, 692s, 672m, 638w, 611w, 600w, 543m, 499m, 459m, 419m cm^{-1}. EIMS: *m*/*z* (% relative intensity): 207 (5), 206 (18), 205 (100), 146 (5), 116 (9), 115 (23), 77 (4), 73 (45). HRMS Calcd for $C_{19}H_{22}F_2OSSi$ (M^+): 364.1128; found: 364.0031.

3.2.6. 1,1-Difluoro-4-(2-methoxyphenyl)-1-phenylsulfanyl-3-buten-2-ol (3f) and 1,1-difluoro-4-(2-methoxyphenyl)-1-phenylsulfanyl-2-trimethylsiloxy-3-butene (4f). The reaction of **1** (1.86 g, 8 mmol) with 2-methoxycinnamaldehyde (1.298 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3f** (1.367 g, 53% yield) and a white powder of **4f** (1.138 g, 37% yield, mp=43.5–45 °C). **3f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.66 (d, J=6.7 Hz, 2H, Ar*H*), 7.53–7.36 (m, 4H, Ar*H*), 7.35–7.25 (m, 1H, Ar*H*), 7.17 (d, J=16.1 Hz, 1H, PhC*H*=CH), 7.02–6.85 (m, 2H, Ar*H*), 6.33 (dd, J=16.1, 6.6 Hz, 1H, PhCH=C*H*), 4.63 (dd, J=15.7, 8.1 Hz, 1H, C*H*OH), 3.89 (s, 3H), 2.51 (br s, 1H, CHO*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.1 (C), 136.5 (2×CH), 130.5 (CH), 129.8 (CH), 129.5 (CH), 129.1 (2×CH), 129.0 (t, J=283.5 Hz, CF_2), 127.4 (CH), 126.0 (C), 124.9 (C), 123.0 (t, J=2.3 Hz, CH), 120.7 (CH), 111.0 (CH), 75.60 (t, J=26.8 Hz, CH), 55.5 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.15 (dd, J=208.9, 9.2 Hz, 1F), −83.33 (dd, J=208.0, 8.4 Hz, 1F). IR (Nujol): ν_{max} 3264br s, 2924s, 2855s, 2722w, 1651w, 1597m, 1580w, 1489s, 1463s, 1439s, 1377m, 1349m, 1294m, 1247s, 1175w, 1154m, 1118w, 1100w, 1087w, 1053s, 1028s, 981m, 959s, 866m, 852w, 779m, 758s, 747s, 725w, 703w, 690m, 630w, 582w, 554w, 530w, 498w, 448w cm^{-1}. EIMS: *m*/*z* (% relative intensity): 322 (M^+, 5), 164 (11), 163 (100), 145 (10), 135 (21), 107 (11), 91 (7), 77 (6), 55 (16). HRMS Calcd for $C_{17}H_{16}F_2O_2S$ (M^+): 322.0839; found: 322.0844. **4f**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d,

J=7.8 Hz, 2H, Ar*H*), 7.51–7.18 (m, 5H, Ar*H*), 7.05 (d, J=16.0 Hz, 1H, PhC*H*=CH), 6.98–6.82 (m, 2H of Ar*H*), 6.28 (dd, J=16.1, 6.7 Hz, 1H, PhCH=C*H*), 4.61 (app. dd, J=16.1, 7.9 Hz, 1H, C*H*OSiMe$_3$), 3.86 (s, 3H, OCH_3), 0.2 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0 (C), 136.4 (2×CH), 129.4 (2×CH), 129.2 (CH), 129.0 (t, J=283.5 Hz, CF_2), 128.8 (2×CH), 127.3 (CH), 126.7 (C, t, J=2.0 Hz), 125.2 (C), 124.6 (t, J=2.4 Hz, CH), 120.6 (CH), 111.0 (CH), 77.0 (t, J=27.2 Hz, CH), 55.0 (CH_3), 0.2 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.35 (dd, J=203.5, 9.0 Hz, 1F), −81.59 (dd, J=202.8, 8.8 Hz, 1F). IR (Nujol): ν_{max} 3057w, 2998m, 2958s, 2926s, 2855s, 1650w, 1599m, 1580m, 1492s, 1466s, 1439s, 1377w, 1356m, 1338m, 1298m, 1265m, 1251s, 1179s, 1158m, 1128s, 1105s, 1079s, 1047s, 1030s, 973s, 883s, 842s, 814w, 758s, 750s, 703m, 688s, 671w, 639w, 610w, 583w, 524m, 502m, 439w cm^{-1}. EIMS: m/z (% relative intensity): 394 (M^+, 0.63), 237 (6), 236 (19), 235 (100), 177 (5), 147 (4), 146 (11), 145 (27), 117 (4), 77 (2), 73 (37). HRMS Calcd for $C_{20}H_{24}F_2O_2SSi$ (M^+): 394.1234; found: 394.1234.

3.2.7. 2,2-Difluoro-1-(4-methylphenyl)-2-phenylsulfanylethanol (3g) and 2,2-difluoro-1-(4-methylphenyl)-2-phenylsulfanyl-1-trimethylsiloxyethane (4g). The reaction of **1** (1.86 g, 8 mmol) with 4-methylbenzaldehyde (0.96 g, 8 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a white powder of **3g** (0.786 g, 35% yield, mp=49–50 °C) and a white powder of **4g** (1.437 g, 51% yield, mp=55–57 °C). **3g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.54 (m, 2H, Ar*H*), 7.47–7.31 (m, 5H, Ar*H*), 7.21 (d, J=7.9 Hz, 2H, Ar*H*), 4.98 (t, J=9.6 Hz, 1H, C*H*OH), 2.68 (br s, 1H, CHO*H*), 2.38 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (C), 137.0 (2×CH), 132.9 (C), 130.4 (CH), 129.7 (2×CH), 129.6 (2×CH), 129.6 (t, J=283.0 Hz, CF_2), 128.3 (2×CH), 126.6 (C), 76.7 (t, J=26.7 Hz, CH), 21.9 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.14 (dd, J=209.0, 11.3 Hz, 1F), −82.03 (dd, J=208.9, 7.4 Hz, 1F). IR (Nujol): ν_{max} 3331br m, 2955s, 2925s, 2855s, 1516w, 1459m, 1441m, 1377m, 1310w, 1279w, 1241w, 1201w, 1182w, 1158m, 1149m, 1116w, 1061m, 1021m, 1002w, 970m, 860w, 824w, 779m, 749m, 719w, 691m, 621w, 568w, 519w, 498w cm^{-1}. EIMS: m/z (% relative intensity): 280 (M^+, 0.7), 171 (5), 162 (4), 161 (7), 160 (91), 123 (12), 122 (10), 121 (97), 110 (7), 109 (7), 103 (5), 93 (100), 91 (77), 77 (30), 65 (10), 51 (8). HRMS Calcd for $C_{15}H_{14}F_2OS$ (M^+): 280.0733; found: 280.0731. **4g**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63–7.51 (2H, m, Ar*H*), 7.44–7.29 (5H, m, Ar*H*), 7.18 (d, J=7.9 Hz, 2H, Ar*H*), 4.97 (dd, J=10.8, 7.8 Hz, 1H, C*H*OSiMe$_3$), 2.37 (s, 3H, CH_3), 0.14 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1 (C), 136.9 (2×CH), 134.4 (C), 130.0 (CH), 129.6 (t, J=283.5 Hz, CF_2), 129.4 (4×CH), 128.5 (2×CH), 127.4 (C), 77.9 (t, J=27.2 Hz, CH), 21.9 (CH_3), 0.6 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.35 (dd, J=203.9, 11.0 Hz, 1F), −80.40 (dd, J=203.2, 7.6 Hz, 1F). IR (Nujol): ν_{max} 3407br w, 2926s, 2730w, 2305w, 1948w, 1923w, 1878w, 1711w, 1614w, 1583w, 1513m, 1461s, 1442s, 1414w, 1377s, 1303w, 1253s, 1202m, 1173m, 1126s, 1103s, 1065s, 1028m, 984s, 954w, 878s, 844s, 805m, 775m, 746s, 706w, 689s, 632w, 640w, 601w, 554m, 513s, 496w, 443w, 419w cm^{-1}. EIMS: m/z (% relative intensity): 333 (2), 263 (4), 213 (24), 193 (100), 171 (3), 151 (3), 133 (3), 119 (4), 104 (2), 77 (2), 73 (30). HRMS Calcd for $C_{18}H_{22}F_2OSSi$ (M^+): 352.1128; found: 352.1128.

3.2.8. 2,2-Difluoro-1-(4-bromophenyl)-2-phenylsulfanylethanol (3h) and 2,2-difluoro-1-(4-bromophenyl)-2-phenylsulfanyl-1-trimethylsiloxyethane (4h). The reaction of **1** (1.86 g, 8 mmol) with 4-bromobenzaldehyde (1.48 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a white powder of **3h** (1.679 g, 61% yield, mp=69–69.5 °C) and a white powder of **4h** (1.039 g, 31% yield, mp=94–96 °C). **3h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.50 (m, 4H, Ar*H*), 7.47–7.41 (m, 1H, Ar*H*), 7.41–7.33 (m, 4H, Ar*H*), 4.96 (dd, J=11.1, 7.6 Hz, 1H, C*H*OH), 2.86 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.1 (2×CH), 134.7 (C), 132.1 (2×CH), 130.7 (CH), 130.1 (2×CH), 129.8 (2×CH), 129.3 (t, J=283.0 Hz, CF_2), 126.1 (C), 124.0 (C), 76.2 (t, J=26.9 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.65 (dd, J=210.4, 10.9 Hz, 1F), −81.55 (dd, J=210.6, 7.8 Hz, 1F). IR (Nujol): ν_{max} 3585s, 2955s, 2926s, 2855s, 1592m, 1472m, 1441m, 1404w, 1377m, 1306w, 1226w, 1194w, 1169w, 1150w, 1117w, 1102w, 1080s, 1047s, 1011m, 985s, 955w, 845w, 819m, 772s, 752s, 692m, 659w, 631w, 618w, 534w, 502m, 419w cm^{-1}. EIMS: m/z (% relative intensity): 345 (M^+, 6), 343 (6), 328 (6), 187 (58), 185 (56), 161 (13), 160 (100), 159 (21), 157 (20), 110 (8), 109 (9), 108 (5), 78 (26), 77 (37), 51 (10). HRMS Calcd for $C_{14}H_{11}F_2OS$ (M^+): 343.9682; found: 343.9677. **4h**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60–7.47 (m, 4H, Ar*H*), 7.40–7.30 (m, 5H, Ar*H*), 4.96 (dd, J=10.6, 7.3 Hz, 1H, C*H*OSiMe$_3$), 0.13 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0 (2×CH), 136.6 (C), 131.9 (2×CH), 130.2 (3×CH), 129.5 (2×CH), 129.2 (t, J=284.1, 283.4 Hz, CF_2), 127.0 (C), 123.5 (C), 77.5 (t, J=27.4 Hz, CH), 0.5 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.64 (dd, J=204.8, 11.0 Hz, 1F), −80.04 (dd, J=204.8, 7.0 Hz, 1F). IR (Nujol): ν_{max} 3065w, 2956s, 2924s, 2855s, 1658w, 1591m, 1486m, 1463m, 1441m, 1404m, 1377m, 1346w, 1306w, 1292w, 1255s, 1200m, 1173m, 1124s, 1110s, 1096s, 1066s, 1025w, 1011m, 985s, 953m, 860s, 845s, 797s, 773s, 751s, 703s, 690m, 657m, 634w, 600w, 512m, 498m, 454m, 416w cm^{-1}. EIMS: m/z (% relative intensity): 417 (M^+, 0.8), 322 (4), 309 (5), 307 (6), 280 (10), 279 (64), 278 (12), 277 (64), 261 (8), 260 (25), 259 (93), 258 (29), 257 (68), 198 (5), 197 (5), 196 (9), 170 (5), 109 (5), 91 (4), 77 (5), 74 (82), 73 (100). Anal. Calcd for $C_{17}H_{19}BrF_2OSSi$: C, 48.92; H, 4.59. Found: C, 49.32; H, 4.47.

3.2.9. 2,2-Difluoro-1-(furan-2-yl)-2-phenylsulfanylethanol (3i). The reaction of **1** (0.464 g, 2 mmol) with 2-furaldehyde (0.185 g, 1.9 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a pale yellow liquid of **3i** (0.363 g, 73% yield). **3i**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.6 (d, J=6.9 Hz, 2H, Ar*H*), 7.49–7.31 (m, 4H, Ar*H*), 6.53 (d, J=3.2 Hz, 1H, Ar*H*), 6.43 (dd, J=3.0, 1.8 Hz, 1H, Ar*H*), 5.01 (dd, J=15.4, 9.3 Hz, 1H, C*H*OH), 2.77 (d, J=6.6 Hz, 1H, CHO*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.4 (t, J=1.95 Hz, C), 143.2 (CH), 136.5 (2×CH), 130.0 (CH), 129.1 (2×CH), 127.8 (t, J=283.6 Hz, CF_2), 125.5 (t, J=2.25 Hz, C), 110.6 (CH), 110.0 (CH), 70.5 (t, J=28.2 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.03 (dd, J=210.9, 10.6 Hz, 1F), −83.46 (dd, J=210.9, 9.0 Hz, 1F). IR (neat): ν_{max} 3418s, 3064m,

2913w, 1960w, 1888w, 1808w, 1738w, 1621w, 1584w, 1504m, 1475s, 1442s, 1384m, 1310m, 1266m, 1232m, 1212m, 1150s, 1063s, 1015s, 972s, 927s, 886s, 798s, 747s, 705s, 691s cm^{-1}. EIMS: *m/z* (% relative intensity) 256 (M^+, 56), 239 (46), 219 (14), 171 (11), 160 (60), 127 (5), 110 (9), 109 (7), 99 (10), 98 (5), 97 (100), 77 (5), 69 (30), 65 (6), 51 (8). Anal. Calcd for $C_{12}H_{10}F_2O_2S$: C, 56.24; H, 3.93. Found: C, 56.32; H, 3.65.

3.2.10. 1,1-Difluoro-1-phenylsulfanylpentan-2-ol (3j). The reaction of **1** (0.464 g, 2 mmol) with *n*-butanal (0.144 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a pale yellow liquid of **3j** (0.319 g, 69% yield). **3j**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (d, J=6.6 Hz, 2H, Ar*H*), 7.47–7.33 (m, 3H, Ar*H*), 3.89 (dq, J=8.9, 2.7 Hz, 1H, C*H*OH), 1.96 (br s, 1H, CHO*H*), 1.83–1.52 (m, 3H, 2H of CH_2CH_2 and 1H and C*H*HCH_3), 1.50–1.32 (m, 1H, CH*H*CH_3), 0.97 (t, J=7.1 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.4 (2×CH), 129.9 (t, J=281.9 Hz, CF_2), 129.8 (CH), 129.0 (2×CH), 125.8 (t, J=2.2 Hz, C), 73.9 (t, J=26.0 Hz, CH), 32.4 (t, J=1.6 Hz, CH_2), 18.7 (CH_2), 13.7 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −86.43 (dd, J=209.5, 9.8 Hz, 1F), −83.13 (dd, J=209.5, 9.1 Hz, 1F). IR (neat): ν_{max} 3404br s, 3064w, 2963s, 2935s, 2876s, 1956w, 1885w, 1806w, 1711w, 1584w, 1475s, 1442s, 1383m, 1309m, 1269m, 1222w, 1182s, 1121s, 1057s, 1028s, 991s, 897m, 857m, 749s, 705s, 691s, 668m cm^{-1}. EIMS: *m/z* (% relative intensity) 232 (M^+, 30), 215 (2), 178 (6), 160 (100), 159 (9), 137 (5), 126 (15), 123 (7), 110 (71), 109 (21), 97 (5), 84 (8), 78 (18), 77 (16), 66 (14), 65 (3), 55 (33). Anal. Calcd for $C_{11}H_{14}F_2OS$: C, 56.88; H, 6.07. Found: C, 56.84; H, 6.21.

3.2.11. (*E*)-1,1-Difluoro-1-phenylsulfanylpent-3-en-2-ol (3k). The reaction of **1** (0.464 g, 2 mmol) with crotonaldehyde (0.140 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a pale yellow liquid of **3k** (0.321 g, 70% yield). **3k**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, J=6.6 Hz, 2H, Ar*H*), 7.47–7.37 (m, 3H, Ar*H*), 6.02–5.88 (m, 1H, CH_3C*H*=CH), 5.65–5.53 (m, 1H, CH_3CH=C*H*), 4.37 (app. dd, J=16.2, 8.9 Hz, 1H, C*H*OH), 1.95 (br s, 1H, CHO*H*), 1.78 (dd, J=6.6, 0.7 Hz, 3H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.9 (2×CH), 133.4 (CH), 130.3 (CH), 129.5 (2×CH), 129.4 (t, J=282.5 Hz, CF_2), 126.3 (t, J=2.0 Hz, C), 125.2 (t, J=2.4 Hz, CH), 75.5 (t, J=26.7 Hz, CH), 18.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −85.82 (dd, J=207.8, 9.5 Hz, 1F), −83.78 (dd, J=207.8, 9.0 Hz, 1F). IR (neat): ν_{max} 3404br s, 3063m, 2970m, 2943m, 2918m, 2857m, 1957w, 1887w, 1807w, 1674m, 1584m, 1475s, 1442s, 1379m, 1309m, 1286m, 1170s, 1134m, 1058s, 964s, 924m, 823m, 750s, 704s, 691s, 663m cm^{-1}. EIMS: *m/z* (% relative intensity) 230 (M^+, 100), 213 (42), 193 (4), 160 (87), 159 (11), 139 (3), 110 (33), 109 (16), 84 (4), 77 (13), 71 (35), 65 (13), 53 (12). Anal. Calcd for $C_{11}H_{12}F_2OS$: C, 57.37; H, 5.25. Found: C, 57.41; H, 5.22.

3.2.12. 1-(Difluoro(phenylsulfanyl)methyl)-1,2,3,4-tetrahydronapthalen-1-ol (3l) and (1-(difluoro(phenylthio)methyl)-1,2,3,4-tetrahydronaphthalen-1-yloxy)trimethylsilane (4l). The reaction of **1** (1.86 g, 8 mmol) with α-tetralone (1.17 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3l** (0.529 g, 22% yield) and a white powder of **4l** (0.78 g, 26% yield, mp=34–35.5 °C). **3l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80–7.74 (m, 1H, Ar*H*), 7.62–7.56 (m, 2H, Ar*H*), 7.45–7.33 (m, 3H, Ar*H*), 7.32–7.23 (m, 2H, Ar*H*), 7.20–7.14 (m, 1H, Ar*H*), 2.86 (t, J=6.3 Hz, 2H, PhCH_2CH_2), 2.47 (ddd, J=13.8, 10.2, 3.5 Hz, 1H, C*H*HCOH), 2.28 (br s, 1H, CO*H*), 2.21–2.11 (m, 1H, CH*H*COH), 2.11–2.00 (m, 1H, CH_2C*H*HCH_2), 1.95–1.83 (m, 1H, CH_2CH*H*CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6 (C), 137.2 (2×CH), 135.2 (C), 132.5 (t, J=287.9 Hz, CF_2), 130.3 (CH), 129.8 (CH), 129.6 (2×CH), 129.3 (CH), 128.7 (t, J=3.4 Hz, CH), 127.0 (C), 126.9 (CH), 76.63 (t, J=21.7 Hz, C), 34.9 (CH_2), 31.4 (CH_2), 19.5 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −83.0 (d, J=203.7 Hz, 1F), −79.0 (d, J=203.7 Hz, 1F). IR (neat): ν_{max} 3446br s, 3061m, 3025m, 2943s, 2880m, 2839m, 1957w, 1826w, 1671w, 1583w, 1492s, 1475s, 1452s, 1441s, 1369m, 1331m, 1248m, 1191m, 1140m, 1121s, 1060s, 1024s, 984s, 906s, 876m, 842m, 749s, 704m, 691s cm^{-1}. EIMS: *m/z* (% relative intensity) 306 (M^+, 0.4), 289 (52), 269 (73), 160 (12), 147 (100), 130 (46), 128 (10), 117 (6), 109 (3), 91 (30), 77 (3), 65 (3). Anal. Calcd for $C_{17}H_{16}F_2OS$: C, 66.65; H, 5.26. Found: C, 66.86; H, 5.30. **4l**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.78 (m, 1H, Ar*H*), 7.64–7.52 (m, 2H, Ar*H*), 7.43–7.29 (m, 3H, Ar*H*), 7.28–7.18 (m, 2H, Ar*H*), 7.15–7.07 (m, 1H, Ar*H*), 2.84 (t, J=6.4 Hz, 2H, PhCH_2CH_2), 2.7–2.5 (m, 1H, C*H*HCOH), 2.18–1.99 (m, 2H, 1H of CH*H*COSiMe_3 and 1H of CH_2C*H*HCH_2), 1.98–1.76 (m, 1H, CH_2CH*H*CH_2), 0.07 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.1 (C), 137.2 (2×CH), 136.3 (C), 132.8 (t, J=289.6 Hz, CF_2), 130.1 (CH), 129.9 (CH), 129.3 (2×CH), 129.2 (CH), 128.8 (CH), 128.1 (C), 126.0 (CH), 79.3 (t, J=23.0 Hz, C), 35.0 (CH_2), 29.7 (CH_2), 19.6 (CH_2), 2.6 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −78.90 (d, J=200.1 Hz, 1F), −78.13 (d, J=200.1 Hz, 1F). IR ($CHCl_3$): ν_{max} 3065w, 3009m, 2957s, 2899m, 2841w, 1954w, 1884w, 1604w, 1583w, 1489m, 1474m, 1450m, 1441m, 1407w, 1342w, 1284m, 1253s, 1146s, 1095s, 1084s, 1056s, 1013m, 948m, 992s, 924s, 901s, 886s, 845s, 629m, 586w, 556m cm^{-1}. EIMS: *m/z* (% relative intensity) 269 (4), 221 (6), 220 (20), 219 (100), 177 (4), 159 (5), 130 (4), 129 (10), 77 (2), 73 (39). HRMS Calcd for $C_{20}H_{24}F_2OSSi$ (M^+): 378.1285; found: 378.1291.

3.2.13. 1-(Difluoro(phenylsulfanyl)methyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol (3m) and (1-(difluoro(phenylsulfanyl)methyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yloxy)trimethylsilane (4m). The reaction of **1** (1.86 g, 8 mmol) with 6-methoxy-1-tetralone (1.41 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3m** (0.587 g, 21% yield) and a colourless liquid of **4m** (0.976 g, 29% yield). **3m**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, J=8.8 Hz, 1H, Ar*H*), 7.65–7.55 (m, 2H, Ar*H*), 7.49–7.31 (m, 3H, Ar*H*), 6.82 (dd, J=8.8, 2.7 Hz, 1H, Ar*H*), 6.70 (d, J=2.7 Hz, 1H, Ar*H*), 3.82 (s, 3H, OCH_3), 2.84 (t, J=6.2 Hz, 2H, PhCH_2CH_2), 2.53–2.25 (m, 2H, CH_2COH), 2.25–1.76 (m, 3H, 2H of CH_2CH_2CH_2 and CO*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.4 (C), 140.7 (C), 136.4 (2×CH), 131.9 (CF_2, t, J=288.0 Hz), 129.6 (CH), 128.8 (3×CH), 126.8 (d, J=1.6 Hz, C), 126.5 (d, J=2.8 Hz, C), 113.4 (CH), 112.5 (CH), 75.73 (t, J=21.6 Hz, C), 55.1 (OCH_3), 34.2

(d, J=2.2 Hz, CH_2), 30.2 (CH_2), 18.9 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −83.37 (d, J=203.0 Hz, 1F), −79.24 (d, J=203.0 Hz, 1F). IR (neat): ν_{max} 3463s, 3061w, 3002w, 2942m, 2838w, 1957w, 1890w, 1609s, 1576m, 1505s, 1474s, 1465m, 1441s, 1322m, 1286m, 1244s, 1190m, 1120s, 1047s, 1023s, 985s, 909s, 892m, 870m, 839m, 817m, 790w, 751s, 704m, 691s, 660w, 632w, 587w, 557w, 503m, 420w cm^{-1}. EIMS: *m/z* (% relative intensity) 336 (M^+, 1), 321 (5), 320 (19), 319 (76), 318 (100), 300 (19), 299 (43), 298 (34), 297 (11), 279 (7), 209 (35), 207 (23), 206 (20), 178 (17), 177 (45), 159 (11). HRMS Calcd for $C_{18}H_{18}F_2O_2S$ (M^+): 336.0995; found: 336.1003. **4m**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J=8.8 Hz, 1H, Ar*H*), 7.65–7.52 (m, 2H, Ar*H*), 7.46–7.28 (m, 3H, Ar*H*), 6.81 (dd, J=8.8, 2.8 Hz, 1H, Ar*H*), 6.64 (d, J=2.7 Hz, 1H, Ar*H*), 3.84 (s, 3H, OCH_3), 2.82 (t, J=6.4 Hz, 2H, PhCH_2CH$_2$), 2.49–2.63 (m, 1H, C*H*HCOSiMe$_3$), 2.17–1.98 (m, 1H of CH*H*COSiMe$_3$ and 1H of CH_2C*H*HCH$_2$), 1.96–1.77 (m, 1H, CH_2CH*H*CH$_2$), 0.07 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.9 (C), 140.8 (C), 137.1 (2×CH), 132.9 (t, J=289.5 Hz, CF_2), 131.6 (t, J=2.6 Hz, CH), 129.9 (CH), 129.3 (2×CH), 128.5 (C), 128.3 (C), 113.4 (CH), 112.4 (CH), 79.1 (t, J=23.4 Hz, C), 55.7 (CH_3), 35.2 (CH_2), 30.3 (CH_2), 19.8 (CH_2), 2.6 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −79.47 (d, J=199.4 Hz, 1F), −78.31 (d, J=199.4 Hz, 1F). IR (neat): ν_{max} 3440br w, 3062w, 2956s, 2837m, 1884w, 1609s, 1576m, 1500s, 1475m, 1465m, 1441m, 1341m, 1324m, 1283m, 1251s, 1196m, 1135s, 1086s, 1052s, 1011m, 992s, 952m, 906m, 894m, 881s, 842s, 774m, 793m, 750s, 705m, 691s, 633w, 597w, 573w, 530w, 503m cm^{-1}. EIMS: *m/z* (% relative intensity) 408 (M^+, 0.1), 284 (2), 249 (100), 159 (7), 91 (1), 77 (3), 73 (36). HRMS Calcd for $C_{21}H_{26}F_2O_2SSi$ (M^+): 408.1391; found: 408.1391.

3.2.14. 1,1-Difluoro-2-phenyl-1-phenylsulfanylpropan-2-ol (3n) and (1,1-difluoro-2-phenyl-1-phenylsulfanylpropan-2-yloxy)trimethylsilane (4n). The reaction of **1** (1.86 g, 8 mmol) with acetophenone (0.96 g, 8 mmol) and TBAF (0.8 mL, 0.8 mmol, 1 M solution in THF) gave a pale yellow liquid of **3n** (0.669 g, 30% yield) and a colourless liquid of **4n** (0.740 g, 21% yield). **3n**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J=7.8 Hz, 2H, Ar*H*), 7.58–7.52 (m, 2H, Ar*H*), 7.46–7.31 (m, 6H, Ar*H*), 2.62 (br s, 1H, CO*H*), 1.85 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.7 (C), 137.2 (2×CH), 131.6 (t, J=287.5 Hz, CF_2), 130.3 (CH), 129.7 (3×CH), 128.9 (CH), 128.7 (2×CH), 127.0 (t, J=1.7 Hz, CH), 126.8 (C), 78.6 (t, J=24.4 Hz, C), 25.1 (t, J=1.9 Hz, CH_3). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −84.70 (d, J=204.5 Hz, 1F), −82.00 (d, J=204.5 Hz, 1F). IR (neat): ν_{max} 3474br s, 3062m, 2995m, 2943w, 1957w, 1889w, 1811w, 1762w, 1671w, 1603w, 1584w, 1497m, 1475s, 1449s, 1442s, 1380m, 1374m, 1179m, 1149m, 1055s, 1028s, 984s, 914s, 801m, 749s, 701s, 676m cm^{-1}. EIMS: *m/z* (% relative intensity) 280 (M^+, 8), 263 (19), 243 (1), 241 (2), 213 (11), 185 (13), 160 (64), 123 (10), 121 (100), 110 (10), 109 (8), 103 (7), 77 (15), 65 (6), 51 (9). HRMS Calcd for $C_{15}H_{14}F_2OS$ (M^+): 280.0733; found: 280.0733. **4n**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 (d, J=7.4 Hz, 2H, Ar*H*), 7.39 (d, J=6.6 Hz, 2H, Ar*H*), 7.3–7.1 (m, 6H, Ar*H*), 1.78 (s, 3H, CH_3), 0.10 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.6 (d, J=1.4 Hz, C), 136.4 (2×CH), 130.8 (t, J=289.0 Hz, CF_2), 129.2 (CH), 128.6 (3×CH), 127.9 (CH), 127.7 (2×CH), 127.2 (t, J=1.8 Hz, C), 127.1 (CH), 80.6 (t, J=25.0 Hz, C), 23.7 (t, J=2.1 Hz, CH_3), 2.22 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −84.08 (d, J=199.8 Hz, 1F), −82.49 (d, J=199.8 Hz, 1F). IR (neat): ν_{max} 3418w, 3062w, 3027w, 3002w, 2959m, 2899w, 1953w, 1885w, 1584w, 1496w, 1475m, 1441m, 1376m, 1253s, 1237s, 1202m, 1099s, 1081s, 1064s, 1028s, 988m, 963s, 948s, 863s, 844s, 804w, 750s, 699s, 691s, 661w, 627w, 596m, 504m cm^{-1}. EIMS: *m/z* (% relative intensity) 352 (M^+, 0.08), 241 (5), 195 (4), 194 (17), 193 (100), 163 (5), 123 (4), 104 (6), 103 (5), 75 (5), 73 (50). HRMS Calcd for $C_{18}H_{22}F_2OSSi$ (M^+): 352.1128; found: 352.1129.

3.2.15. 2,2-Difluoro-1,1-diphenyl-2-phenylsulfanylethanol (3o) and (2,2-difluoro-1,1-diphenyl-2-phenylsulfanylethoxy)trimethylsilane (4o). The reaction of **1** (0.698 g, 3 mmol) with benzophenone (0.546 g, 3 mmol) and TBAF (0.3 mL, 0.3 mmol, 1 M solution in THF) gave a white powder of **3o** (0.348 g, 33% yield, mp=45–46 °C) and a white powder of **4o** (86.1 mg, 6% yield, mp=92–94 °C). **3o**: ^1H NMR (400 MHz, $CDCl_3$): δ 7.67–7.61 (m, 4H, Ar*H*), 7.61–7.56 (m, 2H, Ar*H*), 7.46–7.31 (m, 9H, Ar*H*), 3.1 (br s, 1H, CO*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.3 (2×C), 136.6 (2×CH), 131.2 (t, J=290.9 Hz, CF_2), 129.7 (CH), 128.9 (2×CH), 128.2 (2×CH), 127.9 (4×CH), 127.8 (t, J=1.9 Hz, CH), 127.8 (3×CH), 126.4 (C), 81.6 (t, J=23.9 Hz, C). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −77.88 (2F, s). IR (Nujol): ν_{max} 3473m, 3059w, 2955s, 2925s, 2855s, 1493w, 1459m, 1449m, 1377w, 1343w, 1310w, 1184w, 1169w, 1152w, 1094w, 1054m, 1040m, 1020m, 931w, 897m, 826m, 749m, 700m, 639m, 501w, 424w, 327w cm^{-1}. EIMS: *m/z* (% relative intensity) 342 (M^+, 31), 325 (24), 275 (5), 247 (10), 213 (22), 185 (5), 184 (14), 183 (100), 166 (6), 165 (17), 106 (23), 105 (56), 77 (19), 51 (6). HRMS Calcd for $C_{20}H_{16}F_2OS$ (M^+): 342.0890; found: 342.0892. **4o**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.64–7.19 (m, 15H, Ar*H*), −0.05 (s, 9H, OSi(CH_3)$_3$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5 (2×C), 136.7 (2×CH), 131.8 (t, J=292.7 Hz, CF_2), 129.4 (CH), 128.8 (2×CH), 128.7 (4×CH), 127.8 (2×CH), 127.6 (4×CH), 127.1 (d, J=2.3 Hz, C), 84.5 (t, J=23.7 Hz, CF_2), 1.7 (3×CH_3). ^{19}F NMR (376 MHz, $CDCl_3/CFCl_3$): δ −77.66 (s, 2F). IR (Nujol): ν_{max} 3416br w, 3063w, 2926s, 2855s, 1951w, 1895w, 1808w, 1711w, 1601w, 1581w, 1494w, 1461s, 1447s, 1406w, 1377m, 1307w, 1263m, 1247s, 1217w, 1195m, 1178w, 1163m, 1152m, 1104s, 1076s, 1063s, 1040s, 1021m, 999w, 936m, 912m, 879s, 847s, 825s, 755s, 742s, 697s, 637m, 628m, 536w, 503m, 425w cm^{-1}. EIMS: *m/z* (% relative intensity): 414 (M^+, 0.12), 303 (13), 255 (100), 166 (34), 73 (61). HRMS Calcd for $C_{23}H_{24}F_2OSSi$ (M^+): 414.1285; found: 414.1292.

3.2.16. 1-(Difluoro(phenylsulfanyl)methyl)cyclohexanol (3p). The reaction of **1** (0.464 g, 2 mmol) with cyclohexanone (0.196 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a white powder of **3p** (0.325 g, 63% yield, mp=55–56 °C). **3p**: ^1H NMR (300 MHz, $CDCl_3$): δ 7.61–7.49 (m, 2H, Ar*H*), 7.40–7.24 (m, 3H, Ar*H*), 1.88–1.47 (m, 9H, 8H of (CH_2)$_4$C*H*H and CO*H*), 1.24–1.04 (m, 1H, (CH$_2$)$_4$CH*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.7 (2×CH), 132.1 (t, J=285.5 Hz, CF_2),

129.6 (CH), 128.9 (2×CH), 126.2 (t, J=1.9 Hz, C), 75.9 (t, J=23.0 Hz, C), 31.0 (2×CH_2, t, J=1.6 Hz), 25.3 (2×CH_2), 20.8 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −87.42 (s, 2F). IR (Nujol): ν_{max} 3602w, 3412br m, 2927s, 2855s, 2724w, 1711w, 1583w, 1461s, 1377s, 1267m, 1192m, 1154m, 1078m, 1039m, 989m, 975m, 951m, 906m, 884m, 847w, 811m, 747m, 704w, 690m cm^{-1}. EIMS: *m/z* (% relative intensity) 258 (M^+, 100), 241 (28), 221 (13), 191 (14), 160 (38), 110 (12), 109 (10), 99 (34), 81 (99), 80 (31), 77 (8), 65 (5). Anal. Calcd for $C_{13}H_{16}F_2OS$: C, 60.44; H, 6.24. Found: C, 60.60; H, 6.19.

3.2.17. 1-(Difluoro(phenylsulfanyl)methyl)cyclopentanol (3q). The reaction of **1** (0.464 g, 2 mmol) with cyclopentanone (0.168 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a white powder of **3q** (0.219 g, 45% yield, mp=37–38 °C). **3q**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67–7.62 (m, 2H, Ar*H*), 7.47–7.36 (m, 3H, Ar*H*), 2.16–2.05 (m, 2H, $CH_2CH_2CH_2$), 1.8–1.56 and 1.95–1.8 (m, 7H, 6H of $(CH_2)_2CH_2CH_2$ and CO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.2 (2×CH), 131.9 (t, J=283.5 Hz, CF_2), 130.3 (CH), 129.6 (2×CH), 126.9 (C), 86.5 (C, t, J=24.7 Hz), 36.5 (2×CH_2), 25.1 (2×CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −84.60 (s, 2F). IR (Nujol): ν_{max} 3335br s, 3064m, 2958s, 2874s, 1951w, 1880w, 1802w, 1582w, 1474s, 1440s, 1396s, 1330m, 1291m, 1265m, 1238m, 1137m, 1052s, 995s, 946s, 920s, 895s, 747s, 690s, 625m, 499s, 418w cm^{-1}. EIMS: *m/z* (% relative intensity) 244 (M^+, 100), 227 (12), 207 (10), 205 (8), 160 (7), 110 (6), 109 (3), 85 (4), 77 (1), 68 (26), 65 (3). Anal. Calcd for $C_{12}H_{14}F_2OS$: C, 59.00; H, 5.78. Found: C, 59.33; H, 5.98.

3.2.18. 1,1-Difluoro-2-methyl-1-phenylsulfanylpropan-2-ol (3r). The reaction of **1** (0.464 g, 2 mmol) with acetone (0.116 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a pale yellow liquid of **3r** (0.283 g, 65% yield). **3r**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69–7.56 (m, 2H, Ar*H*), 7.46–7.31 (m, 3H, Ar*H*), 2.11 (br s, 1H, CO*H*), 1.45 (s, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6 (2×CH), 131.6 (t, J=285.3 Hz, CF_2), 129.6 (CH), 128.9 (2×CH), 126.0 (t, J=1.7 Hz, C), 75.0 (t, J=24.1 Hz, C), 24.1 (t, J=1.8 Hz, 2×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −86.42 (s, 2F). IR (neat): ν_{max} 3419br s, 3064m, 2991s, 2943m, 1956w, 1886w, 1811w, 1636w, 1584s, 1475s, 1442s, 1376s, 1250m, 1200s, 1158m, 1099s, 1054s, 1016s, 979s, 953s, 854m, 833s, 750s, 704m, 691s, 664m cm^{-1}. EIMS: *m/z* (% relative intensity) 218 (M^+, 100), 201 (24), 199 (5), 181 (7), 160 (18), 151 (5), 135 (3), 123 (2), 110 (13), 109 (8), 77 (3), 65 (7), 59 (19). Anal. Calcd for $C_{10}H_{12}F_2OS$: C, 55.03; H, 5.54. Found: C, 55.05; H, 5.20.

3.2.19. 1-(Difluoro(phenylsulfanyl)methyl)cyclohex-2-enol (3s). The reaction of **1** (0.464 g, 2 mmol) with 2-cyclohexenone (0.192 g, 2 mmol) and TBAF (0.2 mL, 0.2 mmol, 1 M solution in THF) gave a pale yellow liquid of **3s** (0.307 g, 60% yield). **3s**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68–7.54 (m, 2H, Ar*H*), 7.47–7.28 (m, 3H, Ar*H*), 6.15 (dq, J=10.1, 2.8 Hz, 1H, C*H*=CHCOH), 5.86 (d, J=10.1 Hz, 1H, CH=C*H*COH), 2.23–2.03 (m, 3H, 2H of CH_2CH=CH and CO*H*), 2.02–1.92 (m, 2H, CH_2CH_2COH), 1.85–1.71 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.6 (2×CH), 135.4 (CH), 131.3 (t, J=285.8 Hz, CF_2), 129.6 (CH), 128.9 (2×CH), 126.1 (t, J=1.7 Hz, C), 124.53 (dd, J=3.3, 1.3 Hz, CH), 73.6 (t, J=23.4 Hz, C), 30.3 (CH_2), 24.9 (CH_2), 17.7 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −87.3 (d, J=203.0 Hz, 1F), −85.7 (d, J=203.0 Hz, 1F). IR (neat): ν_{max} 3418br s, 3062w, 3035w, 2941s, 2873m, 2834w, 1818w, 1650w, 1583w, 1474s, 1441s, 1397w, 1383w, 1350w, 1324w, 1262w, 1195m, 1161s, 1032s, 996s, 967s, 934s, 895s, 838m, 750s, 735s, 704m, 691s, 650w, 593w, 502m cm^{-1}. EIMS: *m/z* (% relative intensity): 256 (M^+, 2), 239 (7), 160 (27), 110 (8), 109 (10), 98 (7), 97 (100), 79 (31), 77 (25), 65 (7), 55 (10). HRMS Calcd for $C_{13}H_{14}F_2OS$ (M^+): 256.0733; found: 256.0733.

3.3. Desilylation of compound 4b to provide compound 3b

A solution of compound **4b** (2.066 g, 5.62 mmol) in CH_2Cl_2 (10 mL) was treated with potassium fluoride (KF) in CH_3CN (10 mL). The reaction mixture was stirred at room temperature overnight and quenched with a saturated NH_4Cl solution and extracted with EtOAc (3×50 mL). The organic phase was washed successively with brine, water and dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by chromatotron (SiO_2, 5% EtOAc in hexanes) to give a pale yellow liquid of **3b** (1.528 g, 91% yield).

3.4. Preparation of sulfoxide 5

3.4.1. 2,2-Difluoro-1-(4-methoxyphenyl)-2-phenylsulfinylethanol (5b). *General procedure*: A solution of compound **3b** (269.7 mg, 0.9 mmol) in THF (15 mL) at −78 °C was treated with a solution of 70% *m*-chloroperbenzoic acid (MCPBA) (235.3 mg, 0.94 mmol) in THF (5 mL). The reaction mixture was stirred at −78 °C and slowly warmed to room temperature overnight. The reaction was quenched with a saturated $NaHCO_3$ solution (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3×20 mL). The combined extracts were dried over anhydrous Na_2SO_4. After solvent removal, the crude product was purified by column chromatography (SiO_2, 20% EtOAc in hexanes and then 2% MeOH in hexanes) to give a white powder of **5b** as a mixture (62:38) of two diastereomers (210.5 mg, 74% yield, mp=111–115 °C). ^{1}H NMR (500 MHz, $CDCl_3$/MeOD): δ 7.67 and 7.63 (d each, J=7.0 and 6.8 Hz, respectively, 2H, Ar*H*), 7.59–7.46 (m, 3H, Ar*H*), 7.4–7.3 (m, 2H, Ar*H*), 6.87 and 6.83 (d each, J=7.9 and 8.0 Hz, respectively, 2H, Ar*H*), 5.23 (d, J=23.5 Hz) and 4.90 (t, J=12.7 Hz) (1H, C*H*OH), 3.74 and 3.72 (s each, 3H, OCH_3), 3.35 (br s, 1H, CHO*H*). ^{13}C NMR (125 MHz, $CDCl_3$/MeOD): δ 159.9 and 159.8 (C), 136.0 and 135.3 (C), 132.4 and 132.2 (CH), 129.1 and 128.8 (2×CH), 129.7 (2×CH), 126.8 and 126.6 (C), 126.3 and 126.2 (CH), 113.6 and 113.4 (2×CH), 71.5 (t, J=21.9 Hz) and 68.9 (dd, J=29.1, 19.1 Hz) (CH), 55.0 and 54.9 (CH_3). ^{19}F NMR (470 MHz, $CDCl_3$/MeOD/$CFCl_3$): δ −117.92 and −117.66 (d each, J=213.4 and 220.0 Hz, 1F), −114.14 and −112.58 (d each, J=213.8 and 220.0 Hz, 1F). IR (KBr): ν_{max} 3266s, 3068w, 2998w, 2954m, 2929m, 2908m, 2835w, 2679w, 2551w, 2055w, 1735w, 1719w, 1609s, 1587w, 1509s, 1459m, 1445s, 1420w, 1350w, 1330w, 1304m, 1294m, 1250s, 1202s, 1175s, 1110s, 1085s,

1041s, 975s, 846m, 824w, 793s, 785s, 754s, 748s, 699m, 688m, 626w, 5814m, 568s, 529s, 481m, 450m cm^{-1}. EIMS: *m/z* (% relative intensity) 312 (M^+, 9), 295 (42), 187 (13), 186 (93), 170 (22), 167 (38), 139 (100), 137 (33), 135 (12), 127 (19), 126 (95), 109 (36), 108 (13), 97 (10), 94 (18), 79 (13), 78 (89), 77 (27). HRMS Calcd for $C_{15}H_{14}F_2O_3S$ (M^+): 312.0632; found: 312.0628.

3.4.2. 2,2-Difluoro-1-(2,4-dimethoxyphenyl)-2-phenylsulfinylethanol (5c). Treatment of compound **3c** (451.6 mg, 1.38 mmol) in THF (20 mL) with a solution of 70% MCPBA (358 mg, 1.45 mmol) in THF (8 mL) afforded a white powder of **5c** as a mixture (54:46) of two diastereomers (324.4 mg, 69% yield, mp=108–111 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.71 (m, 2H, Ar*H*), 7.64–7.50 (m, 3H, Ar*H*), 7.36 and 7.31 (d each, *J*=8.4 and 8.4 Hz, respectively, 1H, Ar*H*), 6.55–6.40 (m, 2H, Ar*H*), 5.65 (d, *J*=24 Hz) and 5.42 (dd, *J*=17.4, 8.6 Hz) (1H, C*H*OH), 4.12 (br s, 1H, CHO*H*), 3.86 and 3.80 (s each, 3H, OCH_3), 3.82 and 3.76 (s each, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 and 162.1 (C), 159.5 and 159.4 (C), 137.5 and 137.0 (C), 133.2 and 133.0 (CH), 131.2 and 131.1 (CH), 129.7 and 129.6 (2×CH), 127.1 and 127.0 (2×CH), 125.7 and 125.1 (CF_2, dd each, *J*=305.1, 295.3 and 306.0, 295.0 Hz, respectively), 115.2 and 115.0 (C), 105.6 and 105.4 (CH), 99.6 and 99.4 (CH), 70.5 and 67.8 (CH, dd each, *J*=22.7, 22.7 and 29.0, 19.6 Hz, respectively), 56.4 and 56.1 (2×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −119.48 and −117.49 (dd each, *J*=216.8, 17.2 and 223.0, 24.0 Hz, respectively, 1F), −111.41 (d, *J*=223.0 Hz) and −109.49 (dd, *J*=216.4, 8.0 Hz), (1F). IR ($CHCl_3$): ν_{max} 3674w, 3598w, 3495br m, 3066w, 3013m, 2964m, 2941m, 2841w, 2455w, 1888w, 1719w, 1614s, 1589s, 1509s, 1466s, 1446s, 1439m, 1422m, 1296s, 1269m, 1185m, 1160s, 1128s, 1086s, 1039s, 999w, 974m, 936w, 922m, 839m, 825m, 638w, 593w, 566m cm^{-1}. EIMS: *m/z* (% relative intensity) 342 (M^+, 0.27), 217 (35), 216 (41), 198 (13), 197 (100), 187 (18), 169 (28), 167 (50), 165 (23), 151 (17), 149 (12), 139 (64), 137 (32), 126 (39), 121 (72), 109 (21), 91 (38), 78 (40), 77 (36). HRMS Calcd for $C_{16}H_{16}F_2O_4S$ (M^+): 342.0737; found: 342.0732.

3.4.3. 2,2-Difluoro-1-(3,4-dimethoxyphenyl)-2-phenylsulfinylethanol (5d). Treatment of compound **3d** (372.3 mg, 1.14 mmol) in THF (18 mL) with a solution of 70% MCPBA (294 mg, 1.19 mmol) in THF (6 mL) afforded a white powder of **5d** as a mixture (51:49) of diastereomers (275 mg, 70% yield, mp=121–125 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79–7.69 (m, 2H, Ar*H*), 7.66–7.51 (m, 3H, Ar*H*), 7.11–6.95 (m, 2H, Ar*H*), 6.89 and 6.85 (d each, *J*=8.8 and 8.4 Hz, respectively, 1H, Ar*H*), 5.43–5.31 (m, 1H, C*H*OH), 4.22 (br s, 1H, CHO*H*), 3.90 and 3.88 (s each, 6H, 2×CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.6 and 150.4 (C), 149.8 and 149.6 (C), 136.6 (d, *J*=3.5 Hz) and 136.3 (CH), 133.4 and 133.2 (CH), 129.8 and 127.0 (2×CH), 127.5 and 127.1 (C), 127.0 (2×CH), 124.9 and 124.2 (CF_2, dd each, *J*=303.0, 295.6 and 309.8, 291.4 Hz, respectively), 121.6 and 121.1 (CH), 111.4 (2×CH), 73.9 and 71.3 (CH, dd each, *J*=21.7, 21.7 and 28.9, 19.5 Hz, respectively), 56.5 (2×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −119.81 and −117.39 (dd each, *J*=218.2, 14.2 and 224.4, 22.1 Hz, respectively, 1F), −110.75 (d, *J*=224.4 Hz) and −109.86 (dd, *J*=218.2, 9.6 Hz), (1F). IR ($CHCl_3$): ν_{max} 3673w, 3597w, 3392br m, 3066w, 3019s, 2963m, 2938m, 2840m, 1960w, 1608m, 1596m, 1519s, 1465s, 1446s, 1423m, 1344w, 1309w, 1267s, 1188m, 1158s, 1143s, 1108s, 1087s, 1026s, 984m, 909m, 867w, 646w, 625w, 590w, 566w cm^{-1}. EIMS: *m/z* (% relative intensity) 342 (M^+, 1), 324 (4), 216 (100), 187 (51), 169 (38), 139 (41), 126 (38), 78 (42), 77 (24). Anal. Calcd for $C_{16}H_{16}F_2O_3S$: C, 56.13; H, 4.71. Found: C, 56.22; H, 4.30.

3.4.4. 1,1-Difluoro-4-phenyl-1-phenylsulfinyl-3-buten-2-ol (5e). Treatment of compound **3e** (369.5 mg, 1.26 mmol) in THF (21 mL) with a solution of 70% MCPBA (320 mg, 1.32 mmol) in THF (6 mL) afforded a white powder of **5e** as a mixture (60:40) of two diastereomers (212 mg, 50% yield, mp=110–114 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.71 (m, 2H, Ar*H*), 7.67–7.53 (m, 3H, Ar*H*), 7.47–7.38 (m, 2H, Ar*H*), 7.38–7.24 (m, 3H, Ar*H*), 6.88 (d, *J*=16 Hz, 1H, PhC*H*=CH), 6.34 and 6.27 (dd each, *J*=15.6, 7.0 and 16.0, 6.0 Hz, respectively, 1H, PhCH=C*H*), 5.05 (dd, *J*=21.0, 5.0 Hz) and 4.98–4.86 (m), (1H, C*H*OH), 4.11 and 3.40 (br s each, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.3 and 136.6 (CH), 136.4 and 136.2 (2×C), 133.4 (CH), 129.9 (2×CH), 129.3 (2×CH), 129.1 and 127.6 (CH), 127.5 (2×CH), 127.1 (2×CH), 121.9 and 121.8 (CH), 73.4 and 70.9 (CH, t each, *J*=22.8 and 27.4 Hz, respectively). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −118.49 and −116.78 (dd each, *J*=220.6, 11.8 and 224.8, 20.7 Hz, respectively, 1F), −112.62 (d, *J*=224.7 Hz) and −109.98 (dd, *J*=220.6, 10.9 Hz), (1F). IR (KBr): ν_{max} 3285br s, 3058m, 3027m, 2897w, 2688w, 2364w, 2345w, 1891w, 1813w, 1648w, 1496m, 1475m, 1446s, 1424m, 1358w, 1331w, 1306w, 1282w, 1262w, 1192s, 1115s, 1085s, 1062s, 1034s, 1020s, 998s, 970s, 950s, 869w, 850w, 804w, 767s, 748s, 728m, 689s, 669w, 605w, 547m, 521s, 488m, 444m cm^{-1}. EIMS: *m/z* (% relative intensity) 308 (46), 291 (100), 233 (31), 186 (21), 182 (76), 146 (26), 133 (32), 126 (62), 115 (50), 78 (64), 77 (20). HRMS Calcd for $C_{16}H_{14}F_2O_2S$ (M^+): 308.0683; found: 308.0678.

3.4.5. 1,1-Difluoro-4-(2-methoxyphenyl)-1-phenylsulfinyl-3-buten-2-ol (5f). Treatment of compound **3f** (190 mg, 0.59 mmol) in THF (9 mL) with a solution of 70% MCPBA (149 mg, 0.62 mmol) in THF (3 mL) afforded a white powder of **5f** as a mixture (65:35) of two diastereomers (118.9 mg, 60% yield, mp=127–130 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 and 7.77 (d each, *J*=8.0 and 7.6 Hz, respectively, 1H, Ar*H*), 7.65–7.53 (m, 3H, Ar*H*), 7.47 (dd, *J*=7.6, 1.6 Hz, 1H, Ar*H*), 7.32–7.23 (m, 1H, Ar*H*), 7.18 and 7.17 (d each, *J*=16.0 and 16.0 Hz, respectively, 1H, Ar*H*), 6.97–6.84 (m, 2H, 1H of Ar*H* and 1H of PhC*H*=CH), 6.38 and 6.31 (dd each, *J*=16.0, 7.2 and 16.0, 6.8 Hz, respectively, 1H, PhCH=C*H*), 5.09–5.00 and 4.90–4.80 (m each, 1H, C*H*OH), 3.84 and 3.83 (s each, 3H, CH_3), 3.10 (br s, 1H, CHO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.8 and 157.7 (C), 137.1 and 136.3 (C), 133.2 (CH), 132.5 and 131.9 (CH), 130.4 and 130.2 (CH), 129.7 (2×CH), 128.2 and 128.1 (CH), 127.1 (2×CH), 125.4 and 125.2 (C), 122.4 and 122.3 (CH), 121.3 (CH), 111.6 (CH), 73.8 and 71.4 (CH, dd each, *J*=22.9, 22.9 and 28.5, 20.6 Hz, respectively), 56.10 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −118.4 and −117.1 (dd each, *J*=219.8,

12.4 and 223.5, 21.0 Hz, respectively, 1F), −112.4 (d, J=223.5 Hz) and −110.4 (dd, J=219.8, 10.3 Hz), (1F). IR (neat): ν_{max} 3354br s, 3063w, 3003w, 2939w, 2839w, 1897w, 1732m, 1714m, 1650m, 1599s, 1579m, 1489s, 1464s, 1446s, 1374w, 1357w, 1293s, 1247s, 1194s, 1163m, 1104s, 1049s, 998m, 977s, 951s, 867m, 751s, 688s, 606w, 583w, 526m, 489m, 433w, 417w cm^{-1}. EIMS: m/z (% relative intensity) 338 (M^+, 1.22), 212 (100), 192 (63), 164 (41), 126 (44), 115 (33), 91 (48), 78 (66). HRMS Calcd for $C_{17}H_{16}F_2O_3S$ (M+): 338.0788; found: 338.0788.

3.4.6. 1-(Difluoro(phenylsulfinyl)methyl)-1,2,3,4-tetrahydronapthalen-1-ol (5l). Treatment of compound **3l** (309.0 mg, 1.00 mmol) in THF (15 mL) with a solution of 70% MCPBA (273 mg, 1.10 mmol) in THF (4 mL) afforded a diastereomeric mixture of **5l**, which was separated by radial chromatography (20% EtOAc in hexanes) to give 123 mg (38% yield, mp=139–142 °C) of diastereomer **A** and 97 mg (30% yield, mp=115–118 °C) of diastereomer **B**. Diastereomer **A**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.91–7.81 (m, 1H, Ar*H*), 7.70 (d, J=8.0 Hz, 2H, Ar*H*), 7.63–7.47 (m, 3H, Ar*H*), 7.36–7.23 (m, 2H, Ar*H*), 7.22–7.12 (m, 1H, Ar*H*), 2.92–2.77 (m, 2H, PhCH_2), 2.77–2.64 (m, 1H, C*H*HOH), 2.45 (br s, 1H, CO*H*), 2.13–1.94 (m, 2H, 1H of CH*H*OH and 1H of CH_2CHHCH_2), 1.93–1.75 (m, 1H, CH_2CHHCH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.7 (C), 137.1 (C), 134.9 (C), 133.2 (CH), 129.9 (CH), 129.6 (2×CH), 129.5 (CH), 128.3 (d, J=2.7 Hz, CH), 127.5 (2×CH), 126.8 (CH), 124.6 (dd, J=317.0, 300.0 Hz, CF_2), 76.7 (t, J=19.3 Hz, C), 34.0 (CH_2), 29.4 (CH_2), 19.2 (CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −115.73 (d, J=219.5 Hz, 1F), −99.57 (d, J=219.6 Hz, 1F). Diastereomer **B**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (d, J=7.6, 3H, Ar*H*), 7.69–7.57 (m, 3H, Ar*H*), 7.33–7.16 (m, 3H, Ar*H*), 4.10 (br s, 1H, CO*H*), 2.97–2.86 (m, 2H, PhCH_2), 2.86–2.77 (m, 1H, C*H*HCOH), 2.52–2.40 (m, 1H, C*H*HCOH), 2.18–2.00 (m, 2H, $CH_2CH_2CH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.4 (C), 136.2 (C), 133.8 (C), 133.4 (CH), 129.8 (2×CH), 129.6 (CH), 129.5 (CH), 129.2 (d, J=4.3 Hz, CH), 127.2 (2×CH), 126.9 (CH), 124.1 (dd, J=319.1, 295.3 Hz, CF_2), 76.7 (t, J=3 Hz, C), 35.4 (CH_2), 29.9 (CH_2), 19.4 (d, J=2.6 Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −115.31 (d, J=220.9 Hz, 1F), −100.50 (d, J=221.5 Hz, 1F). IR (KBr): ν_{max} 3238s, 3081w, 3014w, 2959m, 2919m, 2887w, 2837w, 2817w, 2613w, 2489w, 1655w, 1601w, 1486m, 1477m, 1456m, 1448m, 1431m, 1414w, 1353w, 1341m, 1292w, 1232w, 1200m, 1184w, 1166m, 1149s, 1131s, 1078s, 1065m, 1030s, 1021s, 980s, 959m, 910w, 891m, 874s, 807w, 766s, 752s, 686s, 659m, 623m, 582m, 518m, 495m, 466m, 436m, 897w cm^{-1}. EIMS: m/z (% relative intensity) 177 (14), 164 (5), 159 (10), 149 (23), 147 (31), 130 (12), 129 (100), 128 (32), 127 (18), 126 (73), 91 (21), 78 (48), 77 (10), 73 (2), 65 (5). Anal. Calcd for $C_{17}H_{16}F_2O_2S$: C, 63.34; H, 5.00. Found: C, 63.34; H, 5.16.

3.4.7. 2,2-Difluoro-1,1-diphenyl-2-phenylsulfinylethanol (5o). Treatment of compound **3o** (662.6 mg, 1.93 mmol) in THF (20 mL) with a solution of 70% MCPBA (496 mg, 2.02 mmol) in THF (10 mL) afforded a white powder of **5o** (493.1 mg, 71% yield, mp=158–161 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88–7.78 (m, 2H, Ar*H*), 7.77–7.67 (m, 2H, Ar*H*), 7.67–7.38 (m, 8H, Ar*H*), 7.37–7.24 (m, 3H, Ar*H*), 5.18 (br s, 1H, CO*H*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.4 (C), 139.5 (C), 136.3 (C), 133.5 (CH), 129.8 (2×CH), 129.4 (CH), 129.3 (2×CH), 129.0 (CH), 128.6 (2×CH), 128.4 (2×CH), 128.0 (CH), 127.9 (CH), 127.1 (2×CH), 123.0 (dd, J=318.7, 299.9 Hz, CF_2), 82.5 (t, J=19.9, 19.8 Hz, C). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −112.44 (d, J=220.2 Hz, 1F), −98.60 (d, J=220.2 Hz, 1F). IR (KBr): ν_{max} 3255s, 3053m, 1491m, 1450s, 1411m, 1289w, 1261w, 1172m, 1120s, 1083s, 1063s, 1039s, 1021s, 998m, 905m, 821m, 749s, 706s, 698s, 687s, 659m, 618m, 572m, 512m, 483m, 437m, 397w cm^{-1}. EIMS: m/z (% relative intensity) 359 (M^++1, 3.32), 213 (62), 185 (40), 183 (19), 166 (17), 165 (100), 127 (12), 126 (33), 106 (5), 105 (35), 78 (37), 77 (45), 50 (15). Anal. Calcd for $C_{20}H_{16}F_2O_2S$: C, 67.02; H, 4.50. Found: C, 67.10; H, 4.08.

3.5. Preparation of 1,1-difluoroalkene 6

3.5.1. 1,1-Difluoro-2-(4-methoxyphenyl)ethene (6b).[12] *General procedure A*: Sulfoxide **5b** (110 mg, 0.35 mmol) was heated at 170–200 °C (0.05 mmHg) to give a pure oil of **6b** (47.1 mg, 79% yield), which was trapped at −78 °C (see Fig. 1).

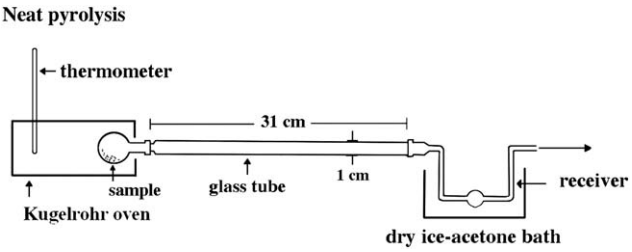


Figure 1.

General procedure B: Flash vacuum pyrolysis of sulfoxide **5b** (105.2 mg, 0.34 mmol) (conditions: oven temperature 120 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a pure oil of **6b** (46.4 mg, 82% yield), which was trapped at −78 °C (see Fig. 2); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, J=8.4 Hz, 2H, Ar*H*), 6.87 (d, J=8.7 Hz, 2H, Ar*H*), 5.20 (dd, J=26.4, 3.8 Hz, 1H, C*H*=CF_2), 3.79 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.6 (t, J=2.1 Hz, C), 155.8 (dd, J=294.8, 284.9 Hz, CF_2), 128.8 (2×CH, dd, J=6.3, 3.4 Hz), 122.7 (t, J=6.1 Hz, C), 114.1 (2×CH), 81.5 (dd, J=29.0, 14.1 Hz, CH), 55.2 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −86.86 (d, J=36.9 Hz, 1F), −85.04 (dd, J=43.8, 36.7 Hz, 1F). IR (neat): ν_{max} 3450w, 3038m, 3006m, 2959m, 2938m, 2912m, 2839m, 2666w, 2550w, 2066w, 2024w, 1886w, 1733s, 1613s, 1578m, 1515s, 1466m, 1443m, 1421m, 1351s, 1317w, 1299s, 1248s, 1182s, 1166s, 1113w, 551s, 523s, 475w cm^{-1}. EIMS: m/z (% relative intensity) 170 (M^+, 100), 139 (9), 127 (10), 107 (3), 77 (1).

3.5.2. 1,1-Difluoro-2-(2,4-methoxyphenyl)ethene (6c). According to *general procedure A*, neat pyrolysis of sulfoxide **5c** (104.2 mg, 0.30 mmol) at 170–200 °C (0.05 mmHg) gave a pure oil of **6c** (44.5 mg, 74% yield). According to

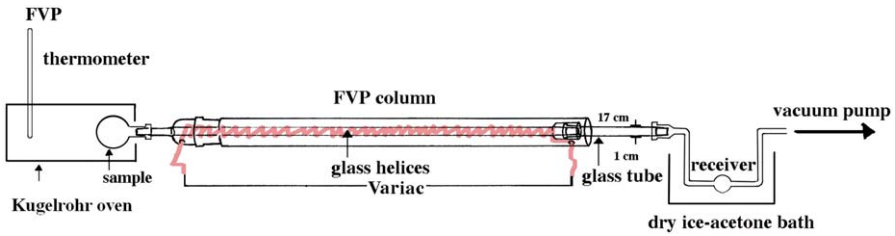


Figure 2.

general procedure B, flash vacuum pyrolysis of sulfoxide **5c** (103.0 mg, 0.30 mmol) (conditions: oven temperature 120 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a pure oil of **6c** (42.1 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (dd, J=8.4, 1.2 Hz, 1H, Ar*H*), 6.51 (dd, J=8.4, 2.4 Hz, 1H, Ar*H*), 6.46 (d, J=25.6, 5.6 Hz, 1H, Ar*H*), 5.56 (dd, J=25.8, 5.5 Hz, 1H, C*H*=CF_2), 3.82 (s, 6H, 2×CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.9 (C), 157.2 (dd, J=4.1, 1.5 Hz, C), 155.9 (dd, J=292.8, 284.8 Hz, CF_2), 128.8 (dd, J=8.8, 2.2 Hz, CH), 111.8 (t, J=5.0 Hz, C), 104.7 (CH), 98.4 (CH), 75.8 (dd, J=29.7, 14.6 Hz, CH), 55.5 (CH_3), 55.4 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −86.31 (dd, J=36.6, 25.6 Hz, 1F), −86.11 (dd, J=36.6, 6.4 Hz, 1F). IR (neat): ν_{max} 3446w, 3005w, 2942w, 2840w, 1868w, 1732s, 1614s, 1582s, 1508s, 1465s, 1439m, 1420m, 1346m, 1312s, 1291s, 1236s, 1210s, 1169s, 1115m, 1036s, 993w, 942s, 836m, 792w, 753w, 688w, 630w, 588w, 547w, 466w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 200 (M^+, 100), 185 (22), 157 (10), 149 (5), 121 (5). HRMS Calcd for $C_{10}H_{10}F_2O_2$ (M^+): 200.0649; found: 200.0653.

3.5.3. 1,1-Difluoro-2-(3,4-methoxyphenyl)ethene (6d). According to *general procedure A*, neat pyrolysis of sulfoxide **5d** (101.3 mg, 0.29 mmol) at 170–200 °C (0.05 mmHg) gave a pure oil of **6d** (40.9 mg, 71% yield). According to *general procedure B*, flash vacuum pyrolysis of sulfoxide **5d** (117.0 mg, 0.34 mmol) (conditions: oven temperature 120 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a pure oil of **6d** (46.0 mg, 68% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.91–6.80 (m, 3H, Ar*H*), 5.21 (dd, J=26.4, 3.9 Hz, 1H, C*H*=CF_2), 3.89 (s, 3H, CH_3), 3.88 (s, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.5 (dd, J=294.7, 285.1 Hz, CF_2), 149.6 (C), 148.8 (C), 123.6 (t, J=6.0 Hz, C), 121.0 (t, J=4.4 Hz, CH), 111.9 (CH), 111.1 (d, J=4.4 Hz, CH), 82.5 (dd, J=15.5, 13.7 Hz, CH), 56.5 (2×CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −86.54 (dd, J=36.5, 3.8 Hz, 1F), −84.81 (dd, J=36.7, 25.4 Hz, 1F). IR (neat): ν_{max} 3546w, 3004m, 2959m, 2939m, 2912m, 2838m, 2592w, 2018w, 1836w, 1731s, 1607m, 1585m, 1519s, 1466s, 1418s, 1345s, 1322s, 1293s, 1269s, 1246s, 1212s, 1178s, 1157s, 1145s, 1028s, 978m, 918s, 892m, 857s, 826m, 805m, 764m, 746m, 638m, 596w, 562m, 405w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 200 (M^+, 100), 185 (25), 157 (14), 139 (5), 127 (6), 110 (11), 109 (51), 107 (19), 77 (3). HRMS Calcd for $C_{10}H_{10}F_2O_2$ (M^+): 200.0649; found: 200.0655.

3.5.4. (*E*)-1-(4,4-Difluoro-1,3-butadienyl)benzene (6e).[11b] According to *general procedure A*, neat pyrolysis of sulfoxide **5e** (120.5 mg, 0.39 mmol) at 170–200 °C (0.05 mmHg) gave a pure oil of **6e** (45.1 mg, 70% yield). According to *general procedure B*, flash vacuum pyrolysis of sulfoxide **5e** (168.5 mg, 0.547 mmol) (conditions: oven temperature 120 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a crude pyrolyzate, which was purified by chromatotron (SiO_2, hexanes) to give a pale yellow oil **6e** (54.8 mg, 60% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42–7.35 (m, 2H, Ar*H*), 7.35–7.29 (m, 2H, Ar*H*), 7.29–7.21 (m, 1H, Ar*H*), 6.68 (ddd, 1H, J=15.8, 10.8, 1.2 Hz, 1H, PhCH=C*H*), 6.48 (d, J=15.8 Hz, 1H, PhC*H*=CH), 5.14 (dddd, J=24.1, 10.8, 1.5, 0.6 Hz, 1H, C*H*=CF_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.5 (dd, J=295.4, 289.8 Hz, CF_2), 137.5 (C), 131.7 (dd, J=11.4, 3.3 Hz, CH), 129.3 (2×CH), 128.3 (CH), 126.8 (2×CH), 118.5 (CH), 83.5 (dd, J=27.6, 16.8 Hz, CH). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −87.46 (d, J=26.4 Hz, 1F), −85.74 (t, J=25.4 Hz, 1F). IR (neat): ν_{max} 3447br m, 3084w, 3062w, 3028w, 2960m, 2926m, 2853m, 2646w, 2363w, 1812m, 1717s, 1648w, 1630w, 1597w, 1578w, 1519w, 1498w, 1451w, 1418w, 1353m, 1329m, 1295m, 1276s, 1210w, 1184s, 1116w, 1073w, 1028w, 962m, 934s, 851w, 828m, 747m, 692m, 605w, 563w, 516w, 505w cm^{-1}. EIMS: m/*z* (% relative intensity) 166 (M^+, 28), 149 (100), 115 (54), 105 (46), 95 (35), 91 (35), 77 (50).

3.5.5. (*E*)-1-(4,4-Difluoro-1,3-butadienyl)-2-methoxybenzene (6f). According to *general procedure A*, neat pyrolysis of sulfoxide **5f** (107.5 mg, 0.32 mmol) at 170–200 °C (0.05 mmHg) gave a pure oil of **6f** (48.7 mg, 78% yield). According to *general procedure B*, flash vacuum pyrolysis of sulfoxide **5f** (104.0 mg, 0.31 mmol) (conditions: oven temperature 120 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a pure oil of **6f** (43.5 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.46 (dd, J=7.3, 1.6 Hz, 1H, Ar*H*), 7.25–7.20 (m, 1H, Ar*H*), 6.98–6.91 (m, 1H, Ar*H*), 6.88 (dd, J=8.3, 1.0 Hz, 1H, Ar*H*), 6.82 (d, J=16.1 Hz, 1H, PhC*H*=CH), 6.70 (ddd, J=16.0, 10.7, 1.2 Hz, 1H, PhCH=C*H*), 5.17 (ddd, J=23.7, 10.7, 0.3 Hz, 1H, C*H*=CF_2), 3.87 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.3 (dd, J=295.1, 289.3 Hz, CF_2), 157.2 (C), 131.3 (C), 129.2 (CH), 127.2 (CH), 126.6 (dd, J=11.3, 3.2 Hz, CH), 121.4 (CH), 119.1 (dd, J=4.1, 2.2 Hz, CH), 111.5 (CH), 84.1 (dd, J=17.2, 16.8 Hz, CH), 56.1 (CH_3). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −88.17 (d, J=27.8 Hz, 1F), −86.40 (dd, J=27.7, 23.7 Hz, 1F). IR (neat): ν_{max} 3415w, 3004w, 2927m, 2839w, 2644w, 1812w, 1716s, 1625w, 1597m, 1578w, 1489s, 1465m, 1438m, 1354s, 1295m, 1279m, 1246s, 1180s, 1104w, 1052w, 1030m, 970m, 934s, 854w, 841w, 821w, 775w, 749s, 731w, 607w, 578w, 508w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 196 (M^+, 14), 165 (43), 118 (61), 77 (24), 63 (75), 50 (100). HRMS Calcd for $C_{11}H_{10}F_2O$ (M^+): 196.0700; found: 196.0699.

3.5.6. 1-(Difluoromethylene-1,2,3,4-tetrahydronaphthalene (6l).[11b] According to *general procedure B*, flash vacuum pyrolysis of sulfoxide **5l** (110.1 mg, 0.34 mmol) (conditions: oven temperature 205 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a crude pyrolyzate, which was purified by chromatotron (SiO_2, hexanes) to give a colourless oil of **6l** (25.0 mg, 41% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.5 (d, J=7.4 Hz, 1H, Ar*H*), 7.17–6.98 (m, 3H, Ar*H*), 2.72 (t, J=6.2 Hz, 2H, PhCH_2), 2.47–2.33 (m, 2H, $CH_2CH_2CH_2$), 1.84–1.70 (m, 2H, CH_2COH). ^{13}C NMR (100 MHz, $CDCl_3$): δ 152.8 (dd, J=294.3, 282.7 Hz, CF_2), 137.6 (d, J=6.0 Hz, C), 129.0 (CH), 127.3 (d, J=1.5 Hz, C), 127.1 (d, J=1.6 Hz, C), 126.6 (CH), 126.1 (CH), 88.2 (dd, J=23.6, 8.6 Hz, C), 30.4 (CH_2), 23.3 (t, J=2.1 Hz, CH_2), 22.2 (t, J=1.4 Hz, CH_2). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −88.5 (d, J=42.1 Hz, 1F), −88.1 (d, J=43.7 Hz, 1F). IR (neat): ν_{max} 3065w, 3025w, 2931s, 2857m, 1855m, 1713s, 1602w, 1488m, 1453m, 1350w, 1323m, 1270w, 1231s, 1160w, 1119m, 1071w, 989s, 945w, 909w, 878w, 784w, 759s, 727w, 688w cm^{-1}. EIMS: *m*/*z* (% relative intensity) 180 (M^+, 39), 159 (21), 147 (100), 129 (72), 91 (25), 77 (6).

3.5.7. 1,1-Difluoro-2,2-diphenylethene (6n).[11b] According to *general procedure B*, flash vacuum pyrolysis of sulfoxide **5n** (110.8 mg, 0.31 mmol) (conditions: oven temperature 205 °C, column temperature 425 °C; pressure 0.05 mmHg) gave a crude pyrolyzate, which was purified by chromatotron (SiO_2, hexanes) to give a colourless oil **6n** (53.6 mg, 80% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32–7.12 (m, 10H, Ar*H*). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8 (t, J=291.5 Hz, CF_2), 134.3 (2×C), 129.6 (3×CH, t, J=3.3 Hz), 128.4 (4×CH), 127.5 (3×CH), 96.2 (t, J=18.0 Hz, C). ^{19}F NMR (376 MHz, $CDCl_3$/$CFCl_3$): δ −88.27 (s, 2F). IR (neat): ν_{max} 3086w, 3061w, 3027w, 2927w, 2484w, 1952w, 1879w, 1810w, 1707s, 1599w, 1578w, 1541w, 1498m, 1446s, 1338w, 1323w, 1245s, 1211s, 1158w, 1075w, 1035w, 1001m, 985s, 933w, 912m, 844w, 761s, 732w, 696s, 636m, 600m, 515m cm^{-1}. EIMS: *m*/*z* (% relative intensity) 216 (100), 197 (13), 195 (11), 165 (86).

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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.2006.04.015.

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A free radical Mannich type reaction: selective α-CH aminomethylation of ethers by Ti(III)/*t*-BuOOH system under aqueous acidic conditions

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Abstract—*tert*-Butoxy radical, generated by Ti(III)-one electron reduction of *tert*-butylhydroperoxide, selectively abstracts an α-H atom from ethers. The resulting α-ethereal radicals add to the C-atom of methylene iminium salts, formed in situ under aqueous acidic conditions, leading to a one-pot aminomethylation of ethers at room temperature. The aminoalkylation of ethers is also considered and the role of the metal ion is discussed.

1. Introduction

The classical Mannich aminomethylation of R–H acidic substrates is one of the most important carbon–carbon bond forming reaction in organic chemistry.[1] Aminomethylation of nucleophilic radicals, formed by H-atom abstraction from R–H substrates, would represent the radical version of the classical Mannich reaction with the substantial difference such that the functional groups directly bonded to the reactive carbon atoms in R–H must have opposite polarity.

Whereas electron-withdrawing groups (EWG) are suitable for the ionic addition, electron-donor groups (EDG) favour the nucleophilic radical addition to methylene-iminium salts. As a consequence, the type of products accessible by the classical and the radical-type Mannich reactions would be complementary concerning the polarity of the substituents in β-position to the amino groups (Fig. 1).

Recently,[2–7] the carbon–nitrogen double bond has attracted significant attention as an excellent acceptor of nucleophilic radicals, however, only water-resistant imine derivatives may be used in aqueous radical reactions.

As a consequence, studies involving the reductive intermolecular radical addition to water-sensitive simple aldimines are scattered[2,8] in comparison to those dealing with various C═N containing functional groups, such as oxime ethers, glyoxylic oxime ethers, *N*-sulfonylimines, hydrazones and nitrones.[3–7] These substrates are less sensitive to hydrolysis than the former and show higher radical addition rates due to extra-stabilisation in the addition transition state.[9]

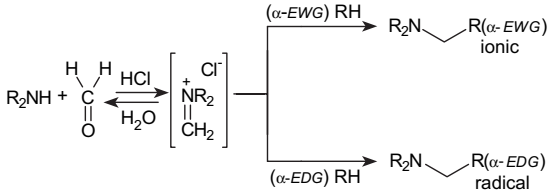

Figure 1. Classical and radical-type Mannich reaction.

Even more so, studies concerning intermolecular radical addition to highly water-sensitive and easily polymerisable[10] formaldehyde-imines and formaldehyde-iminium salts, generated in situ either in anhydrous organic solvents or in aqueous co-solvents, have not attracted the organic chemists' attention.

We report here that the exceptional coordinative properties of Ti(IV) make feasible the addition of α-ether radicals to the C-atom of methylene iminium salts and formaldehyde-imines formed in situ under aqueous conditions, leading to α-aminomethylation of ethers in a free radical Mannich type reaction (Fig. 1).

2. Results and discussion

Our recent studies[8d,e] have shown that, under aqueous conditions, a phenyl radical, generated by Ti(III)-induced

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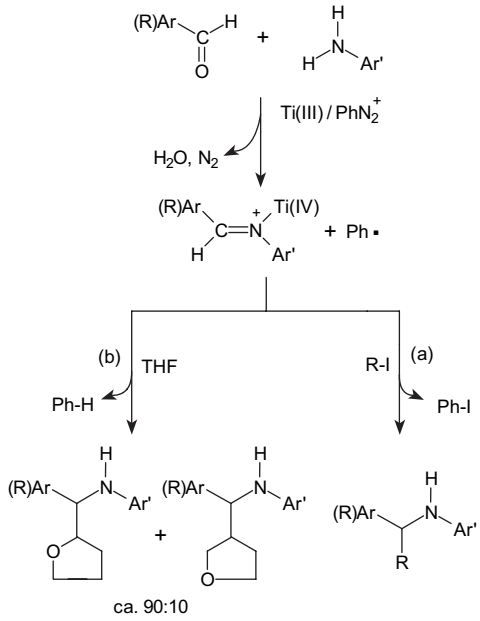
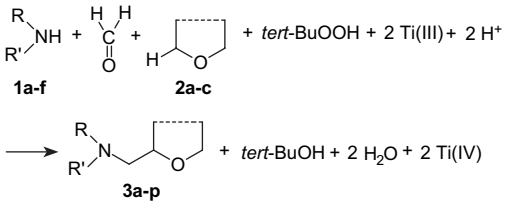
decomposition of phenyldiazonium cation, abstracts either an iodine-atom from alkyl iodides (Scheme 1, path a) or an α-H atom from ethers (Scheme 1, path b), leading to a one-pot addition of nucleophilic alkyl or α-alkoxyalkyl radicals to the C-atom of aldimines, formed in situ and activated towards radical addition by Ti(IV)–N complexation.



Scheme 1. Ti(III)/PhN_2^+ mediated radical addition to aldimines.

Continuing our research on the manifold roles simultaneously played by Ti(III) and Ti(IV) ions in promoting tandem radical one-pot multicomponent reactions, we report here that the aqueous acidic $TiCl_3$/*t*-BuOOH system is a more practical, efficient and selective radical precursor of α-alkoxyalkyl radicals from ethers[11] than the previously reported $TiCl_3/PhN_2^+$ system[8e] and that even methylene iminium salts and formaldehyde-imines may be successfully used as radical acceptors. In fact, notwithstanding the aqueous medium, these species are formed in situ in an adequate concentration to make the subsequent addition of α-ether radicals preparatively advantageous for the synthesis of 1,2-aminoethers **3**.

According to the stoichiometry of Scheme 2, the Ti(III)/*t*-BuOOH system readily assembles, in 30 min at room temperature, an amine **1**, formaldehyde and an ether **2** leading to **3**.



Scheme 2. Ti(III)/*t*-BuOOH mediated α-aminomethylation of ethers.

After a survey to optimise the reaction conditions, we found that the reaction rapidly occurs at 20 °C by dropwise addition (30 min) of *t*-BuOOH (4 mmol of a 80% aqueous solution) to a homogeneous solution containing amine **1** (2 mmol), formaldehyde (7 mmol of a 40% aqueous solution) and $TiCl_3$ (8 mmol, ca. 8 mL of a 15 wt % in 30 wt % HCl solution) in 10 mL of glacial CH_3COOH and 10 mL of the ether **2** under investigation.[12] The reaction can be followed like a titration and it is over when the blue colour of $TiCl_3$ is completely discharged to give a homogeneous yellow solution.

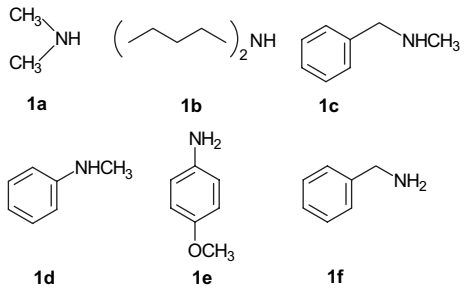


Figure 2. Representative amines **1a**–**f**.

Under these conditions, we tested the reaction of a number of representative amines **1a**–**f** (Fig. 2) in the presence of either THF (**2a**), 1,4-dioxane (**2b**) or Et_2O (**2c**) as co-solvents.

Secondary aliphatic and aromatic amines **1a**–**d** gave the expected products **3a**–**k** in fair to good isolated yields (Table 1).

This one-pot three component reaction proved to be so clean that with low boiling amines **1a**–**b**, no chromatographic separation was required in order to obtain the spectroscopically pure 1,2-aminoethers **3a**–**e** (^{1}H NMR purity of the crude residue was ≥95%, entries 1–5). Pure **3f**–**k** (entries 6–11) were obtained after chromatographic separation from the unreacted amines **1c**–**d**.

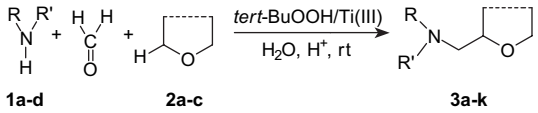
When *p*-methoxyaniline **1e** (PMP–NH_2) was used, as a representative primary aromatic amine,[13] under the reaction conditions adopted for secondary amines (e.g., molar ratio **1e**/HCHO, 1:3.5), the reaction went on and bis-adducts **4l**–**n** were obtained in addition to the desired products **3l**–**n** (Table 2, entries 1, 3 and 5).

However it was possible to control the selective formation of **3l**–**n** by decreasing the amount of formaldehyde to 0.5 equiv (Table 2, entries 2, 4 and 6). The use of **3l**–**n**, as a starting amine component under the conditions developed for secondary amines, led to bis-derivatives **4l**–**n** in ca. 70% isolated yields. The primary aliphatic amine **1f**, under all the experimental conditions tested, gave only the bis-adduct **4p** (Table 2, entry 7).

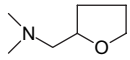
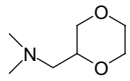
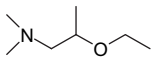
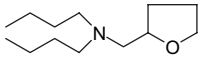
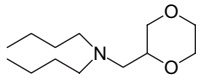
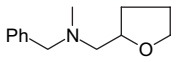
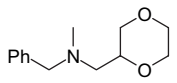
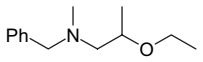
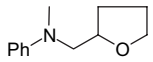
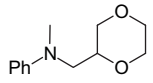
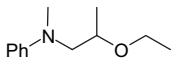
It should be underlined that the product arising from the addition of β-THF radical (Scheme 1) to the C-atom of the imine was not obtained in every case, showing that the Ti(III)/*t*-BuOOH system is more selective than Ti(III)/PhN_2^+ in abstracting a H-atom from THF.

To extend the scope of the reaction from aminomethylation to aminoalkylation and aminoarylation of ethers, we checked the applicability of the method to acetaldehyde,

Table 1. Mannich radical-type addition of ethers **2a–c** to in situ generated methylene iminium salts[a]



1a-d **2a-c** **3a-k**

Entry	Product	**3** yield %[b]
1		**3a**: 88
2		**3b**: 65
3		**3c**: 40
4		**3d**: 55
5		**3e**: 55
6		**3f**: 60 (65)
7		**3g**: 75 (81)
8		**3h**: 54 (63)
9		**3i**: 70 (81)
10		**3j**: 70 (84)
11		**3k**: 50 (65)

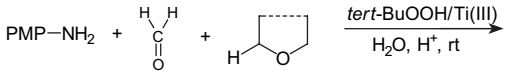
[a] Molar ratio of **1**:HCHO:*t*-BuOOH:Ti(III) was 1:3.5:2:4.
[b] Isolated yields are based on the starting amine **1** (2 mmol); yields in brackets have been determined by ^{1}H NMR with an appropriate internal standard added to the crude reaction mixture; yield of **3**, based on the converted **1**, were always >90%.

p-bromobenzaldehyde, *p*-tolualdehyde, *p*-anisaldehyde, benzaldehyde and cyclohexylaldehyde, but of all the amines screened (Fig. 2) only the primary aromatic amine **1e** gave the desired THF-adducts **3q–v** (Table 3) as a 1:1 mixture of diastereomers with no traces of bis-adduct **4**.

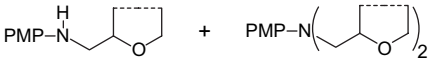
The fact that any attempt to apply this radical addition to in situ generated alkylidene or arylidene iminium ions proved to be unsuccessful implies that steric factors are relevant to the course of the reaction, as they are for the classical Mannich reaction.

In Table 3, the yields of **3l** and **3q–v**, obtained with the present method (**A**), are compared with those previously obtained[8e] by using, under comparable experimental conditions, the Ti(III)/PhN$_2^+$ method (**B**) and the yields of **3t–v** are also compared with those reported by Tomioka[8c] in a three component reaction with the use of dimethylzinc as a radical initiator (**C**).

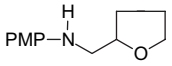
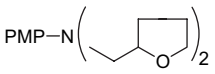
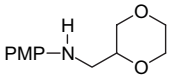
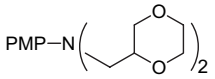
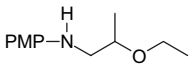
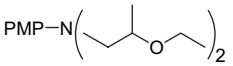
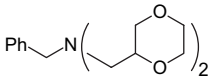
Table 2. Mannich radical-type addition of ethers **2a–c** to an equilibrium mixture of PMP–NH$_2$ (**1e**) and formaldehyde under different experimental conditions



1e **2a-c**

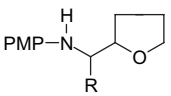


3l-n **4l-n**

Entry	Product; yield %[a]	
1[b]	 **3l** (30)	 **4l** (34)
2[c]	**3l** 68 (80)	**4l** (6)
3[b]	 **3m** (41)	 **4m** (24)
4[c]	**3m** 70 (86)	**4m** (5)
5[b]	 **3n** (36)	 **4n** (30)
6[c]	**3n** 68 (80)	**4n** (6)
7[d]		 **4p** (30)

[a,b] See footnotes a and b of Table 1, respectively.
[c] Molar ratio of **1e**/HCHO/*t*-BuOOH:Ti(III) was 1:0.5:2:4; yields are based on the starting HCHO.
[d] Benzylamine **1f** was used; molar ratio of **1f**/HCHO was 1:0.5.

Table 3. Addition of THF to an equilibrium mixture of PMP–NH$_2$ (**1e**) and aldehydes (R–CHO) by using different radical initiators

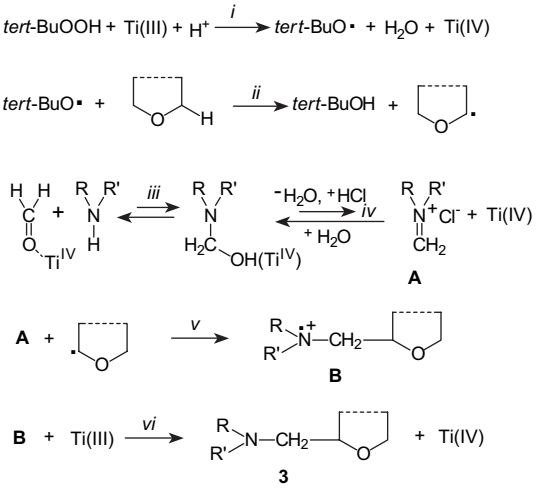
Product **3** 	Molar ratio R–CHO/**1e**	Radical initiator,[a] **3** yield %[b]		
		A (30 min)	**B** (3 h)	**C** (time)
R=H, **3l**	1:1	72	58	—
R=CH_3, **3q**	2:1	80 (90)[c]	55+9[d]	—
R=*p*-Br-C_6H_4, **3r**	1:1.5	63 (70)[c]	55+7[d]	—
R=*p*-CH_3-C_6H_4, **3s**	1:1.5	74 (85)[c]	47+8[d]	—
R=*p*-$OCH_3C_6H_4$, **3t**	1:1.5	80 (89)[c]		57 (45 h)
R=C_6H_5, **3u**	1:1.5	70 (79)[c]	51+9[d]	74 (22 h)
R=cyclohexyl, **3v**	2:1	80 (95)[c]	64	44 (138 h)

[a] **A**: Ti(III)/*t*-BuOOH (this work); **B**: Ti(III)/PhN$_2^+$ (Ref. 8e); **C**: Me_2Zn/air (Ref. 8c).
[b] Isolated yields.
[c] ^{1}H NMR yields with an appropriate internal standard.
[d] β-THF adduct.

other routes in a number of ways: shorter reaction times, titration-like reaction, cheaper and easier to handle radical source and higher-yielding reaction with wide applicability.

2.1. Mechanistic considerations

The sequence of steps *i*–*vi* reported in Scheme 3 would represent a reasonable rationale of the reaction. The one-electron reduction of *t*-BuOOH by Ti(III) ion gives the *tert*-butoxy radical (*i*) which selectively abstracts an α-H atom from the ether generating an α-ethereal radical (*ii*).



Scheme 3. Mechanistic rationale.

Owing to its nucleophilic character, the α-ethereal radical adds to the C-atom of the methylene iminium salt **A** (*v*) (or to the C-atom of the Ti(IV)-complexed imine) formed in situ by a series of equilibrium reactions (*iii*, *iv*). The resulting electrophilic aminium radical **B** is then readily reduced (*vi*) to the final product **3** by a second equivalent of Ti(III).

The H-atom abstraction from ethers by *tert*-butoxy radical (*i*) is a fast process[14] due to a favourable enthalpy balance,[15] and to polar effects, but the series of equilibria involved in the formation of **A** under aqueous conditions[16] (*iii*, *iv*) should be by far shifted to the left. In fact, for the conditions under which the classical Mannich reaction is most commonly performed (aqueous formaldehyde solution), elevated temperature and long reaction time are necessary for generation of a sufficient concentration of **A**.

In the modern variant of the Mannich reaction the methylene iminium ion, rather than being generated under equilibrium conditions, is separately preformed upon exclusion of moisture or generated in situ starting from iminium ion equivalents that permit an aprotic solvent to be used under milder reaction conditions and shorter reaction time.[1]

In view of this, the salient feature of the present radical Mannich type reaction is that aminoethers **3** are formed in good yields at room temperature in ca. 30 min, notwithstanding the aqueous medium (volume ratio H_2O/ether/CH_3COOH, ca. 1:1:1).

A plausible explanation is that Ti(IV) ion, owing to its high oxophilicity, coordinates the carbonyl oxygen, thereby preparing the aldehyde for reaction with the amine (*iii*), and that the transfer of the oxygen atom from the carbon to Ti(IV) makes equilibrium *iv* less unfavourable.

The fast[17] and irreversible step *v* further contributes to shift the total equilibrium to the side of product, rendering the process preparatively advantageous with either formaldehyde, aliphatic or aromatic aldehydes.

Finally, it must be pointed out that, in sharp contrast with the substituent effects found in acid-catalysed condensation of aromatic amines with aromatic aldehydes,[18] the yields of **3s**,**t** are higher than those of **3r** and **3u** (Table 3); however, this experimental finding strongly supports the rationale of Scheme 3.

Under our conditions, an electron-releasing group on the aromatic ring of the aldehyde would increase the equilibrium concentration of the Ti(IV)-complexed aldehyde and would favour the Ti(IV)-assisted loss of water from the intermediate hemiaminal (Scheme 3, paths *iii* and *iv*, ArCHO instead of HCHO).

Beside, the increased basic strength of the imine, brought about by an electron-donor substituent on the aldehyde,[19] would increase the equilibrium concentration of the Ti(IV)-complexed imine, which is the reactive counterpart of the incoming nucleophilic radical (Scheme 1).

3. Conclusions

The success of this one-pot reaction is mainly due to the multiple role played by titanium, which in its lower oxidation state acts both as a radical initiator and as a radical terminator, while in its higher oxidation state acts as a Lewis acid and dehydrating agent providing a relatively high concentration of the iminium salts (or of complexed aldimines), even under aqueous conditions.

Despite the simplicity of 1,2-aminoethers moiety, the synthesis of these compounds is often difficult[20,21]and this new method provides an easy entry to both *N*-aryl[21] and *N*-alkyl aminoethers starting from cheap and readily available reagents under very mild reaction conditions. Further studies are currently under investigation with the aim to extend the aminomethylation and aminoalkylation reaction to other nucleophilic radicals.

4. Experimental

4.1. General

All reactions were performed under N_2 at room temperature (20 °C). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C, measured in $CDCl_3$ and chemical shifts were presented in parts per million (δ). The following aqueous solutions were used: 37% solution of formaldehyde (Aldrich); 80% solution of *tert*-butylhydroperoxide (Fluka); 15% solution $TiCl_3$ (C. Erba). Flash column chromatography was performed by using 40–63 μm silica gel packing. Silica gel 60 F_{254} (1 mm) plates were used for PLC.

4.2. Typical procedure for ether addition to formaldehyde-iminium salts formed in situ

t-BuOOH (4 mmol of a 80% aqueous solution), diluted in 5 mL of CH_3COOH and 5 mL of the ether **2** under investigation, was added dropwise in 30 min to a stirred homogeneous solution containing the amine **1** (2 mmol), formaldehyde (7 mmol, ca. 0.56 mL of a 37% aqueous solution) and $TiCl_3$ (8 mmol, ca. 8 mL of a 15 wt % in 30 wt % HCl solution) in: (a) 10 mL of CH_3COOH and 10 mL of THF or Et_2O; (b) 15 mL of 1,4-dioxane. The end of the reaction was shown by a rapid change of colour from blue to yellow. Work up was as follows with low boiling amines **1a**–**b**: the reaction mixtures were directly added to a 30% aqueous NH_3 solution until pH=9 and extracted with Et_2O (3× 50 mL); the combined extracts layers, washed with water and dried over Na_2SO_4, were carefully concentrated in vacuo (20 mmHg) at room temperature; the crude residues left over resulted to be ^{1}H NMR spectroscopically pure **3a**–**e**. Work up was as follows with amines **1c**–**f**: the reaction mixtures were concentrated in vacuo to eliminate most of the ether and CH_3COOH; the crude residues left were dissolved in EtOAc (50 mL) and added a 30% aqueous NH_3 solution basic pH=9; the organic layers were separated and the aqueous layers were further extracted with EtOAc (2×50 mL); the combined organic layers were then washed with water, dried over Na_2SO_4 and concentrated in vacuo. Purification of the resulting crude materials by FCC gave adducts **3** and/or **4**.

4.2.1. Typical procedure for THF addition to aldimines formed in situ (Table 3). The procedure was as above with the exception of the molar ratio *p*-methoxyaniline **1e**/aldehyde employed: (a) 4 mmol of aliphatic aldehydes were reacted with 2 mmol of **1e**; (b) 2 mmol of aromatic aldehydes were reacted with 3 mmol of **1e**. Work up was as the one reported for amines **1c**–**f**.

4.3. Spectroscopic data

4.3.1. Dimethyl-(tetrahydrofuran-2-yl-methyl) amine (3a). The crude residue left over (227 mg) was **3a** (^{1}H NMR purity≥95%, 88% yield, pale yellow oil). IR (liquid film) ν_{max} 3000–2870, 1630, 1069 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.43–1.54 (1H, CH_2, m), 1.81–1.90 (2H, CH_2, m), 1.95–2.03 (1H, CH_2, m), 2.29 (6H, $2CH_3$, s), 2.31 (1H, CH_2–N, dd, J=12.7, 4.4 Hz), 2.43 (1H, CH_2–N, dd, J=12.7, 7.5 Hz), 3.71–3.76 (1H, CH_2–O, m), 3.87 (1H, CH_2–O, ddd, J=8.3, 7.0, 6.5 Hz), 3.98 (1H, CH–O, qd, J=7.5, 4.4 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_2), 30.1 (CH_2), 45.9 ($2CH_3$), 64.1 (CH_2–N), 67.8 (CH_2–O), 76.9 (CH–O) ppm. EIMS (*m*/*z*) 129 (M^+, 6), 58 (M−THF, 100). HRMS calcd for $C_7H_{15}NO$: 129.11536; found 129.11527.

4.3.2. Dimethyl-(1,4-dioxan-2-yl-methyl) amine (3b).[22] The crude residue left over (195 mg) was pure **3b** (^{1}H NMR purity≥95%, 65% yield, pale yellow oil). IR (liquid film) ν_{max} 2960–2854, 1615, 1110 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.22 (1H, CH_2–N, dd, J=12.9, 4.2 Hz), 2.30 (6H, $2CH_3$, s), 2.43 (1H, CH_2–N, dd, J=12.9, 7.5 Hz), 3.28 (1H, CH_2–O, dd, J=11.9, 10.3 Hz), 3.60 (1H, CH_2–O, dd, J=11.9, 3.4 Hz), 3.69–3.80 (5H, $2CH_2$–O+CH–O, m) ppm. ^{13}C NMR ($CDCl_3$) δ 46.0 ($2CH_3$), 60.6 (CH_2–N), 66.5 (CH_2–O), 66.6 (CH_2–O), 69.9 (CH_2–O), 73.2 (CH–O) ppm. EIMS (*m*/*z*) 145 (M^+, 5), 58 (M−1,4-dioxane, 100), 42 (10). HRMS calcd for $C_7H_{15}NO_2$: 145.1103; found 145.1099.

4.3.3. Dimethyl-(2-ethoxypropyl) amine (3c). The crude residue left over (105 mg) was pure **3c** (^{1}H NMR purity≥95%, 40% yield, yellow oil). IR (liquid film) ν_{max} 2960–2852, 1620, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, CH_3, d, J=6.2 Hz), 1.19 (3H, CH_3, t, J=6.7 Hz), 2.24 (1H, CH_2–N, dd, J=12.7, 5.1 Hz), 2.27 (6H, $2CH_3$–N, s), 2.43 (1H, CH_2–N, dd, J=12.7, 6.7 Hz), 3.44–3.51 (1H, CH, m), 3.52–3.62 (2H, CH_2–O, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 18.4 (CH_3), 46.0 ($2CH_3$–N), 63.7 (CH_2–O), 65.3 (CH_2–N), 73.2 (CH–O) ppm. EIMS (*m*/*z*) 131 (M^+, 2), 58 (M−Et_2O, 100). HRMS calcd for $C_7H_{17}NO$: 131.13101; found 131.13098. According to the literature procedure,[23] quaternisation of **3c** with MeI in anhydrous Et_2O afforded the ethyl ether of β-methylcholine (80%) as white crystals: mp 97–99 °C (lit.[23] 99 °C).

4.3.4. Dibutyl-(tetrahydrofuran-2-yl-methyl) amine (3d). The crude residue left over was pure **3d** (235 mg, ^{1}H NMR purity≥95%, 55% yield, colourless oil). IR (liquid film) ν_{max} 2975–2860, 1467, 1077, 1070 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, $2CH_3$, t, J=7.2 Hz), 1.25–1.34 (4H, $2CH_2$, m), 1.37–1.45 (4H, $2CH_2$, m), 1.49–1.58 (1H, CH_2, m), 1.79–1.90 (2H, CH_2, m), 1.93–2.01 (1H, CH_2, m), 2.41–2.57 (6H, $3CH_2N$, m), 3.69–3.74 (1H, CH_2–O, m), 3.82–3.88 (1H, CH_2–O, m), 3.95 (1H, CH–O, quintet, J=6.5 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 14.0 ($2CH_3$), 20.6 ($2CH_2$), 25.4 (CH_2), 29.2 ($2CH_2$), 30.2 (CH_2), 54.6 (CH_2–N), 58.9 (CH_2–N), 67.8 (CH_2–O), 77.8 (CH–O) ppm. EIMS (*m*/*z*) 213 (M^+, 10), 142 (M−THF, 100), 100 (50). HRMS calcd for $C_{13}H_{27}NO$: 213.2093; found 213.2090.

4.3.5. Dibutyl-(1,4-dioxan-2-yl-methyl) amine (3e). The crude residue left over was pure **3e** (252 mg, ^{1}H NMR purity≥95%, 55% yield, pale yellow oil). IR (liquid film) ν_{max} 2955–2790, 1462, 1107 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.90 (6H, $2CH_3$, t, J=7.2 Hz), 1.23–1.34 (4H, $2CH_2$, m), 1.34–1.43 (4H, $2CH_2$, m), 2.33–2.49 (6H, $3CH_2N$, m), 3.27 (1H, CH_2–O, dd, J=11.6, 9.8 Hz), 3.55–3.64 (1H, CH–O, m), 3.65–3.77 (4H, $2CH_2$–O, m), 3.85 (1H, CH_2O, dd, J=11.6, 2.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 14.0 ($2CH_3$), 20.6 ($2CH_2$), 29.3 ($2CH_2$), 54.9 (CH_2–N), 55.9 (CH_2–N), 66.6 (CH_2–O), 66.8 (CH–O), 70.7 (CH_2–O), 74.0 (CH–O) ppm. EIMS (*m*/*z*) 229 (M^+, 10), 142 (M−1,4-dioxane, 100), 100 (50). HRMS calcd for $C_{13}H_{27}NO_2$: 229.2042; found 229.2038.

4.3.6. *N*-Benzyl-*N*-(tetrahydrofuran-2-yl-methyl)-*N*-methyl amine (3f). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3f** (246 mg, 60% yield, colourless oil). IR (liquid film) ν_{max} 2945–2788, 1495, 1453, 1066, 739, 698 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.48–1.57 (1H, CH_2, m), 1.79–1.87 (2H, CH_2, m), 1.93–2.01 (1H, CH_2, m), 2.29 (3H, N–CH_3, s), 2.47 (1H, CH_2–N, dd, J=12.9, 4.9 Hz), 2.53 (1H, CH_2–N, dd, J=12.9, 6.7 Hz), 3.55 (1H, CH_2–N, d, J=12.93 Hz), 3.62 (1H, CH_2–N, d, J=12.93 Hz), 3.70–3.75 (1H, CH_2–O, m), 3.81–3.87 (1H, CH_2–O, m), 4.02–4.09 (1H, CH_2–O, m),

7.21–7.34 (5H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 25.4 (CH_2), 30.2 (CH_2), 42.9 (CH_3–N), 61.6 (CH_2–N), 62.7 (CH_2–N), 67.9 (CH_2–O), 77.4 (CH–O), 126.9 (CH), 128.1 (2CH), 129.1 (2CH), 138.8 (C) ppm. EIMS (*m*/*z*) 205 (M^+, 10), 134 (M−THF, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{19}NO$: 205.1467; found 205.1464.

4.3.7. *N*-Benzyl-*N*-(1,4-dioxan-2-yl-methyl)-*N*-methylamine (3g). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3g** (332 mg, 75% yield, yellow oil). IR (liquid film) ν_{max} 2955–2790, 1495, 1452, 1119, 1107, 741, 699 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.25 (3H, CH_3, s), 2.33 (1H, CH_2, dd, J=12.9, 5.7 Hz), 2.45 (1H, CH_2, dd, J=12.9, 6.2 Hz), 3.24 (1H, CH_2–O, dd, J=11.4, 9.8 Hz), 3.47 (1H, CH_2–Ph, AB system, J=13.4 Hz), 3.55 (1H, CH–O, m), 3.56 (1H, CH_2–Ph, AB system, J=13.4 Hz), 3.64–3.82 (5H, 3CH_2–O, m), 7.2–7.26 (1H, Ph H, m), 7.26–7.31 (4H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 43.1 (CH_3–N), 58.2 (CH_2–N), 62.8 (CH_2–N), 66.4 (CH_2–O), 66.6 (CH_2–O), 70.16 (CH_2–O), 73.5 (CH–O), 126.9 (CH), 128.1 (CH), 128.9 (3CH), 138.6 (C) ppm. EIMS (*m*/*z*) 221 (M^+, 5), 134 (M−1,4-dioxane, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{19}NO_2$: 221.14158; found 221.14141.

4.3.8. *N*-Benzyl-*N*-(2-ethoxypropyl)-*N*-methylamine (3h). Purification of the crude residue by flash column chromatography ($CHCl_3$ and then EtOAc) gave **3h** (224 mg, 54% yield, yellow oil). IR (liquid film) ν_{max} 2989–2868, 1494, 1453, 1120, 740, 700 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.15 (3H, CH_3, d, J=6.2 Hz), 1.18 (3H, CH_3, t, J=7.0 Hz), 2.23 (3H, N–CH_3, s), 2.34 (1H, CH_2–Ph, dd, J=12.7, 5.9 Hz), 2.51 (1H, CH_2–Ph, dd, J=12.7, 6.0 Hz), 3.47–3.60 (5H, CH–O+CH_2O+CH_2–N, m), 7.19–7.23 (1H, Ph H, m), 7.26–7.33 (4H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.63 (CH_3), 18.6 (CH_3), 43.0 (N–CH_3), 62.9 (CH_2–N), 63.0 (CH_2–N), 63.8 (CH_2–O), 73.6 (CH–O), 126.8 (CH), 128.0 (2CH), 128.9 (2CH), 139.3 (C) ppm. EIMS (*m*/*z*) 207 (M^+, 5), 134 (M−Et_2O, 80), 91 ($PhCH_2$, 100). HRMS calcd for $C_{13}H_{21}NO$: 207.16231; found 207.16225.

4.3.9. *N*-Methyl-*N*-(tetrahydrofuran-2-yl-methyl) aniline (3i). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 9:1) gave **3i** (260 mg, 68% yield, pale yellow oil). IR (liquid film) ν_{max} 2941–2869, 1599, 1507, 1369, 1067, 747, 692 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.53–1.62 (1H, CH_2, m), 1.80–2.0 (3H, 2CH_2, m), 2.99 (3H, N–CH_3, s), 3.40 (2H, CH_2–N, d, J=5.7 Hz), 3.74 (1H, CH_2–O, td, J=8.2, 6.2 Hz), 3.88 (1H, CH_2–O, td, J=8.2, 6.2 Hz), 4.11 (1H, CH–O, quintet, J=5.7 Hz), 6.69 (1H, Ph H, t, J=7.2 Hz), 6.74 (2H, Ph H, d, J=8.0 Hz), 7.21 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 29.6 (CH_2), 39.2 (CH_3–N), 57.1 (CH_2–N), 67.8 (CH_2–O), 77.7 (CH–O), 112.3 (2CH), 116.4 (CH), 129.1 (2CH), 149.5 (C) ppm. EIMS (*m*/*z*) 191 (M^+, 15), 120 (M−THF, 100), 104 (10), 77 (20). HRMS calcd for $C_{12}H_{17}NO$: 191.13101; found 191.13095.

4.3.10. *N*-(1,4-Dioxan-2-yl-methyl)-*N*-methyl-*N*-phenylamine (3j). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 8.5:1.5) gave **3j** (290 mg, 70% yield, yellow oil). IR (liquid film) ν_{max} 2957, 2854, 1599, 1506, 1110, 1107, 746, 693 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.94 (3H, N–CH_3, s), 3.27 (1H, CH_2, AB system, J=15.2, 5.9 Hz), 3.34 (1H, CH_2, AB system, J=15.2, 5.9 Hz), 3.35 (1H, CH_2–O, dd, J=11.4, 9.8 Hz), 3.55–3.78 (6H, 2CH_2–O+2CH–O, m), 6.69–6.72 (3H, Ph H, m), 7.19–7.23 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 39.4 (CH_3), 54.3 (CH_2–N), 66.4 (CH_2–O), 66.6 (CH_2–O), 69.7 (CH_2–O), 73.9 (CH–O), 112.3 (2CH), 116.6 (CH), 129.1 (2CH), 149.3 (C) ppm. EIMS (*m*/*z*) 207 (M^+, 20), 120 (M−1,4-dioxane, 100), 104 (10), 77 (20). HRMS calcd for $C_{12}H_{17}NO_2$: 207.12593; found 207.12580.

4.3.11. *N*-(2-Ethoxypropyl)-*N*-methyl-*N*-phenylamine (3k). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 95:5) gave **3k** (193 mg, 50% yield, pale yellow oil). IR (liquid film) ν_{max} 2955, 2925, 1506, 1115, 746, 687 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.13 (3H, CH_3, t, J=7.0 Hz), 1.14 (3H, CH_3, d, J=6.2 Hz), 2.98 (3H, CH_3, s), 3.28 (1H, CH_2–N, ABX system, J=15.0, 5.2 Hz), 3.35 (1H, CH_2–N, ABX system, J=15.0, 7.0 Hz), 3.39 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.55 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.69 (1H, CH–O, ddq, J=5.2, 6.2, 7.0 Hz), 6.64–6.70 (3H, Ph H, m), 7.20 (2H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3), 18.1 (CH_3), 39.5 (CH_3), 58.7 (CH_2–N), 64.5 (CH_2–O), 73.6 (CH–O), 111.9 (CH), 115.9 (CH), 129.0 (3CH), 149.3 (C) ppm. EIMS (*m*/*z*) 193 (M^+, 20), 120 (M−Et_2O, 100), 104 (5), 77 (20). HRMS calcd for $C_{12}H_{19}NO$: 193.1466; found 193.1462.

4.3.12. *N*-(4-Methoxyphenyl)-*N*-(1-tetrahydrofuran-2-yl-methyl) amine (3l).[21] Purification of the crude residue by flash column chromatography (hexane/EtOAc, 6:4) gave **3l** (282 mg, 68% yield based on the starting HCHO, 2 mmol, pale yellow oil). IR (liquid film) ν_{max} 3380, 2949–2832, 1514, 1235, 1071, 1037, 820 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.6–1.68 (1H, CH_2, m), 1.87–1.95 (2H, CH_2, m), 1.97–2.03 (1H, CH_2, m), 3.02 (1H, CH_2–N, dd, J=12.1, 3.9 Hz), 3.73 (3H, OCH_3, s), 3.7–3.8 (1H, CH_2–O, m), 3.85–3.90 (1H, CH_2–O, m), 4.07–4.14 (1H, CH–O, m), 6.60 (2H, Ar H, d, J=9.0 Hz), 6.77 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_2), 29.1 (CH_2), 49.3 (CH_2–N), 55.8 (OCH_3), 68.0 (CH_2–O), 77.6 (CH–O), 114.5 (2CH), 114.9 (2CH), 142.6 (C–N), 152.3 (C–O) ppm. EIMS (*m*/*z*) 207 (M^+, 5), 136 (M−THF, 100). HRMS calcd for $C_{12}H_{17}NO_2$: 207.12593; found 207.12582.

4.3.13. *N*-(4-Methoxyphenyl)-*N*,*N*-bis-(tetrahydrofuran-2-yl-methyl) amine (4l). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 6:4) gave **4l** contaminated with **3l**; further purification by PLC (hexane/THF, 9:1) afforded pure **4l** (116 mg, 20% yield based on the starting aniline, 2 mmol, thick oil). ^{1}H NMR ($CDCl_3$) δ 1.51–1.60 (2H, CH_2, m), 1.81–2.0 (6H, 3CH_2, m), 3.42 (4H, 2CH_2, m), 3.71 (2H, 2CH, m), 3.74 (3H, CH_3, s), 3.86 (2H, CH_2, m), 4.08 (2H, CH_2, m), 6.79 (4H, Ar H, s) ppm. ^{13}C NMR ($CDCl_3$) δ 25.5 (2CH_2), 29.7 (CH_2), 29.76 (CH_2), 55.7 (2CH_2–N), 56.6 (OCH_3), 67.8 (2CH_2–O), 77.4 (2CH–O), 114.7 (2CH), 115.3 (2CH), 135.1 (C–N), 151.8 (C–O) ppm. EIMS (*m*/*z*) 291 (M^+, 10), 276 (M−Me, 10), 220 (M−THF, 100). HRMS calcd for $C_{17}H_{25}NO_3$: 291.18344; found 291.18330.

4.3.14. *N*-(1,4-Dioxan-2-yl-methyl)-*N*-(4-methoxyphenyl) amine (3m). Purification of the crude residue by flash

column chromatography (hexane/EtOAc/MeOH, 8:1:1) gave **3m** as a yellow solid, mp 55–58 °C (312 mg, 70% yield based on the starting HCHO, 2 mmol). IR (Nujol) ν_{max} 3375, 2960–2800, 1513, 1240, 1108 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.03 (1H, CH_2–N, dd, J=12.7, 7.2 Hz), 3.11 (1H, CH_2–N, dd, J=12.7, 4.1 Hz), 3.43 (1H, CH_2–O, dd, J=11.6, 10.1 Hz), 3.55–3.65 (2H, CH_2–O, m), 3.73 (3H, OCH_3, s), 3.75–3.83 (4H, $2CH_2$–O, m), 6.58 (2H, Ar H, d, J=9.1 Hz), 6.77 (2H, Ar H, d, J=9.1 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 46.2 (CH_2–N), 55.8 (OCH_3), 66.5 (CH_2–O), 66.7 (CH_2–O), 69.4 (CH_2–O), 73.9 (CH–O), 114.6 (2CH), 115.0 (2CH), 142.2 (C–N), 152.6 (C–O) ppm. EIMS (*m*/*z*) 223 (M^+, 20), 136 (M−1,4-dioxane, 100). HRMS calcd for $C_{12}H_{17}NO_3$: 223.1208; found 223.1210.

4.3.15. *N*,*N*-Bis-(1,4-dioxan-2-yl-methyl)-*N*-(4-methoxyphenyl) amine (4m). Purification of the crude residue by flash column chromatography (hexane/EtOAc/MeOH, 8:1:1) afforded **4m** contaminated with **3m**; further purification by PLC (hexane/THF, 85:15) gave pure **4m** as a white solid, mp 88–93 °C. IR (Nujol) ν_{max} 1513, 1258, 1102 cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.19 (1H, CH_2–N, dd, J=15.0, 5.2 Hz), 3.26–3.36 (5H, m), 3.57–3.68 (6H, m), 3.75 (3H, OCH_3, s), 3.74–3.80 (6H, m), 6.73 (2H, m), 6.82 (2H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 54.4 (CH_2–N), 54.8 (CH_2–N), 55.7 (OCH_3), 66.5 ($2CH_2$–O), 66.6 ($2CH_2$–O), 69.7 (CH_2–O), 69.8 (CH_2–O), 73.4 (CH–O), 73.7 (CH–O), 114.8 (CH), 114.9 (CH), 115.8 (CH), 116.1(CH), 142.7 (C–N), 152.5 (C–O) ppm. EIMS (*m*/*z*) 323 (M^+, 20), 236 (M−1,4-dioxane, 60), 150 (M−2(1,4-dioxane), 100). HRMS calcd for $C_{17}H_{25}NO_5$: 323.17327; found 323.17314.

4.3.16. *N*-(2-Ethoxypropyl)-*N*-(4-methoxyphenyl) amine (3n). Purification of the crude residue by flash column chromatography (hexane/THF, 9:1) gave **3n** (293 mg, 70% yield based on the starting HCHO, 2 mmol, pale yellow oil). IR (liquid film) ν_{max} 3376, 2970–2873, 1515, 1241, 1110 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.195 (3H, CH_3, d, J=6.2 Hz), 1.20 (3H, CH_3, t, J=7.0 Hz), 2.98 (1H, CH_2–N, dd, J=12.4, 7.2 Hz), 3.14 (1H, CH_2–N, dd, J=12.4, 3.9 Hz), 3.42 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.60 (1H, CH_2–O, qd, J=7.0, 9.3 Hz), 3.63–3.69 (1H, CH–O, m), 3.73 (3H, OCH_3, s), 6.59 (2H, Ar H, d, J=8.8 Hz), 6.77 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 17.8 (CH_3), 50.4 (CH_2–N), 55.7 (OCH_3), 63.8 (CH_2), 73.5 (CH–O), 114.5 (2CH), 114.9 (2CH), 142.6 (C–N), 152.2 (C–O) ppm. EIMS (*m*/*z*) 209 (M^+, 10), 194 (M^+-CH_3, 5), 136 (M−Et_2O, 100). HRMS calcd for $C_{12}H_{19}NO_2$: 209.1415; found 209.1420.

4.3.17. *N*,*N*-Bis-(2-ethoxypropyl)-*N*-(4-methoxyphenyl) amine (4n). Purification of the crude residue by flash column chromatography (hexane/THF, 9:1) afforded **4n** as a thick oil (first eluted fraction). IR (liquid film) ν_{max} 2973, 2873, 1514, 1241, 1102, 1042 cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.11–1.15 (12H, $4CH_3$, m), 3.21 (1H, CH_2–N, dd, J=15.0, 4.9 Hz), 3.30 (1H, CH_2–N, dd, J=15.0, 5.4 Hz), 3.36–3.58 (6H, CH_2–N+$2CH_2$–O, m), 3.67 (2H, 2CH, sextuplet, J=6.1 Hz), 3.74 (3H, OCH_3, s), 6.69 (2H, Ar H, m), 6.80 (2H, Ar H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 ($2CH_3$), 18.3 ($2CH_3$), 55.7 (OCH_3), 58.4 (CH_2–N), 58.7 (CH_2–N), 64.4 (CH_2), 64.41 (CH_2), 73.1 (CH–O), 73.3 (CH–O), 114.3 (2CH), 114.8 (2CH), 143.1(C–N), 151.2 (C–O) ppm. EIMS (*m*/*z*) 295 (M^+, 20), 222 (M−Et_2O, 100), 178 (80). HRMS calcd for $C_{12}H_{29}NO_3$: 295.2147; found 295.2144.

4.3.18. Benzyl-*N*,*N*-bis-(1,4-dioxan-2-yl-methyl) amine (4p). Purification of the crude residue by flash column chromatography (hexane/EtOAc, 8:2) afforded **4p** (184 mg, 30% yield, thick oil). IR (liquid film) ν_{max} 2955, 2852, 1495, 1452, 1266, 1107 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.45–2.60 (4H, $2CH_2$–N, m), 3.19 (1H, CH_2–N, dd, J=11.4, 10.6 Hz), 3.25 (1H, CH_2–N, dd, J=11.4, 9.8 Hz), 3.50–3.58 (2H, 2CH, m), 3.64–3.82 (12H, $6CH_2O$, m), 7.22–7.33 (5H, Ph H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 56.2 (2CH–N), 60.4 (CH_2–N), 66.5 ($2CH_2$–O), 66.7 ($2CH_2$–O), 70.3 ($2CH_2$–O), 127.1 (CH), 128.3 (2CH), 129.9 (CH), 139.1 (C) ppm. EIMS (*m*/*z*) 307 (M^+, 10), 220 (M−1,4-dioxane, 80), 134 (M−2(1,4-dioxane), 50), 91 ($PhCH_2$, 100). HRMS calcd for $C_{17}H_{25}NO_4$: 307.1783; found 307.1780.

4.3.19. *N*-(4-Methoxyphenyl)-*N*-(1-tetrahydrofuran-2-yl-ethyl) amine (3q).[8e] Purification of the crude reaction mixture by FCC (hexane/EtOAc, 7:3) afforded **3q** (354 mg, 80%) as a 1:1 mixture of diastereomers. Less polar isomer: ^1H NMR ($CDCl_3$) δ 1.18 (3H, CH_3, d, J=6.5 Hz), 1.71–1.79 (1H, CH_2, m), 1.85–1.95 (3H, $2CH_2$, m), 3.40 (1H, CH–N, dq, J=4.6, 6.5 Hz), 3.5 (1H, NH, br), 3.73 (3H, OCH_3, s), 3.76 (1H, CH–O, m), 3.88 (2H, CH_2–O, m), 6.60 (2H, Ar H, d, J=8.8 Hz), 6.76 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 17.8 (CH_3), 26.1 (CH_2), 28.2 (CH_2), 52.8 (CH–N), 55.8 (OCH_3), 68.4 (CH_2–O), 82.3 (CH–O), 115.0 (2CH), 115.2 (2CH), 141.4 (C–N), 152.2 (C–O) ppm. EIMS *m*/*z* 221 (M^+, 15), 150 (M−THF, 100). HRMS calcd for $C_{13}H_{19}NO_2$: 221.1416; found 221.1415. More polar isomer: ^1H NMR ($CDCl_3$) δ 1.14 (3H, CH_3, d, J=6.5 Hz), 1.66–1.74 (1H, CH_2, m), 1.84–1.98 (3H, $2CH_2$, m), 3.2 (1H, NH, br), 3.44 (1H, CH–N, dq, J=4.4, 6.5 Hz), 3.73 (3H, OCH_3, s), 3.77 (1H, CH–O, m), 3.83–3.93 (2H, CH_2–O, m), 6.60 (2H, Ar H, d, J=8.8 Hz), 6.75 (2H, Ar H, d, J=8.8 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 15.7 (CH_3), 25.9 (CH_2), 28.0 (CH_2), 53.2 (CH–N), 55.7 (OCH_3), 68.4 (CH_2–O), 81.9 (CH–O), 114.9 (2CH), 115.4 (2CH), 141.6 (C–N), 152.2 (C–O) ppm. EIMS (*m*/*z*) 221 (M^+, 12), 150 (M−THF, 100).

4.3.20. *N*-[4-Bromophenyl(tetrahydrofuran-2-yl)methyl]-*N*-(4-methoxyphenyl) amine (3r).[8e] Purification by FCC (hexane/EtOAc, 75:25) gave **3r** (456 mg, 63%) as a 1:1 mixture of diastereomers, which were separated by PLC (hexane/EtOAc, 8:2). Less polar isomer: ^1H NMR ($CDCl_3$) δ 1.73–1.98 (4H, $2CH_2$, m), 3.68 (3H, OCH_3, s), 3.79 (1H, m), 3.90 (1H, t, J=6.2 Hz), 3.95 (1H, q, J=6.8 Hz), 4.10 (1H, d, J=6.8 Hz), 4.5 (1H, NH, br), 6.44 (2H, Ar′H, d, J=8.6 Hz), 6.66 (2H; Ar′H, d, J=8.6 Hz), 7.29 (2H, Ar H, d, J=8.6 Hz), 7.44 (2H, Ar H, d, J=8.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 28.6 (CH_2), 55.6 (OCH_3), 62.6 (CH–N), 68.5 (CH_2–O), 82.5 (CH–O), 114.6 (2CH), 115.3 (2CH), 121.1 (C–Br), 129.1 (2CH), 131.6 (2CH), 140.6 (C), 141.1 (C–N), 152.3 (C–O) ppm. EIMS *m*/*z* 363–361 (M^+, 10), 292–290 (M−THF, 100). HRMS calcd for $C_{18}H_{20}NO_2Br$: 361.0677; found 361.0679. More polar isomer: ^1H NMR ($CDCl_3$) δ 1.57–1.82 (4H, $2CH_2$, m), 3.66 (3H, OCH_3, s), 3.79 (2H, OCH_2, m), 4.17 (1H, OCH, m), 4.31 (1H, CH–N, d, J=4.1 Hz), 4.4–4.6

(1H, NH, br), 6.45 (2H, Ar′H, d, J=8.5 Hz), 6.65 (2H, Ar′H, d, J=8.5 Hz), 7.24 (2H, Ar H, d, J=8.0 Hz), 7.40 (2H, Ar H, d, J=8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.5 (CH_2), 27.3 (CH_2), 55.6 (OCH_3), 61.3 (CH–N), 68.7 (CH_2–O), 81.8 (CH–O), 114.7 (2CH), 115.4 (2CH), 121 (C–Br), 129.5 (2CH), 131.4 (2CH), 139.3 (C), 140.9 (C–N), 152.4 (C–O) ppm. EIMS (*m*/*z*) 363–361 (M^+, 20), 292–290 (M−THF, 100).

4.3.21. *N*-(4-Methoxyphenyl)-*N*-[4-methylphenyl-(tetrahydrofuran-2-yl)methyl] amine (3s).[8e] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3s** (440 mg, 74%) as a 1:1 mixture of diastereomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.73–1.93 (4H, $2CH_2$, m), 2.30 (3H, CH_3, s), 3.66 (3H, OCH_3, s), 3.79 (1H, CH_2, m), 3.90 (1H, CH_2, m), 4.01 (1H, CH, q, J=6.7 Hz), 4.09 (1H, CH, d, J=6.7 Hz), 6.50 (2H, Ar′H, d, J=9.0 Hz), 6.65 (2H, Ar′H, d, J=9.0 Hz), 7.11 (2H, Ar H, d, J=8.0 Hz), 7.28 (2H, Ar H, d, J=8.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 25.7 (CH_2), 28.8 (CH_2), 55.7 (OCH_3), 63.3 (CH–N), 68.5 (OCH_2), 82.9 (OCH), 114.7 (2CH), 115.6 (2CH), 127.3 (2CH), 129.3 (2CH), 136.9 (C), 138.4 (C), 141.6 (C–N), 152.4 (C–O) ppm. EIMS (*m*/*z*) 297 (M^+, 12), 226 (M−THF, 100). HRMS calcd for $C_{19}H_{23}NO_2$: 297.1728; found 297.1730. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.54–1.68 (1H, CH_2, m), 1.69–1.87 (3H, CH_2+CH, m), 2.30 (3H, CH_3, s), 3.66 (3H, OCH_3, s), 3.7–3.85 (2H, CH_2, m), 4.22 (1H, OCH, m), 4.33 (1H, CH–N, d, J=4.2 Hz), 6.51 (2H, Ar′H, d, J=8.9 Hz), 6.65 (2H; Ar′H, d, J=8.9 Hz), 7.09 (2H, Ar H, d, J=7.7 Hz), 7.25 (2H, Ar H, d, J=7.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 21.1 (CH_3), 25.6 (CH_2), 27.1 (CH_2), 55.6 (OCH_3), 61.7 (CH–N), 68.7 (OCH_2), 82.1 (OCH), 114.5 (2CH), 115.6 (2CH), 127.6 (2CH), 129.0 (2CH), 136.7 (2C), 141.0 (C–N), 152.3 (C–O) ppm. EIMS (*m*/*z*) 297 (M^+, 10), 226 (M−THF, 100).

4.3.22. *N*-(4-Methoxyphenyl)-*N*-[4-methoxyphenyl-(tetrahydrofuran-2-yl)methyl] amine (3t).[8c] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3t** (500 mg, 80%) as a 1:1 mixture of diastereomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.74–1.81 (2H, CH_2, m), 1.82–1.95 (2H, CH_2, m), 3.68 (3H, OCH_3, s), 3.79 (3H, OCH_3, s), 3.79–3.84 (1H, CH_2, m), 3.87–3.94 (1H, CH_2, m), 3.99 (1H, CH, q, J=6.7 Hz), 4.08 (1H, CH, d, J=6.7 Hz), 4.5 (1H, NH, br s), 6.50 (2H, Ar H, d, J=8.9 Hz), 6.67 (2H, Ar H, d, J=8.9 Hz), 6.86 (2H, Ar′ H, d, J=8.7 Hz), 7.33 (2H, Ar H, d, J=8.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 28.7 (CH_2), 55.2 (OCH_3), 55.7 (OCH_3), 62.7 (CH–N), 68.4 (OCH_2), 83.1 (OCH), 114.0 (2CH), 114.7 (2CH), 115.2 (2CH), 128.3 (2CH), 133.8 (C), 142.2 (C–N), 152.1 (C–O) ppm. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.58–1.66 (1H, CH_2, m), 1.72–1.80 (3H, $2CH_2$, m), 3.68 (3H, OCH_3, s), 3.74–3.83 (2H, CH_2, m), 3.78 (3H, OCH_3, s), 4.20 (1H, CH, dt, J=4.2, 7.2 Hz), 4.33 (1H, CH, d, J=4.2 Hz), 4.4 (1H, NH, br s), 6.49 (2H, Ar H, d, J=9.1 Hz), 6.67 (2H, Ar H, d, J=9.1 Hz), 6.84 (2H, Ar′ H, d, J=8.7 Hz), 7.29 (2H, Ar′ H, d, J=8.7 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 27.2 (CH_2), 55.1 (OCH_3), 55.7 (OCH_3), 61.0 (CH–N), 68.7 (OCH_2), 82.3 (OCH), 113.7 (2CH), 114.6 (2CH), 115.2 (2CH), 128.7 (2CH), 132.3 (C), 141.7 (C–N), 152.0 (C–O), 158.7 (C=O) ppm. EIMS (*m*/*z*) 313 (M^+, 10), 242 (M−THF, 100).

4.3.23. *N*-(4-Methoxyphenyl)-*N*-[phenyl(tetrahydrofuran-2-yl)methyl] amine (3u).[8c,e] Purification by FCC (hexane/EtOAc, 8:2) of the crude mixture gave **3u** (400 mg, 70%) as a 1:1 mixture of diastereomers. Less polar isomer: yellow solid mp 74–5 °C (hexane/Et_2O). ^{1}H NMR ($CDCl_3$) δ 1.7–2.0 (4H, $2CH_2$, m), 3.67 (3H, OCH_3, s), 3.80 (1H, OCH_2, m), 3.90 (1H, OCH_2, m), 4.04 (1H, OCH, m), 4.13 (1H, PhCH, d, J=6.9 Hz), 4.7 (1H, NH, br), 6.51 (2H, Ar′H, d, J=8.8 Hz), 6.65 (2H; Ar′H, d, J=8.8 Hz), 7.24–7.35 (3H, Ph H, m), 7.41 (2H, Ph H, m) ppm. HRMS calcd for $C_{18}H_{21}NO_2$: 283.1572; found 283.1568. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.53–1.67 (1H, CH_2, m), 1.70–1.86 (3H, $2CH_2$, m), 3.67 (3H, OCH_3, s), 3.78 (2H, OCH_2, m), 4.26 (1H, OCH, m), 4.37 (1H, PhCH, d, J=4.0 Hz), 4.7 (1H, NH, br), 6.54 (2H, Ar′H, d, J=8.8 Hz), 6.65 (2H; Ar′H, d, J=8.8 Hz), 7.24–7.35 (3H, Ph H, m), 7.36–7.40 (2H, Ph H, m) ppm. EIMS (*m*/*z*) 283 (M^+, 15), 212 (M−THF, 100).

4.3.24. *N*-[Cyclohexyl(tetrahydrofuran-2-yl)methyl]-*N*-(4-methoxyphenyl) amine (3v).[8c,e] Purification by FCC (hexane/EtOAc, 9:1) afforded **3v** (463 mg, 80%) as a 1:1 mixture of diastereoisomers. Less polar isomer: ^{1}H NMR ($CDCl_3$) δ 0.98–1.24 (5H, cyclohex, m), 1.55–1.64 (2H, m), 1.68–1.75 (3H, m), 1.80–1.86 (5H, m), 3.06 (1H, CH–N, dd, J=2.1, 6.3 Hz), 3.73 (3H, OCH_3, s), 3.75 (1H, CH, m), 3.87 (1H, CH_2, m), 4.11 (1H, CH_2, m), 6.55 (2H, Ar H, d, J=9.0 Hz), 6.73 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 26.0 (CH_2), 26.3 (CH_2), 26.4 ($2CH_2$), 29.2 (CH_2), 30.1 (CH_2), 30.2 (CH_2), 41.9 (CH), 55.7 (OCH_3), 61.3 (CH–N), 68.8 (CH_2–O), 78.6 (CH–O), 113.6 (CH), 113.8 (CH), 114.8 (CH), 114.9 (CH), 143.0 (C–N), 151.3 (C–O) ppm. EIMS (*m*/*z*) 289 (M^+, 12), 218 (M−THF, 100), 136 (30), 122 (10). HRMS calcd for $C_{18}H_{27}NO_2$: 289.2042; found 289.2039. More polar isomer: ^{1}H NMR ($CDCl_3$) δ 1.02–1.15 (2H, qd, J=12.3, 3.3 Hz), 1.18–1.31 (3H, m), 1.62–1.75 (6H, cyclohex, m), 1.75–1.96 (4H, $2CH_2$, m), 3.17 (1H, CH–N, dd, J=3.4, 6.1 Hz), 3.73 (4H, CH+OCH_3, m+s), 3.83 (1H, CH, m), 3.90 (1H, CH, m), 6.59 (2H, Ar H, d, J=9.0 Hz), 6.73 (2H, Ar H, d, J=9.0 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 25.8 (CH_2), 26.3 (CH_2), 26.5 ($2CH_2$), 27.4 (CH_2), 28.8 (CH_2), 30.9 (CH_2), 40.4 (CH), 55.8 (OCH_3), 63.1 (CH–N), 68.0 (CH_2–O), 80.0 (CH–O), 114.9 (4CH), 141 (C–N), 151.9 (C–O) ppm. EIMS (*m*/*z*) 289 (M^+, 10), 274 (M−CH_3, 8), 218 (M−THF, 100), 136 (30), 122 (15).

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds **3a**–**n** and **4l**–**p**) associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.014.

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Synthesis of novel 5-hydroxyalkenylphosphonates by addition of aromatic aldehydes to zirconacyclopentenylphosphonates

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Abstract—Novel 5-hydroxyvinylphosphonates were obtained in a regio- and stereoselective manner, by addition of aromatic aldehydes to zirconacyclopentenylphosphonates in the presence of $AlMe_3$, in 68–82% isolated yields. The reaction is specific for aromatic aldehydes.

1. Introduction

Vinylphosphonates are valuable compounds because of their widespread applications. They are used as intermediates to prepare biologically and pharmacologically active compounds,[1–5] are present in polymers,[6] in agriculture,[7] in flame retardants,[8] and are employed in further organic transformations.[9] In the last few years, we reported the synthesis of several classes of vinylphosphonates utilizing zirconacyclopropenylphosphonates, titanacyclopropenylphosphonates, and zirconacyclopentenylphosphonates.[10] Owing to their importance, vinylphosphonates are also attainable by numerous other methods.[11]

2. Results and discussion

It has been established that when an alkyne is added to the Negishi reagent (Cp_2ZrCl_2/2 *n*-BuLi), ligand exchange occurs to produce the active zirconacyclopropenyl intermediates.[12] On the other hand, alkynes insert into the reagent (Cp_2ZrCl_2/2-EtMgBr) to form zirconacyclopentenes.[13] Utilizing zirconacyclopentenes, we reported the synthesis of 5-hydroxyalkenylboranates through addition of aldehydes to zirconacyclopentenylboronates.[14] Surprisingly, unlike zirconacyclopentenylboronates and other simple alkynes, all efforts to date to implement these conditions to obtain 5-hydroxyalkenylphosphonates from zirconacyclopentenylphosphonates **2** were unsuccessful. Various promoters including, Pd, Ni, Co, Rh, Pt, Zn etc. did not improve the reaction. However, we found that the presence of 2 equiv of AlR_3 (R=Me, Et) or $CeCl_3$ and 1.2 equiv of an aromatic aldehyde are essential to obtain the desired 5-hydroxyvinylphosphonates **5** (Scheme 1). Using less than 2 equiv of the reagent significantly reduced the yield of **5**. The reagents $AlMe_3$, $AlEt_3$, and $CeCl_3$ were all similar with respect to the yields and selectivity of the reaction. In addition, the reaction time was crucial. Stirring the reaction for longer than 1 h at room temperature resulted in the formation of unknown side products.

In a typical experiment, the reaction mixture was extracted into ether and separated on silica gel-chromatography to afford pure **5**. All products were analyzed by NMR spectroscopy, GC–MS, and elemental analysis. Unexpectedly, all efforts to produce compound **5** from aliphatic aldehydes were unsuccessful; the ethylated product, alkenylphosphonate **4**, was obtained together with the alkylated alcohol product of the corresponding aldehydes (Scheme 1). Yields for **5** were obtained in the range of 68–82%, which proceeded in a regio- and stereoselective manner. The insertion of the aldehyde occurrs on C4 relative to phosphorous (Table 1). No other regio- and stereo-isomers were detected. The regio- and stereoselectivity of the products were determined by the ^1H NMR chemical shifts and spin–spin coupling constants. Deuterium labeling of the zirconacycloheptenylphosphonates **3a** showed the incorporation of one deuterium atom in the product **6** (65% yield). Presumably, the two zirconium bonds in **3** were replaced by deuterium atoms, but during the isolation process, the oxygen deuterium bond was hydrolyzed to give a OH bond (Eq. 1).

Keywords: Vinylphosphonates; 5-Hydroxyalkenylphosphonates; Zirconacyclopentene.
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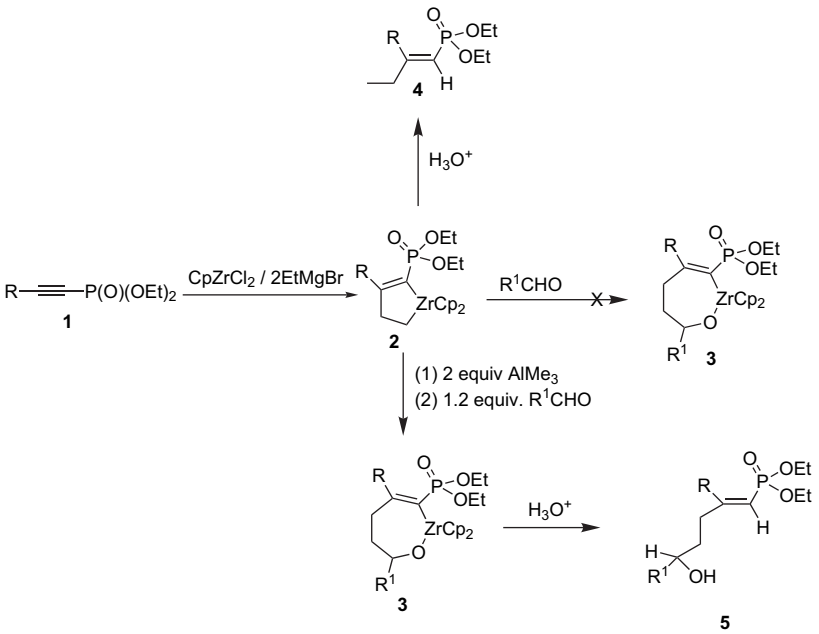
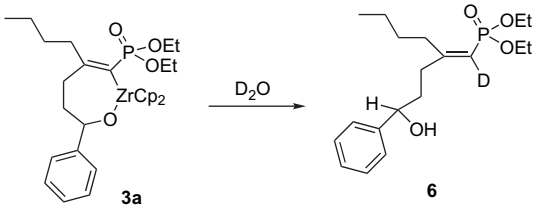


Scheme 1. Addition of aromatic aldehydes to zirconacyclopentenylphosphonates in the presence of $AlMe_3$ to form 5-hydroxyalkenylphosphonates.

Table 1. Synthesis of 5-hydroxyvinylphosphonates **5**, by addition of aromatic aldehydes to zirconacyclopentenylphosphonates in the presence of $AlMe_3$

Entry	Aldehyde	R	R^1	Conversion[a]/yield[b]
3a	Benzaldehyde	*n*-Bu	Phenyl	95/75
3b	*p*-Fluorobenzaldehyde	*n*-Bu	*p*-Fluoro-phenyl	95/72
3c	*o*,*p*-Dichlorobenzaldehyde	*n*-Bu	*o*,*p*-Dichloro-phenyl	95/81
3d	*p*-Nitrobenzaldehyde	*n*-Bu	*p*-Nitro-phenyl	95/82
3e	*o*-Tolualdehyde	*n*-Bu	*o*-Tolyl	95/76
3f	*p*-Tolualdehyde	*n*-Bu	*p*-Tolyl	95/80
3g	*trans*-Cinnamaldehyde	*n*-Bu	*trans*-Cinnamyl	95/80
3h	*p*-Anisaldehyde	*n*-Bu	*p*-Anisyl	95/80
3i	Benzaldehyde	Ph	Phenyl	92/73
3j	*o*,*p*-Dichlorobenzaldehyde	Ph	*o*,*p*-Dichloro-phenyl	90/68

[a] Determined by ^{31}P NMR.
[b] Isolated yield after chromatography.



(1)

In conclusion, hydroxyvinylphosphonates are interesting intermediates for the synthesis of phosphorus containing amino acids, which are known to be active against epilepsy and Parkinson's disease,[15,16] and in organic transformations.[17] In the last few years, we reported the syntheses of 2- and 3-hydroxyvinylphosphontes based on the addition of aldehydes and ketones to zirconacyclopropenylphosphonates, and titanacyclopropenphosphonates, respectively.[18] Also, other protocols have been emerged.[19] However, to the best of our knowledge, the synthesis of 5-hydroxyalkenylphosphonate, has not been previously described. The reaction is general for aromatic aldehydes, and proceeded smoothly for several substituted aromatic aldehydes on various positions of the aromatic ring to give novel 5-hydroxyalkenylphosphonate **5** in high yield and in a regio- and stereoselective manner.

3. Experimental

3.1. General

All reactions were carried out under a nitrogen atmosphere, using vacuum line, a glove-box and schlenk techniques. Solvents were purified by distillation from appropriate drying agents (sodium/benzophenone) under a nitrogen atmosphere. ^1H NMR (300 MHz), ^{13}C NMR (75 MHz), and ^{31}P NMR (121.4 MHz) were recorded in $CDCl_3$. GC–MS analyses were performed on HP GC–MS instrument (Model GCD PLUS), equipped with an EI detector and 30 m methyl silicone column.

3.2. Procedure for the synthesis of 5

To (0.306 g, 1.05 mmol) of zirconocene dichloride dissolved in THF (6 ml) at −78 °C was added 2 M EtMgBr in THF (1.05 ml, 2.1 mmol) dropwise in a 25 ml round-bottom flask.

After stirring for 5 min at −78 °C, 1 mmol of alkynylphosphonate was added and the reaction was gradually warmed to 25 °C and stirred for 3 h. Then the reaction was cooled to 0 °C and $AlMe_3$ (2 mmol) was added under a dry atmosphere, followed by the addition of aldehyde (1.2 mmol). The reaction was then warmed to 25 °C. After stirring for 1 h, the reaction was quenched with dilute HCl solution. The oily product was extracted by Et_2O (2×10 ml) separated by silica gel column chromatography (50% petroleum ether/50% ethyl acetate), and was analyzed by GC–MS, elemental analysis, and NMR spectroscopy.

3.2.1. (*E*)-Diethyl 2-(3-hydroxy-3-phenylpropyl)hex-1-enylphosphonate (5a). ^{1}H NMR (300 MHz): δ 0.86 (t, 3H, J_{HH}=6.9 Hz), 1.28 (dt, 6H, J_{HH}=6.9 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.55 (overlap, 4H), 1.80–1.95 (overlap, 2H), 2.21 (m, 1H), 2.35 (m, 1H), 2.45 (br t, 2H, J_{HH}=6.6 Hz), 2.51 (br s, 1H), 3.95–4.15 (m, 4H), 4.62 (br t, 1H, J_{HH}=6.5 Hz), 5.35 (d, 1H, $^2J_{PH}$=18.5 Hz), 7.20–7.50 (overlap, 5H); ^{31}P NMR (121.4 MHz): δ 19.65; ^{13}C NMR (75.5 MHz): δ 13.8, 16.0 (d, $^3J_{PC}$=6.9 Hz), 22.7, 30.5 (d, $^4J_{PC}$=2.0 Hz), 33.6 (d, $^3J_{PC}$=7.2 Hz), 34.3 (d, $^3J_{PC}$=22.7 Hz), 36.9, 61.1 (d, $^2J_{PC}$=5.7 Hz), 73.5, 110.9 (d, $^1J_{PC}$=190.0 Hz), 125.7, 127.4, 128.3, 144.6, 167.2 (d, $^2J_{PC}$=7.2 Hz); MS(EI): *m*/*z* (%) 354 (0.9), 336 (3.9), 297 (15.7), 248 (35.29), 235 (100), 206 (26.5), 169 (32.35), 107 (24.5), 91 (47.1), 79 (51.0), 77 (34.3), 29 (14.7); Anal. Calcd for $C_{19}H_{31}O_4P$: C, 64.39; H, 8.82; P, 8.74. Found: C, 64.22; H, 8.97; P, 8.71.

3.2.2. (*E*)-Diethyl 2-(3-(4-fluorophenyl)-3-hydroxypropyl)hex-1-enylphosphonate (5b). ^{1}H NMR (300 MHz): δ 0.88 (t, 3H, J_{HH}=6.9 Hz), 1.28 (dt, 6H, J_{HH}=6.9 Hz, $^4J_{PH}$=0.2 Hz), 1.22–1.45 (overlap, 4H), 1.75–1.95 (overlap, 2H), 2.18 (m, 1H), 2.28 (m, 1H), 2.45 (br t, 2H, J_{HH}=6.6 Hz), 2.69 (br s, 1H), 3.95–4.15 (m, 4H), 4.17 (s, 1H), 4.63 (br t, 1H, J_{HH}=6.3 Hz), 5.30 (d, 1H, $^2J_{PH}$=18.3 Hz), 7.00 (t, 2H, J_{HH}=8.7 Hz), 7.28 (dd, 2H, J_{HH}=7.8 Hz); ^{31}P NMR (121.4 MHz): δ 19.42; ^{13}C NMR (75.5 MHz): δ 13.9, 16.3 (d, $^3J_{PC}$=7.3 Hz), 22.8, 30.6 (d, $^4J_{PC}$=2.0 Hz), 33.7 (d, $^3J_{PC}$=6.8 Hz), 34.2 (d, $^3J_{PC}$=22.7 Hz), 36.9, 61.2 (d, $^2J_{PC}$=5.4 Hz), 73.0, 111.2 (d, $^1J_{PC}$=190.0 Hz), 115.1, 127.4, 127.5, 140.3, 166.8 (d, $^2J_{PC}$=6.9 Hz); MS (EI): *m*/*z* (%) 373 (0.1), 372 (0.4), 354 (4.9), 315 (16.7), 248 (36.3), 235 (100), 187 (31.4), 109 (52.0), 97 (42.2), 77 (17.6), 57 (8.7), 41 (8.7); Anal. Calcd for $C_{19}H_{30}FO_4P$: C, 61.28; H, 8.12; F, 5.10; P, 8.32. Found: C, 61.19; H, 8.30; F, 5.03; P, 8.24.

3.2.3. (*E*)-Diethyl 2-(3-(2,4-dichlorophenyl)-3-hydroxypropyl)hex-1-enylphosphonate (5c). ^{1}H NMR (300 MHz): δ 0.87 (t, 3H, J_{HH}=7.2 Hz), 1.27 (dt, 6H, J_{HH}=7.2 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.43 (overlap, 4H), 1.79 (m, 1H), 1.90 (m, 1H), 2.33 (m, 1H), 2.41 (br s, 1H), 2.42 (m, 1H), 2.47 (br t, 2H, J_{HH}=6.7 Hz), 3.90–4.01 (m, 4H), 4.63 (br t, 1H, J_{HH}=6.1 Hz), 5.30 (d, 1H, $^2J_{PH}$=18.6 Hz), 7.30–7.89 (overlap, 3H); ^{31}P NMR (121.4 MHz): δ 19.5; ^{13}C NMR (75.5 MHz): δ 13.8, 16.2 (d, $^3J_{PC}$=6.6 Hz), 22.6, 30.5, 33.7 (d, $^3J_{PC}$=7.2 Hz), 34.8 (d, $^3J_{PC}$=22.7 Hz), 34.9, 36.5, 61.2 (d, $^2J_{PC}$=5.7 Hz), 68.3, 110.9 (d, $^1J_{PC}$=190.0 Hz), 124.1, 127.8, 128.1, 133.4, 140.9, 167.2 (d, $^2J_{PC}$=6.9 Hz); MS (EI): *m*/*z* (%) 426 (0.1), 425 (0.1), 425 (0.1), 424 (0.7), 423 (0.2), 400 (1.0), 364 (7.8), 342 (25.5), 290 (16.7), 249 (40.2), 226 (91.1), 208 (56.9), 191 (59.8), 146 (100), 120 (85.7), 105 (54.9), 92 (53.9), 79 (78.4), 77 (78.4), 67 (53.9), 65 (53.9), 55 (37.3), 41 (30.1); Anal. Calcd for $C_{19}H_{29}Cl_2O_4P$: C, 53.91; H, 6.91; Cl, 16.75; P, 7.32. Found: C, 54.04; H, 7.02; Cl, 16.57; P, 7.20.

3.2.4. (*E*)-Diethyl 2-(3-hydroxy-3-(4-nitrophenyl)propyl)hex-1-enylphosphonate (5d). ^{1}H NMR (300 MHz): δ 0.87 (t, 3H, J_{HH}=6.9 Hz), 1.25 (dt, 6H, J_{HH}=7.2 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.45 (overlap, 4H), 1.80 (m, 1H), 1.90 (m, 1H), 2.25–2.43 (overlap m, 2H), 2.45 (br t, 2H, J_{HH}=6.7 Hz), 3.80 (br s, 1H), 3.90–4.05 (m, 4H), 5.20 (br t, 1H, J_{HH}=6.4 Hz), 5.31 (d, 1H, $^2J_{PH}$=18.6 Hz), 7.37–7.95 (overlap, 4H); ^{31}P NMR (121.4 MHz): δ 19.55; ^{13}C NMR (75.5 MHz): δ 13.9, 16.2 (d, $^3J_{PC}$=6.6 Hz), 22.8, 30.5, 33.6 (d, $^3J_{PC}$=7.1 Hz), 34.7 (d, $^3J_{PC}$=22.7 Hz), 36, 61.2 (d, $^2J_{PC}$=5.7 Hz), 68.3, 111.0 (d, $^1J_{PC}$=189.7 Hz), 124.2, 127.9, 128.0, 133.4, 141.1, 147.4, 167.1 (d, $^2J_{PC}$=7.2 Hz); MS (EI): *m*/*z* (%) 399 (0.5), 364 (5.0), 342 (11.1), 290 (7.5), 249 (22.2), 226 (61.1), 208 (38.9), 191 (50.0), 146 (83.3), 120 (83.3), 104 (61.1), 77 (100), 66 (77.8), 41 (61.1); Anal. Calcd for $C_{19}H_{30}NO_6P$: C, 57.13; H, 7.57; N, 3.51; P, 7.75. Found: C, 56.99; H, 7.71; N, 3.45; P, 7.67.

3.2.5. (*E*)-Diethyl 2-(3-hydroxy-3-*o*-tolylpropyl)hex-1-enylphosphonate (5e). ^{1}H NMR (300 MHz): δ 0.86 (t, 3H, J_{HH}=6.9 Hz), 1.26 (dt, 6H, J_{HH}=7.2 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.50 (overlap, 4H), 1.77–1.91 (overlap, 2H), 2.29 (br s, 3H), 2.15–2.40 (overlap, 2H), 2.47 (br t, 2H, J_{HH}=6.6 Hz), 2.69 (br s, 1H), 3.93–4.11 (m, 4H), 4.89 (br t, 1H, J_{HH}=6.5 Hz), 5.31 (d, 1H, $^2J_{PH}$=18.3 Hz), 7.08–7.26 (overlap, 4H); ^{31}P NMR (121.4 MHz): δ 19.50; ^{13}C NMR (75.5 MHz): δ 13.8, 16.1 (d, $^3J_{PC}$=6.9 Hz), 18.9, 22.8, 30.6, 33.8 (d, $^3J_{PC}$=7.2 Hz), 34.4 (d, $^3J_{PC}$=22.6 Hz), 35.8, 61.1 (d, $^2J_{PC}$=5.4 Hz), 69.7, 111.0 (d, $^1J_{PC}$=190.0 Hz), 125.1, 126.2, 127.1, 130.3, 134.1, 142.7, 167.1 (d, $^2J_{PC}$=7.2 Hz); MS (EI): *m*/*z* (%) 368 (0.3), 350 (16.7), 311 (18.8), 248 (44.1), 235 (67.6), 206 (44.1), 183 (31.4), 170 (29.4), 105 (72.5), 91 (100), 77 (65.7), 55 (29.4), 41 (30.4), 29 (41.2); Anal. Calcd for $C_{20}H_{33}O_4P$: C, 65.20; H, 9.03; P, 8.41. Found: C, 65.34; H, 8.96; P, 8.34.

3.2.6. (*E*)-Diethyl 2-(3-hydroxy-3-*p*-tolylpropyl)hex-1-enylphosphonate (5f). ^{1}H NMR (300 MHz): δ 0.89 (t, 3H, J_{HH}=7.5 Hz), 1.29 (dt, 6H, J_{HH}=7.1 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.50 (overlap, 4H), 1.70–1.99 (overlap, 2H), 2.05 (br s, 1H), 2.12–2.40 (overlap, 2H), 2.34 (s, 3H), 2.48 (br t, 2H, J_{HH}=6.9 Hz), 3.95–4.09 (m, 4H), 4.63 (br t, 1H, J_{HH}=6.6 Hz), 5.34 (d, 1H, $^2J_{PH}$=18.0 Hz), 7.10–7.26 (overlap, 4H); ^{31}P NMR (121.4 MHz): δ 19.45; ^{13}C NMR (75.5 MHz): δ 13.8, 16.2 (d, $^3J_{PC}$=6.6 Hz), 21.0, 22.8, 30.5, 33.7 (d, $^3J_{PC}$=7.2 Hz), 34.2 (d, $^3J_{PC}$=23.2 Hz), 61.1 (d, $^2J_{PC}$=5.7 Hz), 73.5, 111.2 (d, $^1J_{PC}$=190.0 Hz), 116.0, 125.7, 129.1, 137.2, 141.4, 167.1 (d, $^2J_{PC}$=7.2 Hz); MS (EI): *m*/*z* (%) 368 (0.9), 350 (31.4), 321 (3.9), 311 (8.8), 248 (29.4), 235 (100), 206 (42.2), 183 (47.1), 170 (37.3), 138 (16.7), 120 (50.0), 105 (61.8), 91 (90.1), 77 (58.9), 65 (40.1), 55 (27.7), 41 (33.9), 28 (95.1); Anal. Calcd for $C_{20}H_{33}O_4P$: C, 65.20; H, 9.03; P, 8.41. Found: C, 65.39; H, 8.93; P, 8.32.

3.2.7. Diethyl (1*E*,6*E*) 2-butyl-5-hydroxy-7-phenylhepta-1,6-dienylphosphonate (5g). ^{1}H NMR (300 MHz): δ 0.89 (t, 3H, J_{HH}=6.9 Hz), 1.25 (dt, 6H, J_{HH}=6.9 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.52 (overlap, 4H), 1.76–1.80 (overlap, 2H),

2.23–2.34 (overlap, 2H), 2.45 (br s, 1H), 2.49 (br t, 2H, J_{HH}=6.3 Hz), 3.97–4.08 (m, 4H), 4.26 (q, 1H, J_{HH}=6.3 Hz), 5.36 (d, 1H, $^2J_{PH}$=18.3 Hz), 6.20 (dd, 1H, J_{HH}=15.9 Hz), 6.47 (d, 1H, J_{HH}=15.9 Hz), 7.20–7.38 (overlap, 5H); ^{31}P NMR (121.4 MHz): δ 19.52; ^{13}C NMR (75.5 MHz): δ 13.9, 16.3 (d, $^3J_{PC}$=6.6 Hz), 22.8, 30.6 (d, $^4J_{PC}$=1.7 Hz), 33.7 (d, $^3J_{PC}$=7.2 Hz), 33.8 (d, $^3J_{PC}$=30.1 Hz), 35.0, 61.2 (d, $^2J_{PC}$=5.7 Hz), 72.1, 111.0 (d, $^1J_{PC}$=190.0 Hz), 126.4, 126.5, 128.5, 130.3, 132.0, 136.5, 167.1 (d, $^2J_{PC}$=6.8 Hz); MS (EI): *m/z* (%) 381 (2.5), 380 (11.8), 362 (4.9), 323 (5.8), 271 (11.1), 247 (43.1), 235 (100), 224 (49.0), 206 (57.8), 133 (39.2), 115 (40.2), 91 (78.4), 79 (40.2), 77 (34.3), 55 (54.9), 41 (19.6), 29 (22.3); Anal. Calcd for $C_{21}H_{33}O_4P$: C, 66.35; H, 8.75; P, 8.19. Found: C, 66.42; H, 8.66; P, 7.95.

3.2.8. (*E*)-Diethyl 2-(3-hydroxy-3-(4-methoxyphenyl)propyl)hex-1-enylphosphonate (5h). ^{1}H NMR (300 MHz): δ 0.88 (t, 3H, J_{HH}=7.2 Hz), 1.28 (dt, 6H, J_{HH}=7.2 Hz, $^4J_{PH}$=0.2 Hz), 1.20–1.45 (overlap, 4H), 1.80 (m, 1H), 1.95 (m, 1H), 2.14 (m, 1H), 2.29 (m, 1H), 2.43 (br s, 1H), 2.46 (br t, 2H, J_{HH}=6.6 Hz), 3.96–4.09 (m, 4H), 4.60 (br t, 1H, J_{HH}=6.0 Hz), 5.31 (d, 1H, $^2J_{PH}$=18.0 Hz), 6.86 (d, 2H, J_{HH}=8.7 Hz), 7.23 (d, 2H, J_{HH}=9.0 Hz); ^{31}P NMR (121.4 MHz): δ 19.52; ^{13}C NMR (75.5 MHz): δ 13.9, 16.3 (d, $^3J_{PC}$=6.9 Hz), 22.8, 30.6, 33.7 (d, $^3J_{PC}$=6.9 Hz), 34.3 (d, $^3J_{PC}$=22.7 Hz), 36.8, 55.2, 61.1 (d, $^2J_{PC}$=5.7 Hz), 73.3, 111.0 (d, $^1J_{PC}$=190.0 Hz), 113.8, 127.0, 136.60, 159.0, 167.1 (d, $^2J_{PC}$=7.2 Hz); MS (EI): *m/z* (%) 384 (3.1), 366 (3.5), 327 (3.9), 271 (10.3), 248 (28.7), 235 (100), 206 (51.7), 163 (18.4), 150 (51.7), 137 (78.2), 121 (57.5), 109 (47.1), 94 (42.5), 91 (27.8), 77 (57.5), 55 (27.6), 41 (31.0); Anal. Calcd for $C_{20}H_{33}O_5P$: C, 62.48; H, 8.65; P, 8.06. Found: C, 62.42; H, 8.80; P, 7.97.

3.2.9. (*Z*)-Diethyl 5-hydroxy-2,5-diphenylpent-1-enylphosphonate (5i). ^{1}H NMR (300 MHz): δ 1.02 (dt, 6H, J_{HH}=6.9 Hz, $^4J_{PH}$=0.2 Hz), 1.75–1.95 (overlap, 2H), 2.02 (br s, 1H), 2.66 (m, 1H), 2.82 (m, 1H), 3.60–3.80 (m, 4H), 4.62 (br t, 1H, J_{HH}=6.5 Hz), 5.72 (d, 1H, $^2J_{PH}$=17.4 Hz), 7.10–7.40 (overlap, 10H); ^{31}P NMR (121.4 MHz): δ 17.63; ^{13}C NMR (75.5 MHz): δ 16.0 (d, $^3J_{PC}$=6.9 Hz), 36.2, 38.0 (d, $^3J_{PC}$=21.2 Hz), 61.3 (d, $^2J_{PC}$=5.7 Hz), 68.4, 114.2 (d, $^1J_{PC}$=180.14 Hz), 124.3, 127.6, 128.0, 128.1, 128.3, 133.5, 140.3, 147.6, 162.4 (d, $^2J_{PC}$=7.2 Hz); MS(EI): *m/z* (%) 374 (0.9), 359 (3.1), 329 (100), 301 (14.5), 281 (29.7), 273 (59.5), 255 (48.6), 238 (24.3), 207 (75.7), 193 (35.1), 181 (18.4), 165 (32.4), 149 (70.3), 136 (10.8), 105 (24.3), 77 (27.1), 41 (47.9); Anal. Calcd for $C_{21}H_{27}O_4P$: C, 67.37; H, 7.27; P, 8.27. Found: C, 67.22; H, 7.44; P, 8.23.

3.2.10. (*Z*)-Diethyl 5-(2,4-dichlorophenyl)-5-hydroxy-2-phenylpent-1-enylphosphonate (5j). ^{1}H NMR (300 MHz): δ 1.10 (dt, 6H, J_{HH}=7.2 Hz, $^4J_{PH}$=0.2 Hz), 1.70–1.90 (overlap, 2H), 2.02 (br s, 1H), 2.45–2.70 (overlap, 2H), 3.68–3.85 (m, 4H), 4.66 (br t, 1H, J_{HH}=6.3 Hz), 5.72 (d, 1H, $^2J_{PH}$=17.4 Hz), 7.20–7.33 (overlap, 8H); ^{31}P NMR (121.4 MHz): δ 16.00; ^{13}C NMR (75.5 MHz): δ 16.0 (d, $^3J_{PC}$=6.6 Hz), 36.6, 37.7 (d, $^3J_{PC}$=22.4 Hz), 61.3 (d, $^2J_{PC}$=5.7 Hz), 73.5, 114.6 (d, $^1J_{PC}$=191.8 Hz), 125.8, 127.7, 127.7, 128.0, 128.2, 128.5, 128.9, 139.0, 139.7, 144.2, 162.4 (d, $^2J_{PC}$=6.9 Hz); MS (EI): *m/z* (%) 445 (0.1), 444 (0.4), 443 (0.2), 442 (1.0), 390 (1.7), 344 (3.5), 298 (2.2), 196 (100), 165 (5.1), 91 (64.7), 77 (3.2), 65 (3.4), 51 (2.3), 41 (2.1), 29 (3.4); Anal. Calcd for $C_{21}H_{25}Cl_2O_4P$: C, 56.90; H, 5.68; Cl, 16.00; P, 6.99. Found: C, 57.02; H, 5.60; Cl, 15.90; P, 7.05.

3.2.11. (*E*)-Diethyl 2-deuterio-2-(3-hydroxy-3-phenylpropyl)hex-1-enylphosphonate (6). ^{1}H NMR (300 MHz): δ 0.88 (t, 3H, J_{HH}=6.9 Hz), 1.28 (dt, 6H, J_{HH}=7.1 Hz, $^4J_{PH}$=0.2 Hz), 1.22–1.45 (overlap, 4H), 1.78–1.94 (m, 2H), 2.26 (m, 1H), 2.30 (m, 1H), 2.43 (br t, 2H, J_{HH}=7.6 Hz), 2.60 (br s, 1H), 3.95–4.05 (m, 4H), 4.64 (br t, 1H, J_{HH}=7.5 Hz), 7.20–7.35 (overlap, 5H); ^{31}P NMR (121.4 MHz): δ 19.54; ^{13}C NMR (75.5 MHz): δ 13.9, 16.3 (d, $^3J_{PC}$=6.6 Hz), 22.8, 30.6, 33.6 (d, $^3J_{PC}$=6.9 Hz), 34.3 (d, $^3J_{PC}$=23.9 Hz), 36.8, 61.1 (d, $^2J_{PC}$=5.7 Hz), 73.7, 109.8 (d, $^1J_{PC}$=189.22 Hz), 125.8, 127.6, 128.4, 144.5, 166.9 (d, $^2J_{PC}$=6.9 Hz); MS (EI): *m/z* (%) 356 (1.0), 337 (4.4), 298 (15.7), 249 (30.7), 236 (100), 207 (21.6), 170 (30.4), 105 (20.6), 91 (47.1), 79 (45.1), 77 (34.3), 55 (5.9), 41 (5.8); Anal. Calcd for $C_{19}H_{30}DO_4P$: C, 64.21; H, 9.07; P, 8.71. Found: C, 64.32; H, 9.02; P, 8.64.

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Synthesis of novel halo-oxybispyridines, new building blocks in cholinergic medicinal chemistry

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Abstract—This paper describes a method for the preparation of oxybispyridines bearing several halogens, which could be further transformed into other functional groups thus giving access to libraries with the bis-pyridyl ether moiety as the common structural feature of interest in cholinergic medicinal chemistry. Scope and limitation of the method are outlined.

1. Introduction

A considerable amount of literature has been published concerning the pyridylethers as nicotinic cholinergic receptor ligands. For example, A-85380 and its derivatives,[1] ABT-594[2] and ABT-089[3] have been described to be highly selective agents of $\alpha_4\beta_2$ receptors (Fig. 1).

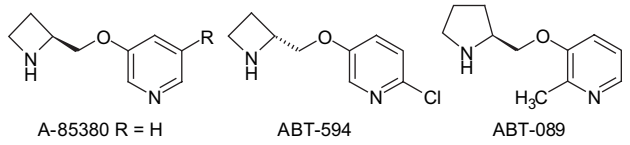

Figure 1. Pyridylethers as nicotinic cholinergic agonists ($\alpha_4\beta_2$).

Besides, synthesis and structure–activity relationship of novel pyridylethers have been published by Lee et al.[4] The authors described that the only criteria left on the molecule was to place the second nitrogen in an optimal distance from the 3-position of the pyridine.

From these observations, numerous derivatives have been synthesized and among them, RWJ-314313[4] as a potent ligand bound to the $\alpha_4\beta_2$ nAChR subtype (Fig. 2).

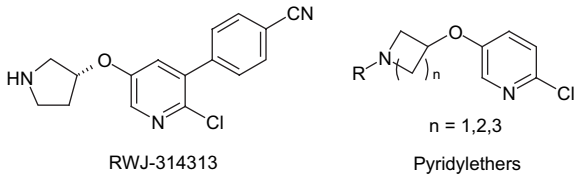

Figure 2.

In this study, we chose to develop the synthesis of novel pyridylethers such as halo-oxybispyridines. A few examples of symmetrical and dissymmetrical oxybispyridines have been described[5–8] and some of these were obtained through nucleophilic substitution.[9–12]

Indeed, from a synthetic point of view, halo-oxybispyridines afford more potentialities because of particular reactivity in metal-catalyzed cross-coupling reactions like Suzuki coupling, either as electrophilic agents or in preparing their own boronic acids. In this study, we pay particular attention to synthesize various halo-oxybispyridines as valuable building blocks.

The two methodologies allowing the preparation of oxybispyridines (Scheme 1) are as follows: either the Chan–Lam coupling reaction[13–15] or the nucleophilic substitution. For these two reactions, halohydroxypyridines have to be prepared. Recently, we described a general method for the synthesis of halohydroxypyridines from novel halopyridylboronic acids and esters using an efficient hydroxydeboronation reaction.[17]

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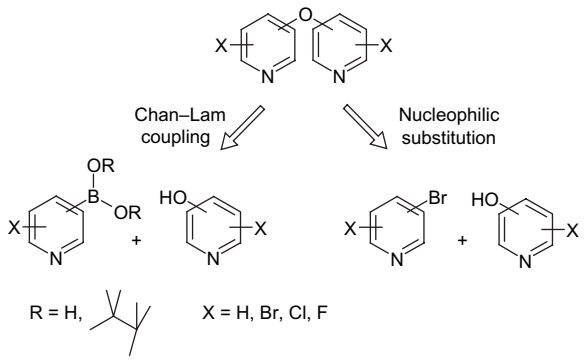


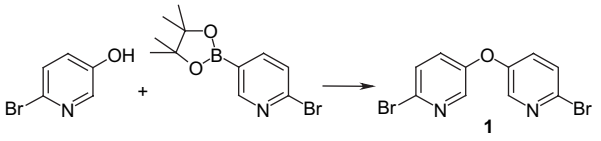
Scheme 1. Two synthetic approaches to halo-oxybispyridines.

2. Results and discussion

The Chan–Lam coupling reaction has been considered first because of our knowledge in the halopyridylboronic acid synthesis[18–21] and in the study of their reactivity in cross-coupling reactions illustrated, for example, by the synthesis of the quaterpyridine nemertelline[22] and in the Petasis reaction.[23]

Firstly, halopyridylboronic acids have been used under classical conditions,[13–14] but the reaction was unsuccessful. Secondly, halopyridylboronic esters have been involved, considering our precedent and fruitful works concerning N-arylations.[24] Several conditions were then tested at room temperature (if no reaction occurred, the mixture was then heated to reflux). All these tests are summarized in Table 1.

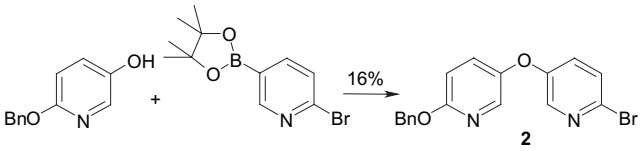
Table 1. Several conditions for Chan–Lam coupling reaction (NR: no reaction)



Entry	$Cu(OAc)_2$	Base	Solvent	Yields
1[13,14]	1 equiv	Pyridine	CH_2Cl_2	11%
2[13,14]	1 equiv	Pyridine	DMF	NR
3[13,14]	1 equiv	$N(Et)_3$	CH_2Cl_2	NR
4[13,14]	1 equiv	$N(Et)_3$	DMF	NR
5	1.5 equiv	Pyridine	CH_2Cl_2	NR
6	1.5 equiv	$N(Et)_3$	CH_2Cl_2	NR
7[16]	Cat., 5% TEMPO/air	Pyridine	CH_2Cl_2	NR
8[16]	Cat., 5% TEMPO/air	$N(Et)_3$	CH_2Cl_2	NR

The coupling reaction of 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-bromo-pyridin-3-ol gave the expected dibromo-oxybispyridine **1** when the reaction was carried out as follows: 1 equiv of copper(II) acetate, 5 equiv of pyridine in dichloromethane, and 4 Å molecular sieves at room temperature for 4 days (entry 1). Other procedures (entry 2–8) gave either trace of the expected product or degradation products.

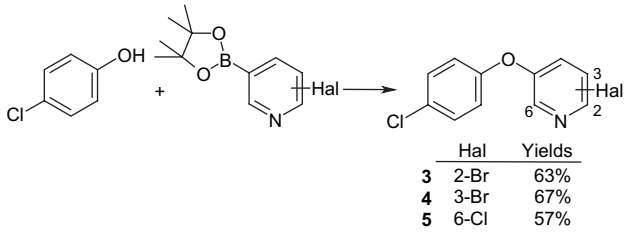
According to these conditions, the reaction of 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 2-benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine gave the expected product **2** (Scheme 2).



Scheme 2. Synthesis of oxybispyridine **2**. Reagents and conditions: $Cu(Ac)_2$ (1 equiv), pyridine (5 equiv), CH_2Cl_2, 4 Å molecular sieves, 25 °C, 4 days.

But, this route to obtain novel halo-oxybispyridines led to poor results even if two examples **1** and **2** have been produced with 11 and 16% yields, respectively.

To explain this lack of reactivity, we suggested that when the hydroxyl compound used in coupling reactions contained an electron-withdrawing group, the reaction was unsuccessful. More precisely, the coordination step seemed to depend on the stability of the anion in accordance with the pK_a of the hydroxyl compound. Indeed, we considered the coupling reaction of *p*-chlorophenol and halopyridylboronic esters in the previous conditions. We obtained arylheteroarylethers **3–5** with 63, 67, and 57% yields, respectively (Scheme 3).



	Hal	Yields
3	2-Br	63%
4	3-Br	67%
5	6-Cl	57%

Scheme 3. Synthesis of arylheteroarylethers **3–5**. Reagents and conditions: $Cu(Ac)_2$ (1 equiv), pyridine (5 equiv), CH_2Cl_2, 4 Å molecular sieves, 25 °C, 4 days.

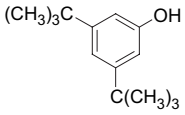
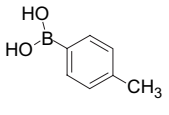
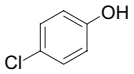
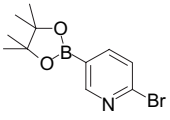
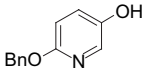
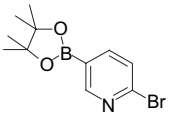
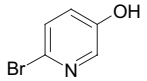
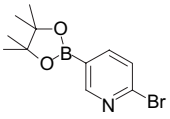
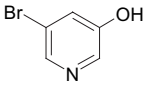
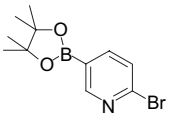
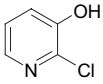
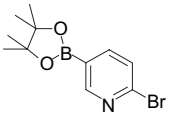
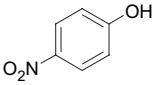
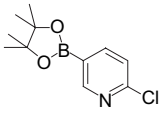
We observed the same trend with several hydroxyl compounds, shown in Table 2: the higher the pK_a value is, the more unstable the anion is and the more efficient the coordination step is.

These results confirmed the lack of reactivity of halohydroxypyridines in Chan–Lam coupling reaction, which did not seem to be good supports because of the electron deficient feature of pyridine derivatives.

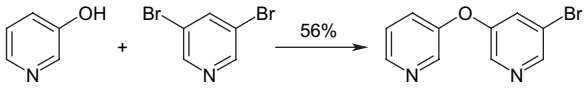
A second strategy has been considered to synthesize halo-oxybispyridines. Recently, Dull et al.[12] have described the synthesis of aryl olefinic azacyclic and aryl acetylenic azacyclic compounds, which is able to affect the nicotinic cholinergic receptors and to be agents for the treatment of central nervous system disorders. Among these compounds, only one halo-oxybispyridine has been described in this patent, 3-bromo-5-(pyridin-3-yloxy)-pyridine. This compound was obtained by nucleophilic substitution from pyridin-3-ol and 3,5-dibromopyridine (Scheme 4).

So, we took into account this strategy and we optimized this reaction in order to make it applicable not only to various 3,3′-oxybispyridines, but also to 2,3′- and 4,4′-oxybispyridines (Scheme 5).

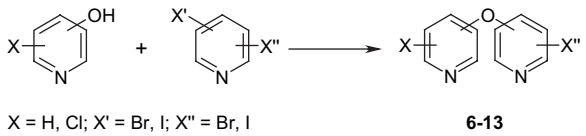
Table 2. Influence of the pK_a value in Chan–Lam coupling reaction[a]

Entry	Hydroxyl components (pK_a^*)	Boronic components	Yields
1[14b]	 (9.63)		79%
2	 (9.26)		63%
3	 (9.17)		16%
4	 (8.53)		11%
5	 (8.32)		NR
6	 (7.78)		NR
7	 (7.04)		NR

[a] Theoretical value.[25]



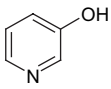
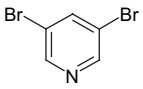
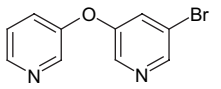
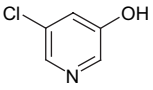
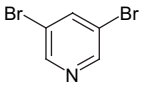
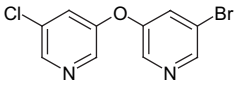
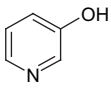
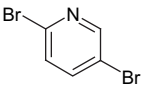
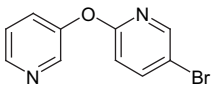
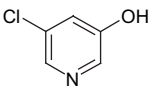
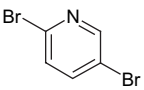
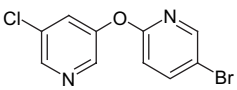
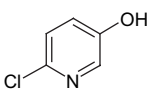
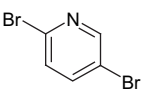
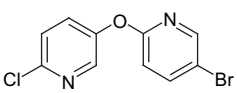
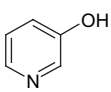
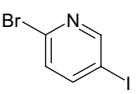
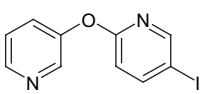
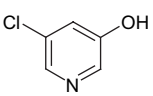
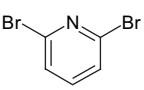
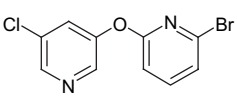
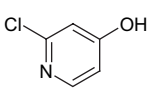
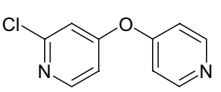
Scheme 4. Synthesis of halo-oxybispyridine. Reagents and conditions: NaH 80% (1 equiv), DMF, 130 °C, 20 h.



Scheme 5. Synthesis of halo-oxybispyridines **6–13**. Reagents and conditions: 60% NaH (1.25 equiv), DMF, reflux, 48 h.

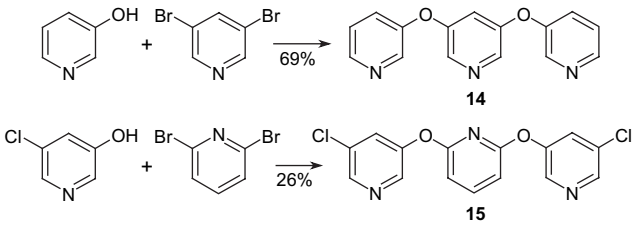
Fortunately, we have easily achieved numerous isomers and this methodology is now applicable to a large scale of starting materials. It has been used with several halohydroxypyridines and halopyridines to obtain novel halo-oxybispyridines **6–13** as shown in Table 3.

Table 3. Novel halo-oxybispyridines **6–13**

Entry	Halohydroxy-pyridines	Halopyridines	Halo-oxybispyridines	Yields
1			 **6**	66%
2			 **7**	31%
3			 **8**	66%
4			 **9**	72%
5			 **10**	63%
6			 **11**	23%
7			 **12**	27%
8			 **13**	63%

The nucleophilic substitution led to good yields whether in 2-position (entries 3, 4, and 5), in 3-position (entry 1) or in 4-position (entry 8) of the nitrogen of pyridine. But, according to the position and the nature of the halogen, yields have been reduced by half. Moreover, the residual halogen of halo-oxybispyridines can be involved in a second nucleophilic substitution. Therefore, the heterogeneity of yields can be warranted by formation of a small amount of secondary products as dioxyterpyridines. In order to clearly identify the structure of these secondary products, we have synthesized 3,5-di-(pyridin-3-yloxy)pyridine **14** by reaction of 3,5-dibromopyridine with pyridin-3-ol and 2,6-di-(5-chloropyridin-3-yloxy)pyridine **15** by reaction of 2,6-dibromopyridine with 5-chloropyridin-3-ol with 69 and 26% yields, respectively (Scheme 6). Those synthesized dioxyterpyridines matched to the by-products previously identified in the reaction.

It is to be noted that the nucleophilic substitution would have been better with chlorinated compounds, but halogen–metal exchange considered in further works is not possible with chlorinated halo-oxybispyridines.



Scheme 6. Synthesis of dioxybisterpyridines **14** and **15**. Reagents and conditions: 60% NaH (1.25 equiv), DMF, reflux, 48 h.

In conclusion, we have produced novel oxybispyridines bearing several halogens. Further experiments concerning the reactivity of these compounds are currently under investigation in order to use them as new building blocks in the production of pyridine compounds with potential cholinergic activity.

3. Experimental

3.1. General

Commercial reagents were used as received without additional purification. Melting points were determined on a Kofler heating bench and are uncorrected. IR spectra were recorded on a Perkin–Elmer BX FTIR spectrophotometer. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a JEOL Lambda 400 spectrometer. Chemical shifts are expressed in parts per million downfield from tetramethylsilane as an internal standard. Chromatography was carried out on a column using flash silica gel 60 Merck (0.063–0.200 mm) as the stationary phase. Thin-layer chromatography (TLC) was performed on 0.2 mm precoated plates of silica gel $60F_{264}$ (Merck) and spots were visualized using with an ultraviolet-light lamp. Elemental analyzes for new compounds were performed at the 'Institut de Recherche en Chimie Organique Fine' (Rouen).

Starting materials were purchased from Aldrich, Acros Organics, and Lancaster and used without purification.

Analytical data for known compounds were always fully consistent with published data.

3.2. General procedure 1 for the synthesis of arylheteroarylethers using Chan–Lam coupling reaction (1 and 5)

To a stirred solution of halopyridylboronic ester (2 equiv) and halopyridinol or halophenol (1 equiv) in dichloromethane was added copper(II) acetate (1 equiv), pyridine (5 equiv), and 4 Å molecular sieves. The reaction was then continued at room temperature for 4 days. The mixture was filtered, concentrated to dryness, and the residue was purified by column chromatography (cyclohexane/ethylacetate, 90/10) to afford ethers **1** and **5**.

3.2.1. 2-Bromo-5-(6-bromopyridin-3-yloxy)pyridine (1). 2-Bromo-5-(6-bromopyridin-3-yloxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-bromopyridin-3-ol according to general procedure 1 as a white solid (11%). Mp 82 °C. IR (KBr): 1680, 1573, 1349, 1329, 1271, 1179, 1069, 929, 754, 642 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.86–7.85 (m, 2H), 7.44–7.43 (m, 2H), 7.27–7.26 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=155.2, 140.9, 138.8, 131.1, 122.0. Anal. Calcd for $C_{10}H_6Br_2N_2O$: C, 36.40; H, 1.83; N, 8.49. Found: C, 36.09; H, 1.54; N, 7.98.

3.2.2. 2-Benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine (2). 2-Benzyloxy-5-(6-bromopyridin-3-yloxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and 6-benzyloxypyridin-3-ol according to general procedure 1 as a white solid (16%). Mp 74 °C. IR (KBr): 1678, 1575, 1420, 1345, 1360, 1276, 1186, 1091, 938, 742, 718, 653 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.06 (d, J=2.9 Hz, 1H), 7.91 (d, J=2.8 Hz, 1H), 7.40–7.24 (m, 7H), 7.06 (dd, J=8.7, 3.0 Hz, 1H), 6.77 (d, J=8.9 Hz, 1H), 5.29 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=159.9, 153.5, 152.9, 141.0, 138.9, 137.6, 136.9, 131.5, 129.8 (2C), 128.3 (2C), 127.4, 126.5, 125.2, 115.5, 69.4. Anal. Calcd for $C_{17}H_{13}BrN_2O_2$: C, 57.16; H, 3.67; N, 7.84. Found: C, 56.68; H, 3.40; N, 7.54.

3.2.3. 2-Bromo-5-(4-chlorophenoxy)pyridine (3). 2-Bromo-5-(4-chlorophenoxy)pyridine was prepared using 2-[3-(6-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxa-borolane and *p*-chlorophenol according to general procedure 1 as a white solid (63%). Mp 68 °C. IR (KBr): 1486, 1449, 1375, 1262, 1088, 1009, 828 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.23 (d, J=4.6 Hz, 1H), 7.64 (d, J=8.3 Hz, 1H), 7.48–7.44 (m, 3H), 7.13 (d, J=8.9 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=154.5, 153.4, 141.2, 135.0, 130.2 (2C), 129.8, 128.7, 128.4, 120.3 (2C). Anal. Calcd for $C_{11}H_7BrClNO$: C, 46.43; H, 2.48; N, 4.92. Found: C, 46.12; H, 2.71; N, 4.71.

3.2.4. 3-Bromo-5-(4-chlorophenoxy)pyridine (4).[26] 3-Bromo-5-(4-chlorophenoxy)pyridine was prepared using 2-[3-(5-bromo)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and *p*-chlorophenol according to general procedure 1 as an orange solid (67%). Mp 79 °C. IR (KBr): 1554, 1484, 1425, 1307, 1250, 1200, 1087, 1009, 894, 871, 844 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.35 (s, 1H), 8.24 (s, 1H), 7.35 (s, 1H), 7.29 (d, J=8.8 Hz, 2H), 6.77 (d, J=8.8 Hz, 2H).

3.2.5. 2-Chloro-3-(4-chlorophenoxy)pyridine (5).[27] 2-Chloro-3-(4-chlorophenoxy)pyridine was prepared using 2-[3-(2-chloro)pyridine]-4,4′,5,5′-tetramethyl-1,3-dioxaborolane and *p*-chlorophenol according to general procedure 1 as a white solid (57%). Mp<50 °C. IR (KBr): 1498, 1454, 1367, 1262, 1087, 1011, 824 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.26 (d, J=4.6 Hz, 1H), 7.59 (d, J=8.1 Hz, 1H), 7.48–7.44 (m, 3H), 7.06 (d, J=8.9 Hz, 2H).

3.3. General procedure 2 for the synthesis of halo-oxybispyridines using nucleophilic substitution (6 and 13)

To a stirred solution of pyridin-3-ol or chloropyridinol (1 equiv) in dimethylformamide was slowly added 60% sodium hydride (1.25 equiv). The mixture was then continued at room temperature for 1 h and mono- or di-halopyridine (0.55 equiv) was added. The mixture was refluxed for 48 h and then was allowed to warm to room temperature. To the resulting suspension was added water. The mixture was then extracted with ether and the extract was washed with

brine, dried over magnesium sulfate, and concentrated on rotary evaporator. The residue was purified by column chromatography (cyclohexane/ethylacetate, 80/20) to afford halo-oxybispyridines **6** and **13**.

3.3.1. 3-Bromo-5-(pyridin-3-yloxy)pyridine (6).[12] 3-Bromo-5-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 3,5-dibromopyridine according to general procedure 2 as an orange oil (66%). IR (KBr): 1565, 1475, 1423, 1305, 1258, 1086, 1021, 902, 798, 708, 673 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.22 (d, J=2.4 Hz, 1H), 8.20–8.19 (m, 2H), 8.36 (d, J=2.7 Hz, 1H), 7.48 (t, J=2.4 Hz, 1H), 7.15 (part A of system AB, $^3J_{AB}$=8.6 Hz, J=2.7, 1.7 Hz, 1H), 7.10 (part B of system AB, $^3J_{AB}$=8.6 Hz, J=4.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=153.7, 152.1, 145.6, 145.5, 141.2, 139.4, 128.3, 126.3, 124.8, 120.1.

3.3.2. 3-Bromo-5-(5-chloropyridin-3-yloxy)pyridine (7). 3-Bromo-5-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 3,5-dibromopyridine according to general procedure 2 as a white solid (31%). Mp 72 °C. IR (KBr): 1555, 1412, 1310, 1251, 1092, 1015, 925, 899, 866, 692, 577 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.54 (d, J=2.2 Hz, 1H), 8.43 (d, J=2.2 Hz, 1H), 8.38 (d, J=2.2 Hz, 1H), 8.33 (d, J=2.2 Hz, 1H), 7.52 (t, J=2.2 Hz, 1H), 7.37 (t, J=2.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=152.7, 152.6, 146.8, 144.7, 139.7, 139.1, 132.5, 128.7, 125.9, 120.7. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 41.91; H, 1.98; N, 9.69.

3.3.3. 3-Bromo-6-(pyridin-3-yloxy)pyridine (8). 3-Bromo-6-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a beige solid (66%). Mp<50 °C. IR (KBr): 1575, 1455, 1367, 1268, 1091, 1004, 881, 707, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.41 (d, J=2.4 Hz, 1H), 8.36 (dd, J=4.6, 1.4 Hz, 1H), 8.07 (d, J=2.4 Hz, 1H), 7.69 (dd, J=8.6, 2.4 Hz, 1H), 7.40 (part A of system AB, $^3J_{AB}$=8.3 Hz, J=2.4, 1.4 Hz, 1H), 7.22 (part B of system AB, $^3J_{AB}$=8.3 Hz, J=4.6 Hz, 1H), 6.81 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.3, 149.9, 147.7, 145.6, 143.2, 141.9, 128.3, 123.6, 113.9, 112.9. Anal. Calcd for $C_{10}H_7BrN_2O$: C, 47.84; H, 2.81; N, 11.16. Found: C, 47.37; H, 2.88; N, 11.42.

3.3.4. 3-Bromo-6-(5-chloropyridin-3-yloxy)pyridine (9). 3-Bromo-6-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a white solid (72%). Mp 80 °C. IR (KBr): 1574, 1458, 1366, 1272, 1094, 1022, 921, 888, 826, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.42 (d, J=1.9 Hz, 1H), 8.39 (d, J=2.4 Hz, 1H), 8.19 (d, J=2.7 Hz, 1H), 7.84 (dd, J=8.7, 2.7 Hz, 1H), 7.57 (t, J=1.9, 2.4 Hz, 1H), 6.94 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.1, 150.1, 147.6, 144.5, 142.9, 141.7, 130.8, 129.2, 114.3, 113.8. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 41.73; H, 2.02; N, 9.47.

3.3.5. 3-Bromo-6-(6-chloropyridin-3-yloxy)pyridine (10). 3-Bromo-6-(6-chloropyridin-3-yloxy)pyridine was prepared using 6-chloropyridin-3-ol and 2,5-dibromopyridine according to general procedure 2 as a white solid (63%). Mp 80 °C. IR (KBr): 1574, 1458, 1427, 1415, 1366, 1273, 1130, 1094, 1022, 922, 888, 826, 679 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=2.8 Hz, 1H), 8.08 (d, J=2.8 Hz, 1H), 8.19 (dd, J=8.7, 2.8 Hz, 1H), 7.42 (dd, J=8.6, 2.8 Hz, 1H), 7.27 (d, J=8.6 Hz, 1H), 6.85 (d, J=8.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=161.2, 149.2, 147.9, 146.6, 143.0, 142.4, 131.8, 124.6, 114.5, 113.3. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 42.19; H, 2.05; N, 9.22.

3.3.6. 3-Iodo-6-(pyridin-3-yloxy)pyridine (11). 3-Iodo-6-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol and 2-bromo-5-iodopyridine according to general procedure 2 as a yellow oil (23%). IR (KBr): 1573, 1469, 1367, 1269, 1102, 1014, 891, 798, 715, 656 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.39 (d, J=2.4 Hz, 1H), 8.36 (dd, J=4.6, 1.4 Hz, 1H), 8.21 (d, J=2.2 Hz, 1H), 7.83 (dd, J=8.6, 2.2 Hz, 1H), 7.39 (part A of system AB, $^3J_{AB}$=8.3 Hz, J=2.4, 1.4 Hz, 1H), 7.22 (part B of system AB, $^3J_{AB}$=8.3 Hz, J=4.6 Hz, 1H), 6.71 (d, J=8.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=162.0, 152.9, 149.9, 147.4, 145.7, 143.2, 128.4, 123.7, 113.7, 84.8. Anal. Calcd for $C_{10}H_7IN_2O$: C, 40.29; H, 2.37; N, 9.40. Found: C, 40.12; H, 2.16; N, 9.18.

3.3.7. 2-Bromo-6-(5-chloropyridin-3-yloxy)pyridine (12). 2-Bromo-6-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol and 2,6-dibromopyridine according to general procedure 2 as a beige oil (27%). IR (KBr): 1609, 1579, 1558, 1509, 1418, 1304, 1242, 1186, 1160, 1090, 1015, 927, 869, 775, 723, 686 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.36 (d, J=2.4 Hz, 1H), 8.29 (d, J=2.0 Hz, 1H), 7.53 (t, J=2.0, 2.4 Hz, 1H), 7.40 (t, J=8.0 Hz, 1H), 6.13 (d, J=8.0 Hz, 1H), 6.08 (d, J=8.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.8, 156.0, 151.0, 143.5, 141.6, 140.7, 131.2, 128.5, 100.4, 96.8. Anal. Calcd for $C_{10}H_6BrClN_2O$: C, 42.07; H, 2.12; N, 9.81. Found: C, 42.54; H, 2.02; N, 9.37.

3.3.8. 2-Chloro-4-(pyridin-4-yloxy)pyridine (13). 2-Chloro-4-(pyridin-4-yloxy)pyridine was prepared using 2-chloropyridin-4-ol and 4-iodopyridine according to general procedure 2 as a beige solid (63%). Mp 75 °C. IR (KBr): 1571, 1430, 1429, 1373, 1257, 1098, 1021, 1009, 929, 890, 823, 653 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.73 (d, J=5.5 Hz, 2H), 8.12 (d, J=5.5 Hz, 1H), 6.79 (d, J=5.5 Hz, 2H), 6.70 (dd, J=5.5, 2.7 Hz, 1H), 6.65 (d, J=2.7 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 162.8, 153.2, 152.1 (2C), 150.8, 116.3, 114.8 (2C), 111.4. Anal. Calcd for $C_{10}H_7ClN_2O$: C, 58.13; H, 3.41; N, 13.56. Found: C, 58.07; H, 3.34; N, 13.45.

3.4. General procedure 2 for the synthesis of dioxyterpyridines using nucleophilic substitution (14 and 15)

3.4.1. 3,5-Di-(pyridin-3-yloxy)pyridine (14). 3,5-Di-(pyridin-3-yloxy)pyridine was prepared using pyridin-3-ol (2 equiv) and 3,5-dibromopyridine (0.55 equiv) according to general procedure 2 as a brown oil (69%). IR (KBr): 3044, 1565, 1475, 1424, 1305, 1253, 1209, 1021, 903, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.37–8.36 (m, 6H), 8.24 (t, J=2.2 Hz, 1H), 7.30–7.23 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=156.6, 152.6, 149.5, 135.0, 134.8,

126.7, 122.3, 111.5. Anal. Calcd for $C_{15}H_{11}N_3O_2$: C, 67.92; H, 4.18; N, 15.84. Found: C, 68.23; H, 4.08; N, 15.86.

3.4.2. 2,6-Di-(5-chloropyridin-3-yloxy)pyridine (15). 2,6-Di-(5-chloropyridin-3-yloxy)pyridine was prepared using 5-chloropyridin-3-ol (2 equiv) and 2,6-dibromopyridine (0.55 equiv) according to general procedure 2 as a yellow solid (26%). Mp 62 °C. IR (KBr): 1572, 1469, 1427, 1418, 1287, 1243, 1189, 1021, 912, 687 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ=8.18 (d, J=1.9 Hz, 2H), 8.10 (d, J=2.0 Hz, 2H), 7.61 (t, J=7.8 Hz, 1H), 7.24 (t, J=2.0 Hz, 2H), 7.24 (t, J=7.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.6, 154.3, 150.9, 144.8, 134.8, 132.4, 120.4, 111.3. Anal. Calcd for $C_{15}H_9Cl_2N_3O_2$: C, 53.92; H, 2.71; N, 12.57. Found: C, 53.65; H, 2.11; N, 12.13.

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Polyhydroxylated pyrrolizidines. Part 8: Enantiospecific synthesis of looking-glass analogues of hyacinthacine A_5 from DADP☆

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Abstract—(1*R*,2*S*,3*S*,5*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine[(−)-3-*epi*hyacinthacine A_5, **1a**] and (1*S*,2*R*,3*R*,5*S* 7a*S*)-1,2-dihydroxy-3-hydroxymethylpyrrolizidine[(+)-3-*epi*hyacinthacine A_5, **1b**] have been synthesized either by Wittig's or Horner–Wadsworth–Emmond's (HWE's) methodology using aldehydes **4** and **9**, both prepared from (2*S*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (**2**, partially protected DADP), and the appropriate ylides, followed by cyclization through an internal reductive amination process of the resulting α,β-unsaturated ketones **5** and **10**, respectively, and total deprotection.

1. Introduction

We have recently reported on the stereocontrolled transformation of D-fructose into a suitably protected derivative of 2,5-dideoxy-2,5-imino-D-allitol (**2**, DADP),[2] which could be considered as an excellent and versatile key intermediate for the enantiosynthesis of polyhydroxylated pyrrolizidines. The necessity for new preparations of enantiomerically pure looking-glass hyacinthacines such as **1a** and **1b** arose from the discovery[3] that synthetic L-DMDP (2,5-dideoxy-2,5-imino-L-mannitol), is a more powerful and more specific α-glucosidase inhibitor than the enantiomeric natural product DMDP (see Fig. 1) one of the most widespread of secondary metabolite sugar mimics.[4] This behaviour occurs in other polyhydroxylated pyrrolidinic and piperidinic alkaloids.[5]

According to Figure 1 below, the pivotal character of compound **2**, would allow the syntheses of (−)-3-*epi* (**1a**) and (+)-3-*epi* isomers of hyacinthacine A_5, a natural polyhydroxylated pyrrolizidinic alkaloid and moderate inhibitor (IC_{50}=110 μM) of amyloglucosidase isolated from an extract of the bulbs of *Scilla sibirica* (Liliaceae),[6] by building-up the bicyclic skeleton from either C(5′) or C(2′).

The former synthetic strategy was successfully achieved and (−)-3-*epi*hyacinthacine A_5 (**1a**) was obtained from **2**

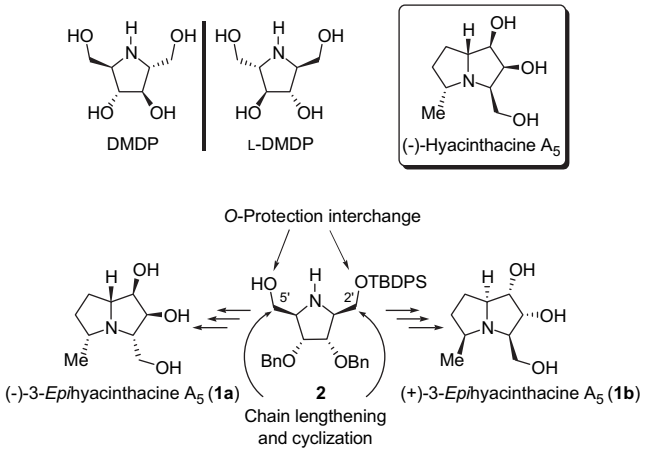

Figure 1. Synthetic strategy for the preparation of (−)-3-*epi* (**1a**) and (+)-3-*epi*hyacinthacine A_5 (**1b**) from orthogonally protected DADP (**2**).

in five steps (28% yield), whereas the application of the second strategy, consisting in a C(5′) *O*-protection and C(2′) *O*-deprotection, adequately functionalized chain-lengthening in this position and finally cyclization to the pyrrolizidine skeleton, afforded the mirror image (+)-3-*epi*-hyacinthacine A_5 (**1b**).

2. Results and discussion

In the synthesis described herein, the starting pyrrolidine **2** was previously *N*-protected as its Cbz derivative **3** that was then oxidized (TPAP/NMO) to the pyrrolidinic aldehyde **4**

☆ For Part 7, see Ref. 1.
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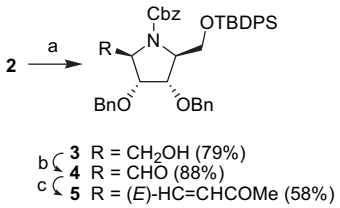
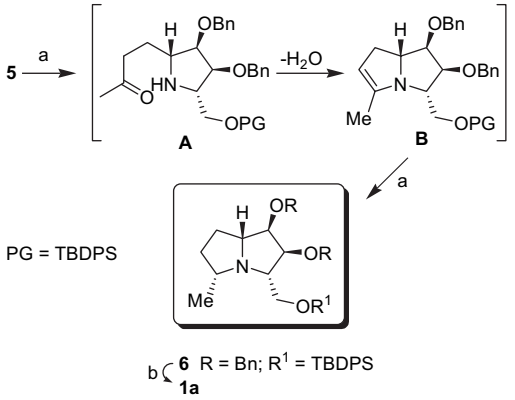
and finally allowed to react with 1-triphenylphosphoranylidene-2-propanone to afford, in a highly stereoselective manner, 4-[(3*E*,2′*R*,3′*R*,4′*S*,5′*S*)-3′,4′-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one (**5**), in accordance with the $J_{3,4}$ values of 16 and 15.6 Hz, showed by H-3 in the mixture of rotamers (Scheme 1).



Scheme 1. Synthesis of pyrrolidinic α,β-unsaturated ketone **5**. Reagents and conditions: (a) $CbzCl/Me_2CO/K_2CO_3$; (b) TPAP/NMO/CH_2Cl_2/4 Å MS and (c) $Ph_3P{=}CHCOCH_3$/MePh, 80 °C.

Catalytic hydrogenation (10% Pd–C)–cyclization of **5** afforded, in only one step, the fully protected (1*R*,2*S*,3*S*,5*R*,7a*R*)-1,2-dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine (**6**).

According to Scheme 2, formation of **6** must take place as follows: concomitant hydrogenation and *N*-deprotection of **5** gave the saturated ketone **A**, not isolated, which on subsequent intramolecular condensation gave the intermediate Δ^5-pyrrolizine **B** that was finally hydrogenated to **6**.



Scheme 2. Synthesis of (−)-3-*epi*hyacinthacine A_5 (**1a**). Reagents and conditions: (a) 10% Pd–C/H_2/MeOH and (b) (i) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form), (ii) TBAF·$3H_2O$/THF.

The stereochemistry of the new C(5) stereogenic centre was established on the basis of extensive NOE experiments. The NOE interactions are shown in Figure 2. The definite NOE effects between C(3)H and C(5)H, and Me(5)H and C(8)H were crucial in order to establish the *R*-configuration at C-5. In addition, the rest of the NOE interactions also confirmed the total stereochemistry of **6** and made possible to assign the resonance signals for H-6α,6β,7α,7β.

Removal of the protecting groups in **6** gave the target molecule (−)-3-*epi*hyacinthacine A_5 (**1a**), in accordance with its analytical and spectroscopic data.

The high stereoselective formation of **6** can be attributed, according to our previous results[7] and to Figure 2, to the

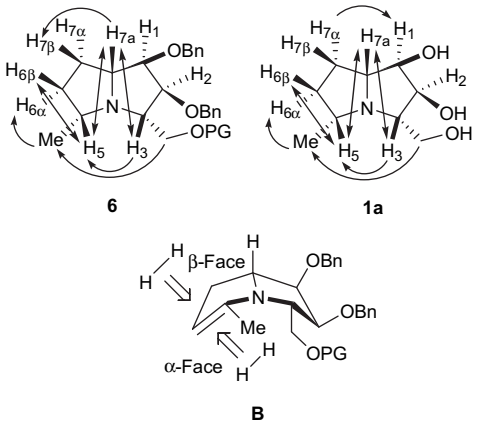
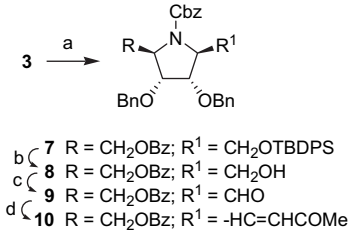


Figure 2. NOE interactions in **6** and **1a** and hydrogenation pathway of intermediate Δ^5-pyrrolizine (**B**).

peculiar shape of Δ^5-pyrrolizine **B**,[6,8] where it is appreciated that the β-face is less hindered for hydrogen attack that the α-face is, affording only compound **6**.

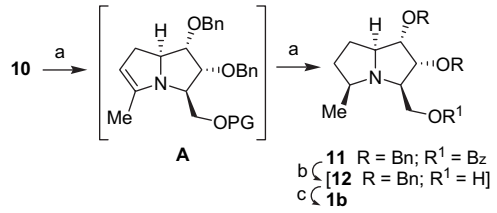
The above mentioned pivotal chiral character of **3**, allows the synthesis of looking-glass molecules, was probed in the synthesis of the mirror image of **1a**, (+)-3-*epi*hyacinthacine A_5 (**1b**). Thus, conventional benzoylation of **3** gave the fully protected derivative **7** (see Scheme 3). O-desilylation of **7** to the corresponding partially protected pyrrolidine **8** and subsequent oxidation (TPAP/NMO) afforded the pyrrolidinic aldehyde **9** that was not investigated, but used in the next step. In order to explore new synthetic possibilities for chain-lengthening and functionalization at C(5′) in **9**, the former C(2′) in **3**, the HWE's methodology was applied. Thus, aldehyde **9** readily reacted with diethyl (2-oxopropyl)phosphonate giving 4-[(2′*S*,3′*S*,4′*R*,5′*R*)-5′-benzoyloxymethyl-3′,4′-dibenzyloxy-*N*-benzyloxycarbonylpyrrolidin-2′-yl]but-3-en-2-one (**10**). On the contrary of compound **5**, the stereochemistry at the carbon–carbon double bond in **10** could not be determined in this case, due to an extensive broadening of the resonance signals.



Scheme 3. Synthesis of pyrrolidinic α,β-unsaturated ketone **10**. Reagents and conditions: (a) BzCl/CH_2Cl_2/TEA/DMAP (cat.); (b) *n*-$Bu_4N^+F^-\cdot 3H_2O$/THF and (c) TPAP/NMO/CH_2Cl_2/4 Å MS; (d) $(EtO)_2P(O)CH_2COCH_3$/NaH/THF, rt.

In Scheme 4 below and as for **5**, catalytic hydrogenation of **10** afforded a single isomeric pyrrolizidine identified as (1*S*,2*R*,3*R*,5*S*,7a*S*)-3-benzoyloxymethyl-1,2-dibenzyloxy-5-methylpyrrolizidine (**11**).

The absolute configuration of the new stereogenic centre C(5) was established on the basis of the NOE effects found (see Fig. 3). Thus, the definite NOE effects between C(3)H–C(5)H, C(3)H–C(7a)H, C(5)H–C(7a)H and Me(5)H–C(8)H



Scheme 4. Synthesis of (+)-3-*epi*hyacinthacine A_5 (**1b**). Reagents and conditions: (a) 10% Pd–C/H_2/MeOH; (b) MeONa (cat.)/MeOH; (c) 10% Pd–C/H_2/HCl, then Amberlite IRA-400 (OH^- form).

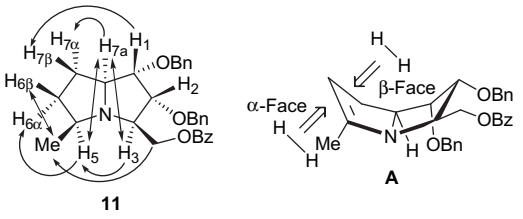


Figure 3. NOE interactions in **11** and hydrogenation pathway of intermediate Δ^5-pyrrolizine (**A**) in Scheme 4.

were essential in order to establish the *S*-configuration at C-5. In addition, the rest of the NOE interactions also confirmed the total stereochemistry of **11** and made possible to assign the resonance signals for H-6α,6β,7α,7β (Fig. 3).

As above, the configuration at the new stereogenic centre C(5), was again controlled by that existing at C(7a) in such a way that Me(5) and C(7a)H had a trans-disposition.[9]

Finally, compounds **1a** and **1b** were tested on a range of glycosidases and their IC_{50} values are included in the Table 1. Thus, **1a** was inhibitor to β-galactosidase (from bovine liver) at 62.4 μM, whereas both (**1a** and **1b**) were shown to be inhibitors to α-mannosidase (from jack beans) at 62.4 μM (**1a**) and 89.6 μM (**1b**). Compound **1a** was a more potent inhibitor (K_i=250 μM) of jack beans α-mannosidase than **1b** (K_i=420 μM). However, only **1a** inhibited of bovine liver β-galactosidase activity (K_i=300 μM). The alkaloids were not inhibitors of α-glucosidase (from baker's yeast), β-glucosidase (from almonds), α-galactosidase (green coffee), β-galactosidase (from *Aspergillus oryzae*) at 62.4 μM (**1a**) and 89.6 μM (**1b**).

Table 1. IC_{50} values for compounds **1a** and **1b** versus different glycosidases[a]

Enzyme	IC_{50} (μM)	
	1a	**1b**
α-Glucosidase (baker's yeast)	NI	NI
β-Glucosidase (almond)	NI	NI
α-Galactosidase (green coffee)	NI	NI
β-Galactosidase (bovine liver)	329	NI
β-Galactosidase (*A. oryzae*)	NI	NI
α-Mannosidase (Jack bean)	253	417

[a] NI=inhibition not observed under assay conditions.

3. Conclusions

Three conclusions can be stated from the above results: (i) that partially protected polyhydroxylated pyrrolidines, derived from common hexuloses, together with classical Wittig's or HWE's methodologies are both suitable for the enantiosynthesis of complex polyhydroxylated pyrrolizidines alkaloids; (ii) the configuration at C(5) in 5-methylpyrrolizidines is controlled by that existing at C(7a), in such a way that C(5)Me group and C(7a)H are in a trans-disposition and (iii) finally, that (−)-3-*epi*hyacinthacine A_5 (**1a**) and its (+)-enantiomer (**1b**) were shown as moderate inhibitors towards Jack bean α-mannosidase (IC_{50} 253 and 417 μM, respectively), whereas the former was specific of bovine liver β-galactosidase.

4. Experimental

4.1. General

Solutions were dried over $MgSO_4$ before concentration under reduced pressure. The ^1H and ^{13}C NMR spectra were recorded with Bruker AMX-300, AM-300 and ARX-400 spectrometers for solutions in $CDCl_3$ (internal Me_4Si). IR spectra were recorded with a Perkin–Elmer FTIR Spectrum One instrument, UV–vis measurements in a Spectronic® Genesys 5 spectrophotometer and mass spectra were recorded with a Hewlett–Packard HP-5988-A and Fisons mod. Platform II and VG Autospec-Q mass spectrometers. Optical rotations were measured for solutions in $CHCl_3$ (1-dm tube) with a Jasco DIP-370 polarimeter. TLC was performed on precoated silica gel 60 F_{254} aluminium sheets and detection by employing a mixture of 10% ammonium molybdate (w/v) in 10% aqueous sulfuric acid containing 0.8% cerium sulfate (w/v) and heating. Column chromatography was performed on silica gel (Merck, 7734). The noncrystalline compounds were shown to be homogeneous by chromatographic methods and characterized by NMR, MS and HRMS.

4.1.1. (2*S*,3*S*,4*R*,5*R*)-3,4-Dibenzyloxy-*N*-benzyloxycarbonyl-2′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxymethyl)pyrrolidine (3). To a well stirred solution of **2**[2] (1.8 g, 3 mmol) in dry acetone (20 mL), anhydrous potassium carbonate (3 g) and a solution of benzyl chloroformate (600 μL, 4.2 mmol) in the same solvent (10 mL) were added and the mixture kept at rt for 30 min. TLC (Et_2O) then revealed the presence of a faster-running compound. The mixture was filtered and the solid thoroughly washed with acetone and the filtrate and washings concentrated to a residue that was submitted to chromatography (Et_2O–hexane, 1:2) to give **3** as colourless syrup. Yield: 1.7 g (79%); $[\alpha]_D^{25}$ +10 (*c*, 1.8). IR (neat): 3448 (OH), 3067 and 3031 (aromatic), 1704 (C=O, Cbz), 740 and 700 cm^{-1} (aromatic). NMR data (300 MHz, inter alia): ^1H, δ 7.68–7.12 (m, 25H, 5Ph), 5.09 and 5.01 (2br d, 2H, *J*=12 Hz, CH_2Ph), 4.61–4.51 (br m, 4H, $2CH_2Ph$), 4.28–3.60 (3br m, 8H, H-2,2′a,2′b,3,4,5,5′a,5′b), 1.05 (s, 9H, CMe_3); ^{13}C (inter alia), δ 155.73 (C=O, Cbz), 77.66 and 76.74 (C-3,4), 71.96 and 71.79 ($2CH_2Ph$), 67.57 (CH_2Ph, Cbz), 64.63 and 62.82 (C-2′,5′), 64.56 and 63.59 (C-2,5), 26.98 (CMe_3) and 19.23 (CMe_3). HRMS (LSIMS): *m*/*z* 738.3221 [M^++Na]. For $C_{44}H_{49}NO_6NaSi$ 738.3227 (deviation +0.9 ppm).

4.1.2. 4-[(3*E*,2′*R*,3′*R*,4′*S*,5′*S*)-3′,4′-Dibenzyloxy-*N*-benzyloxycarbonyl-5′-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2′-yl]but-3-en-2-one (5). To a stirred solution of **3**

(835 mg, 1.17 mmol) in dry CH_2Cl_2 (10 mL) were added activated 4 Å molecular sieves (0.6 g), *N*-oxide-*N*-methylmorpholine (NMO, 213 mg, 1.82 mmol) and tetra-*n*-propylammonium perruthenate (TPAP, 50 mg) and the reaction mixture was kept at rt for 15 min. TLC (Et_2O/hexane, 1:1) then indicated the absence of the starting material and the presence of a faster-running compound. The reaction was diluted with ether (30 mL), filtered through a bed of Silica gel 60 (Scharlau, 230–400 mesh) and thoroughly washed with ether. The combined filtrate and washings were concentrated to aldehyde **4** (730 mg, 88%); $[\alpha]_D^{25}$ −9 (*c*, 0.85). IR (neat): 3068 and 3032 (aromatic), 1735 (CHO), 1710 (C=O, Cbz), 738 and 700 cm^{-1} (aromatic). This material was used in the next step.

To a solution of **4** (730 mg, 1 mmol) in dry toluene (20 mL) was added 1-triphenylphosphoranylidene-2-propanone (1.07 g, 3.36 mmol) and the mixture was heated at 80 °C for 3 h. TLC (ether/hexane, 2:1) then revealed the presence of a slightly slower-running compound. The reaction mixture was filtered and supported on silica gel, then chromatographed (ether/hexane, 1:2) to afford **5** (730 mg, 83%) as a thick syrup; $[\alpha]_D^{26}$ +27 (*c* 1). IR (neat): 3068 and 3032 (aromatic), 1705, 1679 and 1633 (C=O, conjugated ketone, Cbz and C=C conjugated), and 700 cm^{-1} (aromatic). NMR data (400 MHz): ^1H, δ 7.57–7.14 (m, 25H, 5Ph), 6.64 and 6.56 (2br dd, $J_{2',4}$=6.5 and 7.1 Hz, H-4, two rotamers), 6.26 and 6.12 (2br d, $J_{3,4}$=16 and 15.6 Hz, H-3, two rotamers), 5.20–4.97 and 4.64–3.74 (4br m, 12H, 3PhCH_2 and H-2′,3′,4′,5′,5″a,5″b), 2.05 and 1.90 (2br s, 3H, H-1,1,1, two rotamers) and 1.01 (s, 9H, CMe_3). ^{13}C (inter alia), δ 198.16 (C-2), 155.62 (Cbz), 81.52 and 80.47 (C-3′,4′), 72.27, 71.66 and 67.30 (2Ph*C*H_2 and Cbz), 64.21, 63.56, 62.49 and 62.26 (C-2′,5′, two rotamers), 62.72 (C-5″), 27.01 (C-1 and C*Me*$_3$) and 19.33 (*C*Me_3). HRMS (LSIMS): *m*/*z* 776.3381 [M^++Na]. For $C_{47}H_{51}NO_6NaSi$ 776.3383 (deviation +0.3 ppm).

4.1.3. (1*R*,2*S*,3*S*,5*R*,7a*R*)-1,2-Dibenzyloxy-3-*tert*-butyldiphenylsilyloxymethyl-5-methylpyrrolizidine (6). Compound **5** (690 mg, 0.92 mmol) in methanol (30 mL) was hydrogenated at 60 psi over 10% Pd–C (200 mg) for 18 h. TLC (ether/hexane 1:2) then showed the presence of a new compound of higher mobility. The catalyst was filtered off, washed with methanol and the filtrate and washings concentrated to a residue that was submitted to column chromatography (ether/hexane 1:2) to afford pure syrupy **6** (290 mg, 52%), which had $[\alpha]_D^{25}$ +15 (*c* 1.3). IR (neat): 3068, 3030, 738 and 700 cm^{-1} (aromatic). NMR data (400 MHz): ^1H, δ 7.70–7.25 (2m, 20H, 4Ph), 4.70 and 4.63 (2d, 2H, J=11.8 Hz, CH_2Ph), 4.60 and 4.57 (2d, 2H, J=12.8 Hz, CH_2Ph), 4.06 (dd, 1H, $J_{1,2}$=6.2, $J_{2,3}$=3.4 Hz, H-2), 3.75 (dd, 1H, $J_{3,8}$=5.0, $J_{8,8'}$=10.5 Hz, H-8), 3.60 (dd, 1H, H-1), 4.56 (dd, 1H, $J_{3,8'}$=6.6 Hz, H-8′), 3.11 (dt, 1H, $J_{7\beta,7a}$=5.4, $J_{1,7a}$=$J_{7\alpha,7a}$=10.0 Hz, H-7a), 2.83 (m, 1H, H-3), 2.52 (sex, 1H, $J_{5,6\beta}$=$J_{5,6\alpha}$=$J_{5,Me}$=6.2 Hz, H-5), 2.18 (dq, 1H, $J_{6\beta,7\beta}$=$J_{6\beta,7\alpha}$=8.3, $J_{6\alpha,6\beta}$=13 Hz, H-6β), 1.77 (m, 1H, H-7β), 1.58 (m, 1H, H-6α), 1.39 (dq, 1H, $J_{6\alpha,7\alpha}$=7.6, $J_{7\alpha,7\beta}$=10.7 Hz, H-7α), 1.08 (s, 9H, CMe_3) and 0.98 (d, 3H, Me); ^{13}C (inter alia), δ 84.91 (C-2), 79.36 (C-1), 72.20 and 71.73 (2*C*H_2Ph), 72.09 (C-7a), 68.27 (C-3), 65.86 (C-8), 55.03 (C-5), 37.10 (C-6), 26.99 (C*Me*$_3$), 25.21 (C-7), 21.33 (Me) and 19.34 (*C*Me_3). Mass spectrum (LSIMS): *m*/*z* 628.3227 [M^++Na]. For $C_{39}H_{47}NO_3NaSi$ 628.3223 (deviation −0.6 ppm).

4.1.4. (1*R*,2*S*,3*S*,5*R*,7a*R*)-1,2-Dihydroxy-3-hydroxymethyl-5-methylpyrrolizidine [(−)-3-*epi*hyacinthacine A_5, 1a]. A solution of **6** (260 mg, 0.43 mmol) in methanol (30 mL) was acidified (concd HCl) and hydrogenated (10% Pd–C, 110 mg) at 60 psi for 15 h. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form) and concentrated. ^1H NMR of the residue showed the absence of benzyl group and that the TBDPS group still remains. The residue was dissolved in THF (5 mL) and treated with a solution of TBAF·$3H_2O$ (350 mg) in the same solvent (5 mL) at rt overnight. TLC (ether–methanol–aq 30% NH_4OH, 5:1:0.1) then revealed a new compound with R_f 0.46. The solvent was eliminated and the residue chromatographed (ether → ether–methanol–aq 30% NH_4OH, 5:1:0.1) to afford pure **1a** (75 mg, 93%), which had $[\alpha]_D^{29}$ −15 and $[\alpha]_{405}^{29}$ −20 (*c* 0.44, methanol). NMR data (400 MHz, methanol-d_4): ^1H, δ 4.10 (dd, 1H, $J_{1,2}$=7.0, $J_{2,3}$=4.8 Hz, H-2), 3.73 (dd, 1H, $J_{3,8}$=4.4, $J_{8,8'}$=11.9 Hz, H-8), 3.70 (dd, 1H, $J_{3,8'}$=4.6 Hz, H-8′), 3.62 (dd, 1H, $J_{1,7a}$=8.5 Hz, H-1), 2.77 (ddd, 1H, $J_{7a,7\beta}$=5.8, $J_{7a,7\alpha}$=10.4 Hz, H-7a), 2.53 (br sex, 1H, $J_{5,6\alpha}$=$J_{5,6\beta}$=$J_{5,Me}$=6.3 Hz, H-5), 2.43 (q, 1H, H-3), 2.23 (ddt, 1H, $J_{6\beta,7\beta}$=9.0, $J_{6\beta,7\alpha}$=7.9, $J_{6\alpha,6\beta}$=12.8 Hz, H-6β), 1.79 (dddd, 1H, $J_{6\alpha,7\beta}$=2.6, $J_{7\alpha,7\beta}$=11.7 Hz, H-7β), 1.65 (dddd, 1H, $J_{6\alpha,7\alpha}$=10.7 Hz, H-6α), 1.45 (br dq, 1H, H-7α) and 1.19 (d, 3H, Me); ^{13}C, δ 78.26 (C-2), 76.14 (C-7a), 72.45 (C-1), 71.70 (C-3), 63.22 (C-8), 56.95 (C-5), 37.69 (C-6), 24.98 (C-7) and 21.19 (Me). Mass spectrum (LSIMS): *m*/*z* 156.1025 [M^+-CH_2OH]. For $C_8H_{14}NO_2$ 156.1025 (deviation −0.1 ppm).

4.1.5. (2*R*,3*R*,4*S*,5*S*)-2′-*O*-Benzoyl-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-5′-*O*-*tert*-butyldiphenylsilyl-2,5-bis(hydroxylmethyl)pyrrolidine (7). To a stirred solution of **3** (835 mg, 1.17 mmol) in dry dichloromethane (10 mL) were added triethylamine (TEA, 150 μL, 1.8 mmol), DMAP (50 mg) and benzoyl chloride (150 μL, 1.4 mmol) and the mixture left at rt for 20 h. TLC (ether/hexane 2:1) then revealed a faster-running compound. Conventional work-up of the reaction mixture and column chromatography (ether/hexane 1:3) afforded pure **7** (910 mg, 95%) as a colourless syrup, which had $[\alpha]_D^{25}$ +10 and $[\alpha]_{405}^{26}$ +27 (*c* 1.8). IR (neat): 3088 and 3067 (aromatic), 1722 (COPh and >NCO_2Bn), 740 and 700 cm^{-1} (aromatic). NMR data (400 MHz): ^1H, δ 8.14–7.18 (m, 30H, 6Ph), 5.21–5.01 and 4.69–3.68 (2m, 14H, 3CH_2Ph, H-2,2′a,2′b,3,4,5,5′a,5′b), and 1.03 (s, 9H, CMe_3); ^{13}C (inter alia), δ 166.03 (*C*OPh), 155.74 (>N*C*O_2Bn), 76.97, 76.07, 75.78 and 75.07 (C-3,4, two rotamers), 71.85, 71.71 and 71.43 (2O*C*H_2Ph, two rotamers), 67.35 and 67.13 (two rotamers), 63.58, 62.99, 60.41 and 59.88 (C-2,5, two rotamers), 62.57, 62.23, 62.02 and 61.69 (C-2′,5′, two rotamers), 26.98 (C*Me*$_3$) and 19.26 (*C*Me_3). Mass spectrum (LSIMS): *m*/*z* 842.3485 [M^++Na]. For $C_{51}H_{53}NO_7NaSi$ 842.3489 (deviation +0.4 ppm).

4.1.6. (2*R*,3*R*,4*S*,5*S*)-2′-*O*-Benzoyl-3,4-dibenzyloxy-*N*-benzyloxycarbonyl-2,5-bis(hydroxymethyl)pyrrolidine (8). To a stirred solution of **7** (840 mg, 1.03 mmol) in THF (15 mL) was added TBAF·$3H_2O$ (490 mg, 1.55 mmol) and the mixture was kept at rt. TLC (ether/hexane 3:1)

then showed a new compound of lower mobility. The mixture was neutralized with acetic acid, concentrated to a residue that was dissolved in ether, washed with brine, concentrated, and then submitted to column chromatography (ether/hexane 2:1) to yield pure **8** (500 mg, 84%) as a colourless syrup, which had $[\alpha]_D^{26}$ −12 (*c* 0.8). IR (neat): 3470 (OH), 3064 and 3032 (aromatic), 1719 (COPh and >NCO_2Bn), 712 and 698 cm^{-1} (aromatic). NMR data (300 MHz): ^{1}H, δ 7.93–7.27 (m, 20H, 4Ph), 5.26 and 5.12 (2d, 2H, *J*=12.3 Hz, OCH_2Ph), 4.62–3.85 (m, 11H, 2CH_2Ph, H-2,2′a,2′b,3,4,5,5′a) and 3.63 (dd, 1H, $J_{4,5'b}$=4.9, $J_{5'a,5'b}$=11.6 Hz, H-5′b); ^{13}C (inter alia), δ 77.10 and 76.68 (C-3,4), 72.15 and 71.90 (2O*C*H_2Ph), 67.80 (>$NCO_2C H_2$Ph), 64.32 and 61.30 (C-2,5), 63.82 and 63.17 (C-2′,5′). Mass spectrum (LSIMS): *m*/*z* 604.2312 [M$^+$+Na]. For $C_{35}H_{35}NO_7Na$ 604.2311 (deviation −0.1 ppm).

4.1.7. 4-[(2′*S*,3′*S*,4′*R*,5′*R*)-5′-Benzoyloxymethyl-3′,4′-dibenzyloxy-*N*-benzyloxycarbonylpyrrolidin-2′-yl]but-3-en-2-one (10). To a solution of **8** (1.08 g, 1.9 mmol) in dry dichloromethane (10 mL) were added activated powdered 4 Å molecular sieve (700 mg), *N*-methylmorpholine *N*-oxide (325 mg, 2.8 mmol) and TPAP (40 mg) and the reaction mixture kept at rt for 1 h. TLC (ether/hexane 4:1) then showed a faster-running compound. The reaction was diluted with ether (30 mL), filtered through a bed of Silica gel 60 (Scharlau, 230–400 mesh) and thoroughly washed with ether. The combined filtrate and washings were concentrated to aldehyde **9**, that was used in the next step.

To a well stirred suspension of sodium hydride (60% 150 mg, 3.7 mmol) in anhydrous THF (15 mL), diethyl(2-oxopropyl)phosphonate (660 μL, 3.7 mmol) was added and the mixture was left at rt for 1 h, when a solution of aldehyde **9** in THF (10 mL) was added. After 5 min TLC (ether/hexane 4:1) revealed the presence of a new compound of slightly lower mobility. The solvent was eliminated and the residue was partitioned into ether/water. The organic phase was separated and concentrated to a residue that was submitted to column chromatography with ether/hexane (3:1) as eluent to give pure **10** (520 mg, 45% from **8**) as a colourless syrup, which had $[\alpha]_D^{23}$ −15 and $[\alpha]_{405}^{24}$ −46 (*c* 2.1). IR (neat): 3088 and 3063 (aromatic), 1718 and 1678 ($PhCO_2$, >NCO_2Bn and α,β-unsaturated ketone), 713 and 699 cm^{-1} (aromatic). NMR data (300 MHz): ^{1}H, δ 7.85–7.25 (m, 20H, 4Ph), 6.52 (br m, 1H, H-4), 6.20–6.07 (br m, 1H, H-3), 5.22–4.25 (2m, 10H, 3CH_2Ph, H-3′,4′,5″a,5″b), 4.01 (br t, 1H, *J*=4 Hz) and 3.91 (br t, 1H, *J*=5.2 Hz) for H-2′,5′ and 1.90 (br s, 3H, H-1,1,1); ^{13}C (inter alia), δ 197.58 (C-2), 166.09 (*C*OPh), 155.72 (>N*C*O_2Bn), 72.11 (2O*C*H_2Ph), 67.58 (>$NCO_2C H_2$Ph), 62.56 (C-5″) and 27.41 (C-1). Mass spectrum (LSIMS): *m*/*z* 642.2470 [M$^+$+Na]. For $C_{38}H_{37}NO_7Na$ 642.2468 (deviation −0.3 ppm).

4.1.8. (1*S*,2*R*,3*R*,5*S*,7a*S*)-3-Benzoyloxymethyl-1,2-dibenzyloxy-5-methylpyrrolizidine (11). Compound **10** (500 mg, 0.8 mmol) in dry methanol (15 mL) was hydrogenated at 60 psi over 10% Pd–C (100 mg) for 24 h. TLC (ether/hexane 4:1) then showed the presence of a new compound of lower mobility. The catalyst was filtered off, washed with methanol and the filtrate and washings concentrated to a residue that was submitted to column chromatography (ether/hexane 2:1) to afford pure syrupy **11** (280 mg, 74%), which had $[\alpha]_D^{25}$ +8.5 and $[\alpha]_{405}^{25}$ +19 (*c* 1). IR (neat): 3063 and 3031 (aromatic), 1720 (CO benzoate), 712 and 697 cm^{-1} (aromatic). NMR data (400 MHz): ^{1}H, δ 8.03 (d, 2H, $J_{o,m}$=7.5 Hz, H-*ortho* Bz), 7.58 (t, 1H, $J_{m,p}$=7.5 Hz, H-*para* Bz), 7.44 (t, 2H, H-*meta* Bz), 7.39–7.27 (m, 10H, 2CH_2Ph), 4.77 and 4.58 (2d, 2H, *J*=11.7 Hz, CH_2Ph), 4.65 and 4.59 (2d, 2H, *J*=12.0 Hz, CH_2Ph), 4.43 (dd, 1H, $J_{3,8}$=4.8, $J_{8,8'}$=11.4 Hz, H-8), 4.30 (dd, 1H, $J_{3,8'}$=6.3 Hz, H-8′), 4.14 (dd, 1H, $J_{1,2}$=6.4, $J_{2,3}$=4.2 Hz, H-2), 3.68 (dd, 1H, $J_{1,7a}$=8.7 Hz, H-1), 3.10 (dt, 1H, $J_{7a,7\alpha}$=5.5, $J_{7a,7\beta}$=9.9 Hz, H-7a), 3.00 (br q, 1H, H-3), 2.62 (br sex, 1H, $J_{5,6\alpha}$=$J_{5,6\beta}$=7.0 Hz, H-5), 2.22 (dq, 1H, $J_{6\alpha,7\alpha}$=$J_{6\alpha,7\beta}$=8.5, $J_{6\alpha,6\beta}$=13.0 Hz, H-6α), 1.81 (dddd, 1H, $J_{7\alpha,6\beta}$=2.2 Hz, H-7α), 1.65 (dddd, 1H, $J_{6\beta,7\beta}$=10.0 Hz, H-6β), 1.47 (dq, 1H, $J_{7\alpha,7\beta}$=10.9 Hz, H-7β) and 1.16 (d, 3H, $J_{Me,5}$=6.0 Hz, Me); ^{13}C (inter alia), δ 166.46 (*C*OPh), 84.82 (C-2), 79.07 (C-1), 72.73 (C-7a), 72.73 and 71.83 (2*C*H_2Ph), 65.93 (C-8), 65.07 (C-3), 54.81 (C-5), 37.13 (C-6), 25.36 (C-7) and 21.47 (Me). Mass spectrum (LSIMS): *m*/*z* 494.2309 [M$^+$+Na]. For $C_{30}H_{33}NO_4Na$ 494.2307 (deviation −0.4 ppm).

4.1.9. (1*S*,2*R*,3*R*,5*S*,7a*S*)-1,2-Dihydroxy-3-hydroxymethylpyrrolizidine [(+)-3-*epi*hyacinthacine A_5, 1b]. Conventional debenzoylation of **11** (270 mg, 1 mmol) in 0.2 N sodium methoxide in dry methanol (7 mL) gave after work-up compound **12** (280 mg, 0.8 mmol) that was dissolved in dry methanol (30 mL) and hydrogenated (10% Pd–C, 170 mg) in acid medium (concd HCl, four drops) at 50 psi for 48 h. TLC (ether/methanol 3:1) then showed a not mobile compound. The catalyst was filtered off, washed with methanol and the filtrate and washings neutralized with Amberlite IRA-400 (OH^- form), then concentrated. Column chromatography (ether/methanol/TEA 5:1:0.1) of the residue gave pure **1b** (110 mg, 80%), which had $[\alpha]_D^{26}$ +14.5 (*c* 0.8, methanol) and NMR data identical to **1a**.

4.2. Glycosidase inhibitory activities

All pNP-pyranoside substrates, α-glucosidase (from baker's yeast), β-glucosidase (from almonds), α-galactosidase (from green coffee), β-galactosidase (from bovine liver), β-galactosidase (from *A. oryzae*) and α-mannosidase (from Jack beans) were purchased from Sigma Chemical Company. Kinetic studies were performed at 37 °C in 50 mM sodium citrate/phosphate buffer. Enzyme concentrations ranging from 0.5 μg mL^{-1} to 0.1 μg mL^{-1} were used, depending on the substrate studied. The activities of enzymes were determined using *p*-nitrophenyl glycosides as substrates at the optimum pH of each enzyme. Substrates, suitably diluted enzyme solutions and inhibitors were incubated together for 30 min at 37 °C. Reactions were followed in an UV–vis spectrophotometer by measuring the change in the absorbance of light at 400 nm. Data were analyzed using the programme GraFit.[10]

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Supplementary data

^{1}H and ^{13}C NMR (six pages) for compounds **1a**, **6** and **11**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2006.04.003.

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Mild and rapid method for the generation of *o*-quinone methide intermediates. Synthesis of puupehedione analogues

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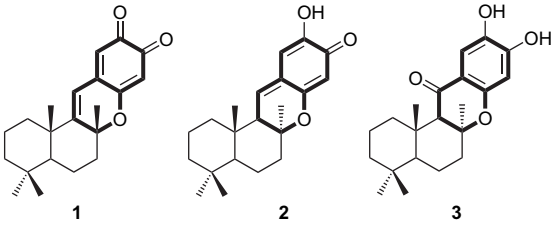
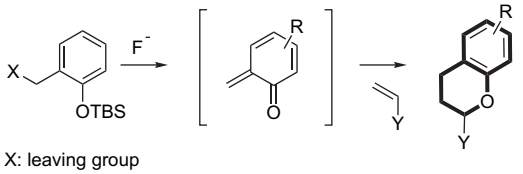
Abstract—A route to simpler analogues to bioactive puupehedione derivatives involving a hetero Diels–Alder cycloaddition of a *o*-quinone methide is described. These intermediate species are generated via fluoride-induced desilylation of silyl derivatives of *o*-hydroxybenzyl iodides. Remarkable short reaction times and very mild experimental conditions are the main features of this method.

1. Introduction

The benzopyran moiety is contained in a variety of natural products, many of which present interesting biological properties.[1] Among them, puupehedione (**1**) and other related marine derivatives, as puupehenone (**2**) and 15-oxo-puupehenol (**3**), have been attracting our attention during the last years due to the wide range of biological properties they present, including antitumor, antiviral antimalarial, antibiotic antituberculosis, antioxidant, insecticidal and antifungal activities.[2]



Thus, as a part of a programme to identify useful anti-angiogenic agents, some of us proved that some puupehedione-related derivatives completely inhibited the in vivo angiogenesis in the CAM assay at doses equal or lower than 30 nmol/egg, which makes them attractive drugs for further evaluation.[3] The scarce availability of many bioactive compounds from their natural sources together with the impracticality of many syntheses for producing amounts of materials appropriate for clinical follow-up has led to much research to develop simpler and more accessible analogues for broad biological evaluation.[4] In this context, we devised that the benzopyran nucleus of these compounds could be generated by reaction of *o*-quinone methides intermediates, obtained via fluoride-induced desilylation *o*-silyloxybenzyl derivatives, with appropriate dienophiles (Scheme 1). Although different reports on this subject were described by Rokita et al.,[5] this group used the *o*-quinone methide in DNA alkylating studies. Thus, to our knowledge, the only use of this reaction in organic synthesis was described by Young et al., in their synthesis of (±)-thielocin Alβ.[6]



Scheme 1.

o-Quinone methides are extremely reactive transient species, which undergo dimerisation processes in the absence of nucleophiles or electron-rich alkenes.[7] Although different strategies have been reported for their generation, most of them rely on the use of catalysts, acidic or basic conditions, high temperatures or long reaction times.[8] Among the recent advances in this subject,[9] special relevance should be given to the works of Pettus et al., which include a low-temperature anionic method for generating *o*-quinone methides and their enantioselective cycloaddition with a chiral enol ether.[10]

Keywords: Cyclisation; Epoxides; Titanium; Radical reaction; Terpenoids.
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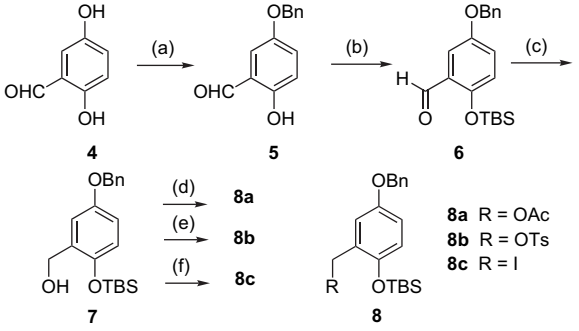
To start the development of this synthetic method, we addressed the search of the corresponding oxa-dienic precursor starting from commercial 2,5-dihydroxybenzaldehyde, **4**, following the straightforward transformations shown in Scheme 2.

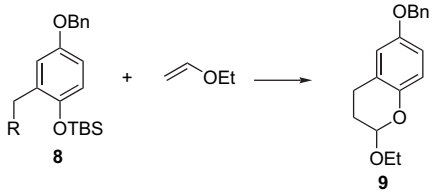


Scheme 2. Reagents and conditions: (a) $NaHCO_3$, KI, BnBr, CH_3CN, reflux, 24 h, 51%; (b) TBSCl, imidazole, DMF, rt, 4 h, 82%; (c) $NaBH_4$, MeOH, rt, 2 h, 98%; (d) Ac_2O, Py, rt, 42 h, 94%; (e) TsCl, Py, DMAP, reflux, 7 h, 68%; (f) Ph_3P, imidazole, I_2, CH_3CN/toluene, 60 °C, 10 min, 83%.

Thus, **4** was monobenzylated using the mixture BnBr, KI and $NaHCO_3$[11] to afford **5** in a 51% yield. An additional 36% of the corresponding dibenzylated derivative was also obtained. Protection of the hydroxyl group of **5** as silyl ether and subsequent treatment with $NaBH_4$ furnished primary alcohol **7**. Different leaving groups were then installed on this primary position (**8a**–**8c**) in order to test our hypothesis. The results obtained in the reaction of these derivatives with ethyl vinyl ether in the presence of TBAF are shown in Table 1.

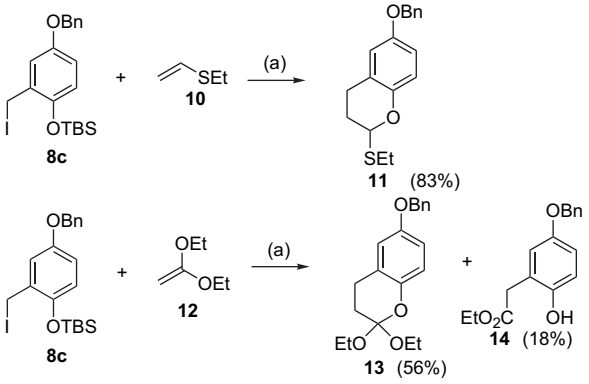
When the corresponding acetate or tosylate benzyl derivatives were treated for 10 min with TBAF (1.5 equiv) in the presence of 100 equiv of ethyl vinyl ether in DCM at 0 °C, only decomposition of starting material was observed. The hoped-for conversion took place when iodide was used as leaving group (entry 3, Table 1). More efficient conversion (up to 88%) occurred when benzene was used as solvent (entry 5, Table 1) (surely due to the less solubility in benzene of the potential nucleophilic salt TBAI, by-product of the reaction). It is worth noting that this yield was obtained in a very short reaction time, 2 min, and at room temperature, which are unprecedently mild experimental conditions for this kind of reaction. Although the use of the corresponding enol ether as the solvent for the reaction has been reported to increase the yield in many of these hetero Diels–Alder processes,[12] different assays were performed in order to check to what extent the quantity of ethyl vinyl ether could be lowered (entries 6–9, Table 1). Thus, an acceptable yield was still obtained using 35 equiv of ethyl vinyl ether, only a moderate result was found when the quantity of this reagent was reduced to 20 equiv, while the use of 10 equiv led to minor quantities of the desired adduct.

Table 1. Reaction of **8a–c** with ethyl vinyl ether



Entry	R	Temperature (°C)	Time	Solvent	Equiv of dienophile	Yield (%)
1	OAc	0	10	DCM	100	0
2	OTs	0	10	DCM	100	0
3	I	0	10	DCM	100	40
4	I	0	2	DCM	100	41
5	I	25	2	Benzene	100	88
6	I	25	2	Benzene	50	87
7	I	25	2	Benzene	35	70
8	I	25	2	Benzene	20	45
9	I	25	2	Benzene	10	5–10

Having found the conditions to efficiently achieve the generation and ensuing cycloaddition of the *o*-quinone methide derived from **8c**, we then turned our efforts to study the versatility of this process. Thus, two variations of this protocol were studied. On one hand, **8c** was caused to react with other dienophiles as **10** and **12** (Scheme 3).

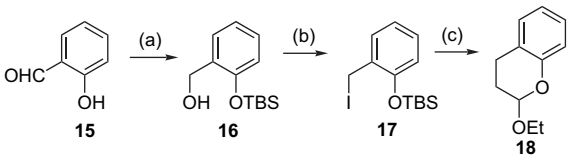


Scheme 3. Reagents and conditions: (a) TBAF, benzene, rt, 2 min.

The results found with **10** and **12** showed that the reaction proceeded as satisfactorily as it did when ethyl vinyl ether was employed. With respect to the formation of the alkylthiochroman derivative **11**, it should be remarked that although *o*-quinone methides have been reported to undergo [4+2] cycloadditions with vinyl ethers, furans, enamines and imines, to the best of our knowledge, this is the first report of a sulfide ether acting as a dienophile in a cycloaddition reaction with an in situ generated *o*-quinone methide. Furthermore, the synthesis of **11** is of additional interest since different thiochromone derivatives related to it are contained in a patent useful for the treatment of Alzheimer disease, Down syndrome, vascular dementia and parkinsonism.[13] Other noteworthy adduct include the direct formation of the *o*-alkyl phenol derivative **14**, since *o*-functionalized phenols are ubiquitous among natural products.[14,12]

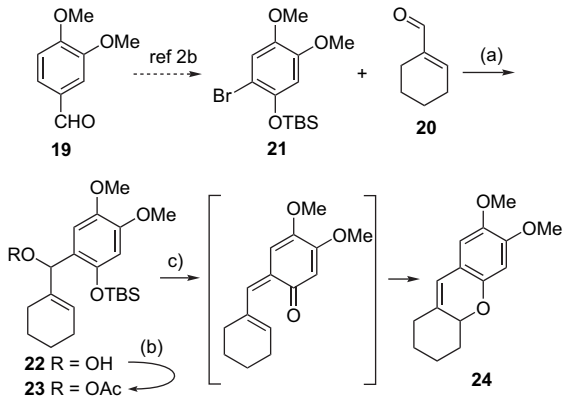
The second variation introduced with the aim of widening the scope of this procedure was the use of a different oxa-dienic moiety. Thus, starting from commercial 2-hydroxybenzaldehyde (**15**), the corresponding *o*-silyloxybenzyl iodide, **17**, was obtained after straightforward transformations (Scheme 4). When this compound was caused to react with ethyl vinyl ether, the reaction was found to proceed similarly. TLC monitoring and NMR control of the reaction

crude showed that chroman **18** was the only compound generated. The noticed volatility of **18** is postulated to account for the moderate yields obtained.



Scheme 4. Reagents and conditions: (a) (i) TBSCl, imidazole, DMF, rt, 4 h; (ii) $NaBH_4$, MeOH, rt, 2 h, 81% in two steps; (b) Ph_3P, imidazole, I_2, CH_3CN/toluene, 60 °C, 10 min, 73%; (c) TBAF, ethyl vinyl ether, benzene, rt, 2 min 51%.

With the above results in mind, we felt that puupehedione analogue **24** could be expeditiously synthesized using this procedure from commercially available 3,4-dimethoxybenzaldehyde (**19**) and 1-cyclohexene-1-carboxaldehyde (**20**) (Scheme 5).



Scheme 5. Reagents and conditions: (a) **21**, THF, −78 °C, *t*BuLi, 15 min, then **20**, 15 min, 81%; (b) Ac_2O, Py, 0 °C, 1 h; (c) benzene, TBAF, 2 min, rt, 62% two steps.

It should be noted that the synthetic proposal for **24** involves an intramolecular hetero Diels–Alder cycloaddition. Thus, the success of this approach would suppose a significant widening of the possibilities of this protocol, although the ultimate aim of this synthesis is to test whether compound **24** or related derivatives would retain the activity of metabolites such as puupehedione (**1**), puupehenone (**2**) and 15-oxopuupehenol (**3**).

The synthesis of **24** began with the addition of the organolithium derived from commercial **19** to aldehyde **20** to give alcohol **22** in 81% yield (Scheme 2). Compound **22** was acetylated and treated without further purification with TBAF. The hoped-for conversion took place efficiently, a 62% of **24** being obtained as a result of an electrocyclic process.[15] Contrary to what were observed in the intermolecular version of the process, an acetate group was now found to be an efficient leaving group.

In conclusion, we have proved that *o*-quinone methides can be generated from *o*-silyloxybenzyl derivatives via fluoride-induced desilylation. These methides reacted with electron-rich alkene to afford different chroman nuclei. This new method compares favourably with existing alternatives in terms of reaction times, reaction temperatures and the ease of generation of the methide precursor. This reaction was applied to the synthesis of a simpler analogue of biologically active puupehedione-related compounds, a part of a programme to identify useful anti-angiogenic agents. In the hope of widening the possibilities offered by this method, further studies with the aim of obtaining more analogues of puupehedione and other interesting chroman derivatives are being carried out.

2. Experimental

2.1. General

All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an atmosphere of argon. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35–70 μm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualising agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. IR spectra were recorded with a Matson model Satellite FTIR instrument as NaCl plates (films). NMR studies were performed with a Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz) spectrometer. The accurate mass determination was carried out with a AutoSpec-Q mass spectrometer arranged in a EBE geometry (Micromass Instrument, Manchester, UK) and equipped with a FAB (LSIMS) source.

2.1.1. General procedure for the generation of benzopyranes via *o*-methide quinone intermediates. To a solution of iodo derivative (0.22 mmol) in dry benzene (4 mL) was added 1.08 mL of ethyl vinyl ether and the resulting solution is stirred for 5 min. Then, it was added 0.32 mL of a 1 M solution of TBAF. The mixture was further stirred for 2 min and then diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography.

2.2. Synthesis of oxa-dienic precursors

2.2.1. Synthesis of 8c.

2.2.1.1. 5-(Benzyloxy)-2-(*t*-butyldimethylsilyloxy) benzaldehyde (6). To a solution of 2 g (14.5 mmol) of commercial 2,5-dihidroxybenzaldehide (**4**), 1.388 g (16.53 mmol) of $NaHCO_3$ and 0.241 g (1.45 mmol) of KI in 30 mL of dry acetonitrile heated to 60 °C, 2.23 mL of BnBr (3.22 g, 18.85 mmol) were added. The reaction mixture was then stirred under argon at reflux for 24 h. The solvent was removed to afford a crude product, which was re-dissolved in EtOAc (50 mL) and washed with 1 N HCl and brine. The residue was purified by column chromatography. Eluting with hexane/EtOAc, 3:1, afforded 1692 mg of the corresponding monobenzylated derivative **5** (51%).[16] To a solution of 1090 mg of **5** in 30 mL of DCM under argon was added imidazole (810 mg, 12.05 mmol) and TBSCl (1090 mg, 7.23 mmol). The reaction was stirred at room

temperature for 4 h and then diluted with EtOAc and washed with H_2O, 1 N HCl, saturated $NaHCO_3$ and brine and worked up as usual. The product obtained was purified by chromatography on silica gel (hexane/EtOAc, 4:1) to give 960 mg (82% yield) of **6** as yellow oil. IR (film) ν: 3065, 3034, 2955, 2930, 2858, 1681, 1611, 1489, 1426, 1388, 1273, 1211, 1155, 1026, 908, 841, 782 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 6H), 1.00 (s, 9H), 5.02 (s, 2H), 6.81 (d, J=9.0 Hz, 1H), 7.12 (dd, J=9.0, 3.4 Hz, 1H), 7.36 (d, J=3.4 Hz, 1H), 7.45–7.30 (m, 5H), 10.39 (1H, s) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, 18.1, 25.6, 70.2, 110.8, 121.4, 124.1, 127.0, 127.3, 127.8, 128.3, 136.5, 153.0, 153.1, 189.2 ppm. HRFABMS calcd for $C_{20}H_{26}O_3NaSi$ $[M+Na]^+$ 365.1549, found 365.1551.

2.2.1.2. [5-Benzyloxy-2-(*t*-butyldimethylsilyloxy)-phenyl] methanol (7). To a solution of 265 mg of $NaBH_4$ (7 mmol) in MeOH (11 mL) was added **6** (400 mg, 1.02 mmol) in 6 mL of MeOH. The mixture was stirred at room temperature and refluxed for 2 h. MeOH was then removed and the resulting crude re-dissolved in EtOAc and washed with 2 N HCl and brine. Removal of the solvent afforded a crude residue, which was purified by flash chromatography (hexane/*t*-BuOMe 6:1) to give 398 mg (98%) of **7**. IR (film) ν: 3402, 3064, 3035, 2955, 2929, 2885, 2858, 1606, 1585, 1494, 1463, 1381, 1268, 1222, 1155, 1027, 902, 839, 780, 736, 696 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 6H), 0.95 (s, 9H), 4.58 (s, 2H), 4.95 (s, 2H), 6.66 (d, J=8.8 Hz, 1H), 6.71 (dd, J=8.8, 3.0 Hz, 1H), 6.92 (d, J=3.0 Hz, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.4, 18.0, 25.7, 61.1, 70.3, 114.2, 114.6, 118.9, 127.4, 127.7, 128.4, 132.4, 137.2, 146.8, 153.2 ppm. HRFABMS calcd for $C_{20}H_{28}O_3NaSi$ $[M+Na]^+$ 367.1705, found 367.1698.

2.2.1.3. 4-Benzyloxy-1-(*t*-butyldimethylsilyloxy)-2-iodomethylbenzene (8c). A solution of 114 mg of **7** (0.33 mmol), 130 mg of PPh_3 (0.5 mmol), 34 mg of imidazole (0.5 mmol) and 127 mg of I_2 (0.5 mmol) in 2 mL of acetonitrile and 8 mL of toluene was heated at 60 °C for 10 min. The reaction mixture was then diluted with EtOAc and subsequently washed with saturated $Na_2S_2O_3$, brine, dried and evaporated. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 4:1) on silica gel to afford 125 mg (83%) of **8c** as yellowish oil. IR (film) ν: 3068, 3036, 2955, 2930, 2884, 2857, 1599, 1581, 1492, 1454, 1267, 1154, 906, 838, 781, 735 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.27 (s, 6H), 1.05 (s, 9H), 4.42 (s, 2H), 4.97 (s, 2H), 6.68 (d, J=8.8 Hz, 1H), 6.78 (dd, J=8.8, 3.0 Hz, 1H), 6.94 (d, J=3.0 Hz, 1H), 7.30–7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 1.8, 18.4, 26.0, 61.1, 70.6, 115.9, 116.5, 119.4, 127.6, 128.0, 128.6, 130.3, 137.1, 147.5, 152.9 ppm. HRFABMS calcd for $C_{20}H_{27}O_2NaSiI$ $[M+Na]^+$ 477.0718, found 477.0723.

2.2.2. Synthesis of 17.

2.2.2.1. 1-(*t*-Butyldimethylsilyloxy)-2-iodomethyl benzene (17). This compound was prepared starting from commercial 2-hydroxybenzaldehyde, **15**. Following the same procedures used for **8c**, this compound was subsequently protected as silyl ether, reduced to give phenol **16**,[17] and treated with I_2 in the presence of PPh_3 to give the iodo derivative **17** in an 60% overall yield. Compound **17**, colourless oil. IR (film) ν: 3069, 3036, 2955, 2929, 2885, 2858, 1599, 1581, 1491, 1454, 1361, 1266, 1202, 1155, 1040, 924, 832, 781, 753, 704, 662 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 0.36 (s, 6H), 1.13 (s, 9H), 4.52 (s, 2H), 6.82 (dd, J=8.1, 1.0 Hz, 1H), 6.92 (dt, J=7.6, 1.0 Hz, 1H), 7.19 (ddd, J=1.6, 8.0, 7.6 Hz, 1H), 7.35 (dd, J=1.6, 7.6 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 1.8, 18.4, 25.8, 118.6, 121.4, 129.4, 129.7, 130.7, 153.5 ppm. HRFABMS calcd for $C_{13}H_{21}ONaSiI$ $[M+Na]^+$ 371.0304, found 371.0300.

2.3. Reactions of heterocyclisation. Synthesis of chromanes

2.3.1. 6-(Benzyloxy)-2-ethoxychroman (9). After subjecting **8c** (133 mg, 0.3 mmol) to the heterocyclisation conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (6:1) furnished 74 mg of **9** (88%) as a colourless oil. IR (film) ν: 3032, 2926, 2856, 1754, 1612, 1465, 1454, 1377, 1192, 1058, 877 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.19 (t, J=7.1 Hz, 3H), 1.93 (m, 1H), 2.03 (m, 1H), 2.60 (ddd, J=3.6, 5.9, 16.3 Hz, 1H), 2.97 (ddd, J=6.1, 11.7, 17.2 Hz, 1H), 3.63 (dq, J=7.0, 9.8 Hz, 1H), 3.88 (dq, J=7.0, 9.8 Hz, 1H), 4.99 (s, 2H), 5.22 (t, J=2.8 Hz, 1H), 6.70 (s, 1H), 6.76 (s, 2H), 7.30–7.45 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 20.9, 26.6, 63.6, 70.6, 96.8, 114.2, 115.1, 117.5, 123.3, 127.5, 127.9, 128.6, 137.5, 146.3, 152.8 ppm. HRFABMS calcd for $C_{18}H_{20}O_3Na$ $[M+Na]^+$ 307.1310, found 307.310.

2.3.2. 6-(Benzyloxy)-2-(ethylthio)chroman (11). After subjecting **8c** (100 mg, 0.22 mmol) to the heterocyclisation conditions but using ethyl vinyl sulfide as dienophile, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (4:1) furnished 55 mg of **11** (83%) as a colourless oil. IR (film) ν: 2964, 2927, 2869, 1732, 1608, 1494, 1453, 1376, 1265, 1193, 1076, 987, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.24 (t, J=7.4 Hz, 3H), 2.02 (m, 1H), 2.21 (m, 1H), 2.37–2.78 (m, 3H), 2.88 (ddd, J=6.4, 10.2, 16.6 Hz, 1H), 4.93 (s, 2H), 5.46 (t, J=4.0 Hz, 1H), 6.62 (s, 1H), 6.68 (s, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 22.9, 24.7, 27.4, 70.6, 80.2, 114.5, 115.3, 118.1, 122.6, 127.5, 127.9, 128.6, 137.5, 146.6, 153.2 ppm. HRFABMS calcd for $C_{18}H_{20}O_2SNa$ $[M+Na]^+$ 307.1310, found 307.1310.

2.3.3. 6-(Benzyloxy)-2,2-diethoxychroman (13). After subjecting **8c** (131 mg, 0.28 mmol) to the heterocyclisation conditions but using 1,1-diethoxyethene as dienophile, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (20:1) furnished 53 mg of **13** (56%) and 16 mg of **14** (18%). Compound **13**, colourless oil. IR (film) ν: 2976, 2928, 1729, 1613, 1496, 1442, 1380, 1205, 1091, 1047, 969, 879, 734 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 6H), 2.00 (t, J=6.8 Hz, 2H), 2.77 (t, J=6.8 Hz, 2H), 3.62 (m, 4H), 4.92 (s, 2H), 6.60–6.85 (m, 3H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.3, 23.9, 27.8, 57.4, 70.6, 112.4, 114.1, 114.7, 117.4, 122.8, 127.6, 127.9, 128.6, 137.4, 148.5, 153.0 ppm. Compound **14**, colourless oil. IR (film) ν: 3417, 2979, 2931, 2869, 1730, 1709, 1505, 1196, 1027, 737 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J=7.2 Hz,

3H), 2.68 (t, J=6.4 Hz, 2H), 2.84 (t, J=6.4 Hz, 2H), 4.12 (q, J=7.2 Hz, 2H), 4.96 (s, 2H), 6.70–6.81 (m, 3H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 24.9, 35.3, 61.4, 70.7, 114.1, 117.0, 118.0, 122.8, 127.6, 127.8, 127.9, 128.6, 128.7, 137.4, 148.5, 153.0, 177.0 ppm. HRFABMS calcd for $C_{18}H_{20}O_4Na$ $[M+Na]^+$ 323.1260, found 323.1261.

2.3.4. 2-Ethoxychroman (18). After subjecting **17** (125 mg, 0.4 mmol) to the heterocyclisation conditions, the resulting crude was purified by column chromatography on silica gel. Eluting with hexane/*t*-BuOMe (6:1) furnished 33 mg of **18**[18] (51%). Compound **18**, colourless oil. IR (film) ν: 2955, 2923, 2853, 1732, 1605, 1456, 1376, 1262, 1097, 1015, 802, 743 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 6H), 1.87 (m, 1H), 1.98 (m, 1H), 2.57 (ddd, J=3.9, 5.7, 16.8 Hz, 1H), 2.91 (ddd, J=5.7, 11.2, 16.8 Hz, 1H), 3.58 (dq, J=7.0, 9.7 Hz, 1H), 3.82 (dq, J=7.1, 9.7 Hz, 1H), 5.18 (t, J=3.0 Hz, 1H), 6.75–6.85 (m, 2H), 6.95–7.10 (m, 2H). HRFABMS calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0892, found 323. 201.0884.

2.4. Synthesis of the puupehedione analogue 24

2.4.1. Synthesis of alcohol 22. A 1.7 M solution of *tert*-butyllithium in pentane (3.4 mL) was added at −78 °C to a solution of **21** (1800, 5.17 mmol) in diethyl ether (75 mL), under argon atmosphere. After stirring for 30 min at this temperature, **20** (625 mg, 5.69 mmol) was added and the mixture was further stirred for 15 min at −78 °C. The reaction crude was diluted with ether and then water was added. The organic layer was then washed with brine, dried and concentrated to give a crude, which was chromatographed on silica gel column (H/E, 2:1) to give 1582 mg of **22** (81%) as a colourless oil. IR (film) ν: 3507, 2966, 2950, 2929, 2856, 1609, 1510, 1463, 1446, 1400, 1255, 1202, 1114, 1008, 909, 837, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.20 (s, 3H), 0.22 (s, 3H), 0.99 (s, 9H), 1.50–1.65 (m, 4H), 1.79–2.00 (m, 2H), 2.03 (m, 2H), 3.80 (s, 6H), 5.28 (br s, 1H), 5.70 (br s, 1H), 6.37 (s, 1H), 6.81 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −3.9, 22.6, 22.7, 25.0, 25.6, 25.9, 55.9, 56.3, 72.2, 103.6, 111.0, 122.6, 123.9, 138.9, 143.4, 146.9, 148.4 ppm. HRFABMS calcd for $C_{21}H_{34}O_4SiNa$ $[M+Na]^+$ 378.2226, found 378.2217.

2.4.2. Acetate 23. To a solution of 150 mg (0.40 mmol) of **22** in 2 mL of pyridine was added 1 mL of Ac_2O at 0 °C. After stirring for 15 min at this temperature, the reaction mixture was worked up as usual to give 160 mg of **23**, which was used without further purification. Colourless oil. IR (film) ν: 3507, 2950, 2931, 2857, 1739, 1612, 1510, 1447, 1400, 1232, 1204, 1115, 1015, 902, 839, 780 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.21 (s, 3H), 0.23 (s, 3H), 1.99 (s, 9H), 1.52–1.70 (m, 4H), 1.82 (m, 1H), 1.93–2.06 (m, 3H), 2.08 (s, 3H), 3.81 (s, 3H), 3.82 (s, 3H), 5.55 (br s, 1H), 6.38 (s, 1H), 6.42 (br s, 1H), 6.79 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −4.9, −3.9, 21.3, 22.3, 22.5, 25.0, 25.7, 25.9, 55.9, 56.5, 72.9, 103.4, 111.2, 120.4, 123.6, 135.9, 143.4, 147.2, 148.9, 169.9 ppm.

2.4.3. Synthesis of 24. To a solution in benzene (5 mL) of the above crude containing **23** was added 0.5 mL of a 1 M solution of TBAF. The mixture was further stirred for 2 min and then diluted with EtOAc and washed with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting crude product was purified by column chromatography to afford 60 mg of **24** (62% for two steps). Colourless oil. IR (film) ν: 3032, 2926, 2856, 1754, 1612, 1465, 1454, 1377, 1192, 1058, 877 cm^{-1}. ^{1}H NMR (400 MHz, $CD_3)_2CO$) δ 1.23 (qt, J=3.6, 12.9 Hz, 1H), 1.42 (qt, J=3.6, 12.9 Hz, 1H), 1.61 (m, 1H), 1.70 (m, 1H), 1.78 (m, 1H), 1.97 (m, 1H), 2.06 (m, 1H), 2.97 (br d, J=14.3 Hz, 1H), 3.64 (s, 3H), 3.68 (s, 3H), 4.79 (br dd, J=5.5, 10.9 Hz, 1H), 5.91 (t, J=1.9 Hz, 1H), 6.25 (s, 1H), 6.46 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CD_3)_2CO$) δ 24.9, 27.4, 33.3, 35.8, 56.2, 57.1, 77.6, 101.3, 111.8, 114.4, 116.9, 136.1, 144.4, 148.4, 150.5 ppm. HRFABMS calcd for $C_{15}H_{18}O_3$ $[M]^+$ 246.1256, found 246.1255.

Acknowledgements

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Synthesis of 5-aryl-2-oxopyrrole derivatives as synthons for highly substituted pyrroles

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Abstract—A small library of 2-oxo-5-(hetero)arylpyrroles was prepared starting from 2,3-dioxo-5-(hetero)arylpyrrolidines. The large synthetic possibilities of these 2-oxopyrroles were investigated. The 2-oxopyrroles offer a large number of possible derivatizations including reactions with electrophiles. The chloroformylation of 2-oxo-5-(hetero)arylpyrroles provides pyrrole carbaldehydes. Some pyrrole carbaldehydes were used to synthesize polycyclic compounds like pyrrolo[3,4-*d*]pyridazinones, a thienopyrrole, a pyrrolobenz[1,4]oxazepine, a pyrrolobenzo[1,4]thiazepine, and a pyrrolobenzo[1,4]diazepine. Hereby we showed through a short exploration that the oxopyrroles and analogues are interesting and versatile synthetic building blocks.

1. Introduction

New versatile and easily available starting materials are of great importance in organic and medicinal chemistry to allow a combinatorial approach.

2-Oxopyrroles **1** show such versatility and they are important substructures in a variety of pharmaca, including products active against viral infections (HIV,[1,2] influenza,[3] cytomegalovirus[4]), anticancer agents,[5] and products active against microbiological diseases[6–8] (bacterial or fungal). Furthermore, 2-oxopyrroles are known as building blocks in the synthesis of alkaloids[9–12] and materials such as 2,2′-bipyrroles, terpyrroles,[13] and pigments.[14–19] Besides the well known 5-alkyl-2-oxopyrroles,[20,21] first described in 1890 by Emery,[22] relatively little attention was given toward 5-aryl-2-oxopyrrole derivatives **2** in the open literature (see Fig. 1). In our research group, we envisaged to use the 5-aryl-2-oxopyrroles as a starting material for the synthesis of highly fluorescent diketopyrrolopyrroles and potential non-nucleoside reverse transcriptase inhibitors (NNRTI). For the screening of the properties of these products a wide variability of possible substituents is necessary. Therefore we wished to develop a short, inexpensive, and simple synthesis of 2-oxopyrroles, which would allow a great variety of substituents.

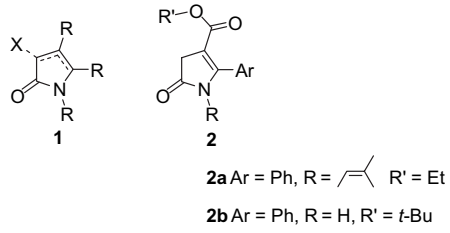

Figure 1. 2-Oxopyrroles **1** and 5-aryl-2-oxopyrroles **2**.

In the open literature, the synthesis of only few *N*-substituted pyrrolinones **2** was described including a five-step synthesis of an *N*-alkenylpyrrolinone **2a** via oxazolinones.[23] In the patent literature the synthesis of **2b** was described in a two-step reaction starting with a base-catalyzed condensation between di-*tert*-butyl succinate and benzonitrile.[24]

2. Results and discussion

Recently Morton et al. have reported a short and convenient method to synthesize **2** starting from commercially available alkyl benzoylacetates **3**.[15,25] We reinvestigated Morton's synthesis of oxopyrroles and found some limitations. The dialkyl benzoylsuccinates **4** are available via monoalkylation of alkyl benzoylacetates **3** with alkyl chloroacetates. Unfortunately, the ring closure affording the corresponding **2** was not possible starting from 4-nitrobenzoylsuccinates **4a** (X=NO_2). Probably the strongly electron withdrawing group did not allow condensation between the ketone function and the amine but the imine/enamine function on this

Keywords: Heterocycles; Pyrrole; Fused ring system; Polycycles; Multicomponent reaction.
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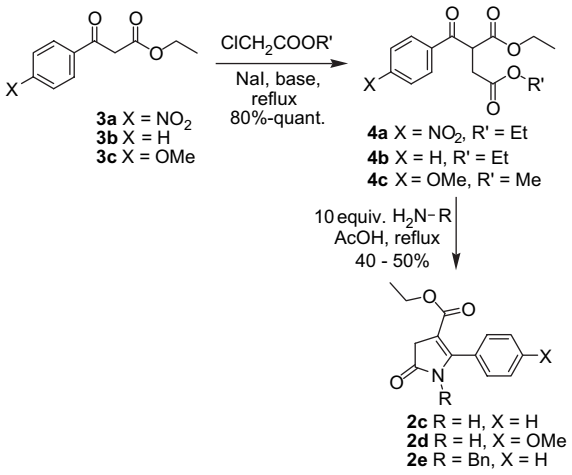
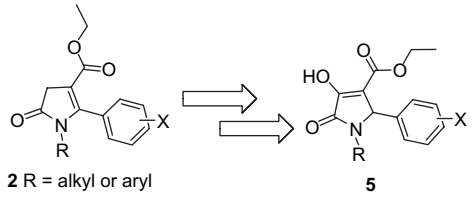
intermediate was deactivated, preventing ring closure (Scheme 1).



Scheme 1. Synthesis of simple 2-oxo-5-arylpyrroles **2c** and **2d** starting from benzoylacetates.

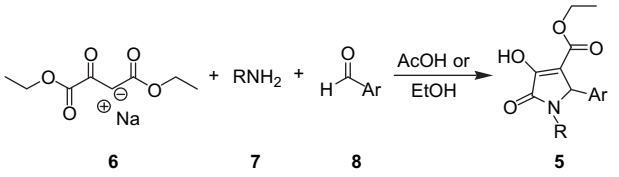
In contrast to **4a**, benzoylsuccinates **4b** and **4c** reacted with ammonium acetate and benzylamine to afford the desired oxopyrroles **2c–e** in moderate yield. The condensation in acetic acid with a large excess (10 equiv) of ammonium acetate or benzylamine gave the best results while aniline did not give any product **2** under these conditions. Clearly, the benzoylsuccinate method suffers from (i) lack of general applicability (e.g., X=NO_2 or aromatic R), (ii) the obligatory use of excess of amine reagent, and (iii) the modest yields in the final step. Moreover, only a few benzoylacetates **3** are commercially available at a reasonable price.

We describe here a more general synthesis of *N*-substituted (or *N*-protected) 2-oxopyrroles **2** starting from 2,3-dioxopyrrolidines **5** (Scheme 2). To obtain the latter compounds, we applied the synthesis described by Merchant and Srinivasan, and before them by Schiff.[26,27] These authors published an interesting three-component reaction starting from sodium alkyl oxalacetate with several amines and aldehydes under various reaction conditions. Most of the 2,3-dioxopyrrolidines **5** synthesized had aryl substituents at the 1- and 5-position. A significant advantage of these products **5** is the fact that most of them can be crystallized out of the reaction mixture.



Scheme 2. Synthesis of a great variety of 2-oxopyrroles **2** starting from **5**.

All three necessary reagents are relatively cheap and a large variety of aldehydes and amines are possible. This allowed us to create a library of **5** and subsequently of the desired oxopyrroles **2**. 2,3-Dioxopyrrolidines **5** that are new to the best of our knowledge were synthesized by us starting from sodium ethyl oxalacetate **6**, ammonia or primary amines **7**, and aromatic aldehydes **8**. Two general methods were used. The first method consists of shortly heating the reagents in acetic acid, stirring for 16–24 h at room temperature, and precipitation after addition of water. The second method consists of dissolving the reagents in ethanol and heating this mixture for about 30 min. After dilution with water and acidifying, the product could be filtered. Both methods gave the desired product **5a–l** in moderate yield but high purity (Scheme 3, Table 1).



Scheme 3. Synthesis of 2,3-dioxopyrrolidines via a multicomponent reaction.

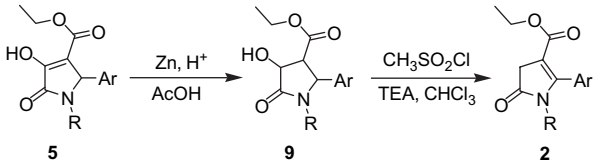
Table 1. Synthesis of 2,3-dioxopyrrolidines via multicomponent reaction

Dioxopyrrolidine	1-R	5-Ar	Yield (%)
5a	4-ClPh	4-ClPh	77[a]
5b	Benzyl	4-ClPh	32[a]
5c	Cyclohexyl	4-ClPh	18[a], 31[b]
5d	PMB[c]	4-CH_3OPh	40[a]
5e	PMB[c]	4-ClPh	64[a]
5f	3,4,5-$(CH_3O)_3$Ph	3-HOPh	38[a]
5g	H	Ph	61[b]
5h	CH_3	4-NO_2Ph	50[b]
5i	CH_3	4-$(CH_3)_2$NPh	48[b]
5j	CH_3	Ph	59[b]
5k	CH_3	2-HOPh	52[b]
5l	Allyl	2-Thienyl	62[b]

[a] Method 1 in acetic acid.
[b] Method 2 in ethanol.
[c] *p*-Methoxybenzyl.

Dioxopyrrole **5i** was prepared in a reasonable yield but the reaction mixture had to be heated at reflux for several days instead of the usual 30 min. Acidification in this case was not necessary because **5i** precipitated out of the reaction mixture after cooling to room temperature. An excess of aqueous ammonia was used in the synthesis of **5g**.

These dioxopyrrolidines **5** could easily be transformed into the desired oxopyrrole **2**. Reduction of the enolates **5** gave the corresponding secondary alcohols **9**. Without further purification these alcohol groups could be eliminated by mesylation and treatment with base affording the pyrrolinones **2c**, **2f–j** after isomerization of the double bond (Scheme 4, Table 2).



Scheme 4. Transformation of dioxopyrrolidines **5** to pyrrolinones **2**.

The alcohols **9** were obtained by reduction of **5** with zinc dust in acetic acid and a few drops of sulfuric acid. As an

Table 2. Transformation of dioxopyrrolidines **5** to pyrrolinones **2**

Oxopyrrole	Educt	Alcohol	*N*-R	5-Ar	Yield (%)[a]
2c	**5g**	**9a**	H	Ph	42
2f	**5j**	**9b**	CH_3	Ph	40
2g	**5i**	**9c**	CH_3	4-$(CH_3)_2$NPh	40
2h	**5b**	**9d**	Benzyl	4-ClPh	42[b]
2i	**5l**	**9e**	Allyl	2-Thienyl	51
2j	**5a**	**9f**	4-ClPh	4-ClPh	66

[a] Isolated overall yield starting from **5**.
[b] Triethylamine (TEA), $POCl_3$.

example the mixture of diastereoisomers of **9c**–**9c′** (87:13), obtained starting from **5i**, was separated by column chromatography. NMR spectroscopy showed that mainly the isomer with the all-trans configuration **9c** was formed. The NOESY spectrum shows that the proton in α of the ester function of the main product **9c** is located in the proximity of the aryl protons. The position of this proton with respect to the aryl ring is confirmed by the low δ-value of this proton in the ^{1}H NMR spectrum due to the anisotropic effect of the ring current. The NOESY spectrum also confirmed that the 3,5-protons in β of the ester group are located at the same side of the five-membered ring. The minor product **9c′** showed in its NOESY spectrum no correlation between the proton at 4.55 and 4.68 ppm. From the ^{1}H NMR and ^{13}C NMR spectra it is clear that the signals of the ester function are shifted upfield. Hence, the ester function and the phenyl ring are on the same side as the pyrrole moiety.

Because there is no NOESY correlation between the protons at 4.55 and 4.68 ppm and the proton signal at 4.55 is shifted to higher field (in comparison with the corresponding proton of **9c**), we can assume that these protons are located on opposite sides of the ring and therefore assign the trans–cis structure **9c′** (Fig. 2).

The reduction rate is increased by heating but the reaction time should be carefully controlled in this case because of the possibility of formation of small amounts of Fischer esterification side products resulting from the alcohol **9** and acetic acid. The next step was the elimination of water from **9** in order to obtain the desired oxopyrroles **2**. Several possibilities were tested. The alcohols **9** react with acid chlorides, sulfonyl chlorides, anhydrides, $POCl_3$, and $SOCl_2$ under the influence of base. With pyridine as the base the reaction with tosyl, mesyl or phosphorus oxychloride was incomplete. With triethylamine as the base at reflux

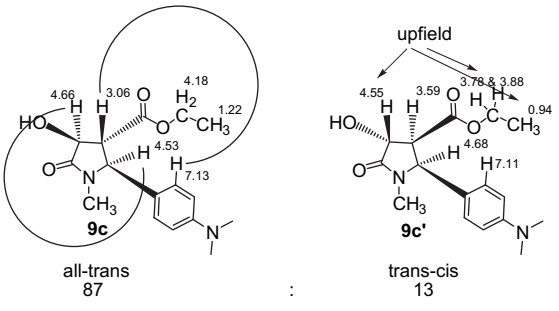


Figure 2. Diastereoisomers of **9c**–**9c′** obtained after reduction of **5** with zinc.

temperature in chloroform, mesylation followed by complete elimination of the corresponding sulfonic acid was accomplished at the same time to afford **2**.

The moderate yield (40–66%) of these oxopyrroles **2c**, **2f**–**j** was more than compensated by the ease of these reactions and the possibility to prepare a library of pyrrolinones **2** from readily available starting materials. Moreover, unsubstituted, *N*-aryl and *N*-alkyl-5-arylpyrrolinones **2** could also be prepared by the described method.

Pyrrolinone **2** possesses an active methylene group, which can react with electrophilic reagents. The ester function (rather a vinylogous carbamate function) and the amide function (if unsubstituted) may react with nucleophilic reagents. In comparison with the 5-alkylpyrrolinones the nitrogen atom of the 5-arylpyrrolinones is relatively shielded from electrophilic reagents. Thus, the aryl group gives the pyrrolinones extra chemical and physical stability.

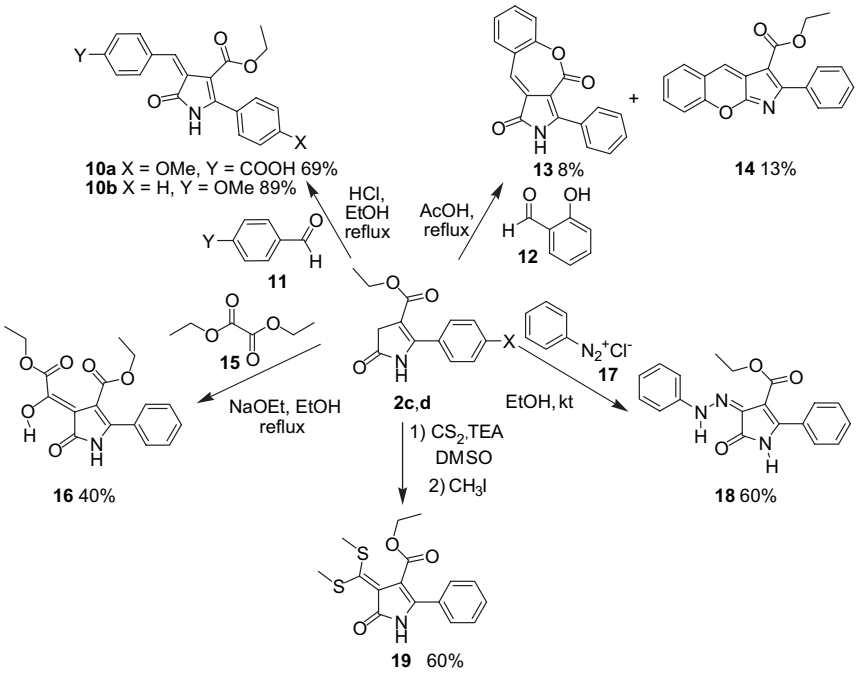
Benzylidenepyrrolinones **10** were synthesized by condensation of pyrrolinone **2** and different arylaldehydes **11**. Bright yellow compounds **10** were obtained in the *Z*-configuration. Using the *ortho*-substituted salicylaldehyde **12** and pyrrolinone **2c** in acetic acid and heating for 20 min under microwave irradiation the dioxopyrrolo[3,4-*c*]benzoxepine (DPO) **13** was obtained next to phenylchromeno[2,3-*b*]pyrrole **14**. The yellow **13** shows a strong yellow fluorescence and is only slightly soluble in common organic solvents.

As an example of a reaction between **2** and an activated ester the condensation of **2c** with diethyl oxalate **15** under basic conditions gave diester **16**, which could be isolated by filtration after acidification. Phenyldiazonium salt **17** reacted smoothly with oxopyrrole **2c** providing hydrazone **18**. Pyrrolinone **2c** was transformed into ketene dithioacetal **19** in a one pot reaction by treatment with carbon disulfide in the presence of triethylamine and subsequent methylation with 2 equiv of methyl iodide (Scheme 5).

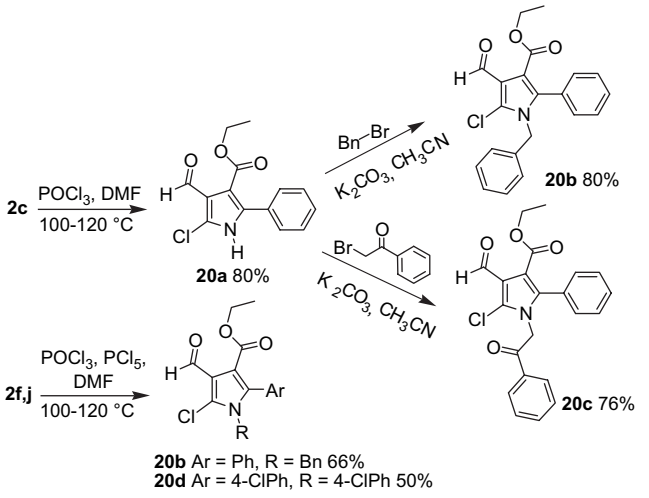
These pyrrolinones **2** seemed to be ideal building blocks for the synthesis of a large variety of multisubstituted pyrroles. In the literature, methods have been described to chloroformylate heterocyclic compounds such as pyrazolones and oxoindoles using Vilsmeier–Haack conditions affording the corresponding pyrazoles and 2-chloroindoles.[28] The synthesis of 5-aryl-2-chloro-3-formylpyrrole **20a** is based on these transformations.

At relatively high temperature (100–120 °C) and a ratio of 1:2:8 pyrrolinone (R=H)–DMF–$POCl_3$, the desired aldehyde **20a** was obtained in reasonable to good yield. The nitrogen atom on this pyrrole **20a** was easily alkylated with benzyl bromide or α-bromoacetophenone using potassium carbonate as a base to form **20b** and **20c**. The transformation of *N*-substituted pyrrolinones **2f** and **2j** into their chloroformylated derivatives **20b** and **20d** was also investigated. The addition of PCl_5 and the use of high temperature (120 °C) were necessary for a complete transformation (Scheme 6).

Pyrrole carbaldehydes **20a**–**d** possess at least three electrophilic reaction sites and thus provide numerous synthetic possibilities. They offer a number of interesting options for



Scheme 5. Reactions of **2** with various electrophiles.

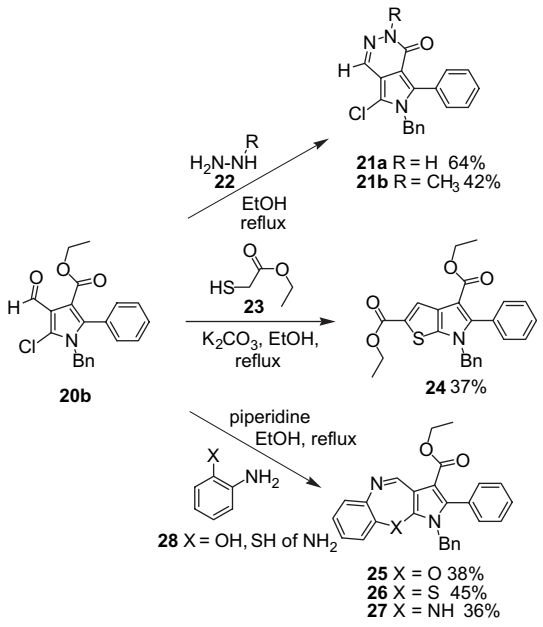


Scheme 6. Synthesis of pyrrole carbaldehydes **20** via chloroformylation of **2**.

ring closure besides the condensation reactions on the independent chloro, aldehyde, and ester functions.

The two adjacent carbonyl functions can react with bis-nucleophilic molecules. Thus a reagent, which contributes two atoms, can provide a six-membered ring fused to the pyrrole moiety. Hydrazines, for example, gave after reaction with **20b** pyrrolo[3,4-*d*]pyridazinones **21a** and **21b** in moderate yields (Scheme 7).

As an example of a ring fusion involving the chloro and aldehyde functions, *N*-benzylated pyrrole **20b** was used as the substrate for the cyclocondensation with ethyl mercaptoacetate **23**. 5-Phenyl-thieno[2,3-*b*]pyrrole **24** precipitated from the reaction mixture. Compounds **25**, **26**, and **27** were prepared by condensing *ortho*-substituted anilines with pyrrole carbaldehyde **21** in yields of about 40%. The synthesis



Scheme 7. Synthesis of poly(hetero)cycles starting from **20**.

of these compounds was based on the work of Latif.[29] All structures could readily be analyzed by ^{1}H NMR spectroscopy.

3. Conclusion

We prepared a small library of pyrrolinones **2** starting from 2,3-dioxopyrrolidines **5**. The 2,3-dioxopyrrolidines **5** are easily prepared through the multicomponent reaction between diethyl oxalacetate and a variety of aldehydes and primary amines.

We have explored the large synthetic possibilities of the oxopyrroles. The 2-oxopyrroles offer a large number of possible derivatizations including reactions with aldehydes, diazonium salts, reactive esters, and carbon disulfide. The chloroformylation of **2** provides pyrrole carbaldehydes **20**. A number of pyrrole carbaldehydes **20** were used to synthesize polycyclic compounds. Pyrrolo[3,4-*d*]pyridazinones **21a** and **21b** were obtained after aldehyde–ester ring fusion of **2** with hydrazines **22** while chloroaldehyde ring fusions provided thienopyrrole **24**, pyrrolobenz[1,4]oxazepine **25**, pyrrolobenzo[1,4]thiazepine **26**, and pyrrolobenzo[1,4]diazepine **27**. Thus we showed by means of a short exploration that the oxopyrroles and analogues are interesting and versatile synthetic building blocks. Many possibilities offered by **2** and **20** show these compounds to be novel key intermediates in the synthesis of highly substituted pyrroles.

4. Experimental

4.1. Instrumental techniques

NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz or Bruker AMX 400 MHz) and chemical shifts (δ) are reported in parts per million referenced to internal residual solvent protons (1H) or the carbon signal of deuterated solvents (13C). Mass spectrometry data were obtained with an HP MS apparatus 5989A, at 70 eV for EI spectra and with methane as reagent gas for CI spectra. UV–vis spectra were taken on a Perkin–Elmer Lambda 20 spectrometer. Melting points (not corrected) were determined using a Reichert Thermovar or Electrothermal 9200 apparatus. The microwave oven used is a Monomode Discover MW Reactor. All reactions were done in a 10 mL glass tube sealed with a Teflon stopper.

4.2. Materials

Chemicals and solvents were either purchased puris p.A. from commercial suppliers or purified by standard techniques. For thin layer chromatography (TLC), precoated 0.25 mm silica plates (Macherey–Nagel 60 Alugram® Sil G/UV254) were used and spots were visualized either with UV light or ethanolic phosphomolybdic acid followed by heating.

4.2.1. 2,3-Dihydro-2-oxo 5-phenyl-1*H*-pyrrole-4-carboxylic acid ethyl ester (2c). A suspension of ethyl benzoylacetate **3b** (20.2 g, 18.3 mL, 105 mmol), K_2CO_3 (15.2 g, 110 mmol), NaI (2.0 g), and ethyl chloroacetate (13.2 g, 11.6 mL, 108 mmol) in acetone/DME 120 mL:80 mL was heated under reflux for 24 h. After cooling to room temperature the salts were filtered and washed with acetone. The combined filtrates were evaporated to dryness under reduced pressure affording **4b** quantitatively with sufficient purity. This crude product **4b** was dissolved in a mixture of acetic acid (200 mL) and ammonium acetate (78.7 g, 1.02 mol) and the reaction mixture was then stirred at reflux for 3 h. After cooling to room temperature, the reaction mixture was added to ice-water (800 mL). The acquired precipitate was filtered and washed with water. The residue was recrystallized from ethanol/water 4:1. After drying under reduced pressure **2c** (11.87 g, 49% starting from benzoylacetate) was obtained as a white powder.

Compound **2c** was also obtained starting from **5g** (general procedure A+D) using 3 equiv of aqueous ammonia as amine (GP D) or starting from alcohol **9a** (general procedure A).

^{1}H NMR (300 MHz, $CDCl_3$): δ=1.21 (t, 3H, J=7.3 Hz), 3.49 (s, 2H), 4.14 (q, 2H, J=7.3 Hz), 7.41–7.49 (m, 3H), 7.58–7.62 (m, 2H), 9.12 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.5, 39.1, 60.4, 105.0, 128.6, 129.1, 130.0, 130.9, 151.6, 163.6, 177.5; LRMS (CI): 232 MH^+; mp: 181–182 °C (lit. 173–176 °C).[30]

4.2.2. 5-(4-Methoxyphenyl)-2-oxo-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2d). A suspension of ethyl (4-methoxybenzoyl)acetate (88.8 g, 0.40 mol), K_2CO_3 (57.9 g, 0.42 mol), NaI (8.0 g), and methyl chloroacetate (45.1 g, 36.7 mL, 0.41 mol) in acetone/DME 160 mL:240 mL was heated under reflux for 24 h. Treatment as for **2c** afforded **2d** (46.2 g, 47%) as a white powder. After extraction of the combined filtrates with dichloromethane (mL), drying over $MgSO_4$ and evaporation in vacuo, additional product **2d** (10.1 g, 10.3%) was isolated by column chromatography of the residue on silica gel (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.23 (t, 3H, J=7.3 Hz), 3.48 (s, 2H), 3.85 (s, 3H), 4.13 (q, 2H, J=7.3 Hz), 6.94 (d, 2H, J=8.8 Hz), 7.62 (d, 2H, J=8.8 Hz), 8.94 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 39.0, 55.4, 60.1, 103.1, 113.7, 121.4, 130.6, 151.4, 161.4, 163.5, 178.0; LRMS (CI): 262 MH^+; mp: 101 °C.

4.2.3. 1-Benzyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2e). To crude product **4b** (1.00 mmol, 278 mg) in ethanol (15 mL) was added acetic acid (10.0 mmol, 0.60 mL) and benzylamine (10.0 mmol, 1.05 g). The reaction mixture was then heated at reflux for 4 h. After cooling to room temperature the reaction mixture was diluted with water (15 mL). The aqueous mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the viscous residue was chromatographed on silica gel (ethyl acetate/petroleum ether 9:1) to furnish the pure **2e** as a yellow oil (128 mg, 40%); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (t, 3H, J=7.1 Hz), 3.53 (s, 2H), 4.07 (q, 2H, J=7.1 Hz), 4.52 (s, 2H), 6.83 (m, 2H), 7.44–7.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.3, 37.7, 44.3, 60.9, 105.4, 126.0, 127.4, 128.1, 128.4, 129.3, 136.0, 154.3, 163.9, 176.2; LRMS (CI): 322 MH^+.

4.3. General procedure A: synthesis of 5-aryl-2-oxopyrroles 2

The crude products or purified alcohols **9** (1 equiv) were dissolved in chloroform. Subsequently mesyl chloride (1.1 equiv) and triethylamine (4 equiv) were added portionwise. After heating under reflux for 30 min the reaction mixture was diluted with 5% HCl solution. The aqueous mixture was extracted with CH_2Cl_2. The combined organic phases were washed with 5% HCl solution, saturated $NaHCO_3$ solution until neutral, water and finally dried with magnesium sulfate. The solvents were evaporated under reduced

pressure and the residue was chromatographed on silica gel (ethyl acetate/petroleum ether 50:50) to furnish the pure oxopyrroles **2**.

Product **2f** (1.96 g, 40%) was prepared as described in the general procedure A (GP A) and was obtained as a red powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.06 (t, 3H, J=7.3 Hz), 2.86 (s, 3H), 3.46 (s, 2H), 4.02 (q, 2H, J=7.3 Hz), 7.31–7.34 (m, 2H), 7.46–7.48 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.3, 28.2, 37.5, 60.1, 105.5, 128.7, 129.1, 130.1, 130.3, 155.4, 163.5, 176.4; LRMS (CI): 246 MH^+; mp: 35 °C.

4.3.1. 5-(4-(Dimethylamino)phenyl)-1-methyl-2-oxo-2,3-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2g). Product **2g** (220 mg, 40%) was prepared as described in the GP A and was obtained as a red powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.14 (t, 3H, J=7.3 Hz), 2.92 (s, 3H), 3.02 (s, 6H), 3.43 (s, 2H), 4.06 (q, 2H, J=7.3 Hz), 6.74 (d, 2H, J=8.2 Hz), 7.22 (d, 2H, J=8.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.6, 28.5, 37.7, 40.5, 60.0, 104.1, 111.5, 116.5, 130.7, 151.5, 156.6, 163.9, 176.9; LRMS (CI): 289 MH^+; mp: 87–88 °C.

4.3.2. 1-Allyl-2-oxo-5-(thien-2-yl)-4,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2i). Product **2i** (7.02 g, 51%) was prepared as described in the GP A and was obtained as a red powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 3H, J=7.3 Hz), 3.49 (s, 2H), 4.02–4.10 (m, 4H), 4.97 (d, 1H, J=14.6 Hz), 5.09 (d, 1H, J=10.1 Hz), 5.62–5.75 (m, 1H), 7.10 (dd, 1H, J=5.5 Hz), 7.16 (d, 1H, J=3.7 Hz), 7.52 (d, 1H, J=6.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.4, 37.8, 43.4, 60.4, 108.8, 117.4, 127.3, 128.9, 130.6, 132.7, 148.1, 163.2, 175.3; LRMS (CI): 278 MH^+; mp: 58 °C.

4.3.3. 1,5-Bis(4-chlorophenyl)-2-oxo-4,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (2j). Product **2j** (7.44 g, 66%) was prepared as described in the GP A and was obtained as a brownish powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.3 Hz), 3.49 (s, 2H), 4.09 (q, 2H, J=7.3 Hz), 6.88 (d, 2H, J=8.2 Hz), 7.13 (d, 2H, J=8.2 Hz), 7.18–7.27 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ=14.4, 37.9, 60.6, 106.9, 127.8, 128.5, 129.1, 129.6, 131.3, 132.8, 134.0, 136.1, 152.8, 163.2, 174.9; LRMS (CI): 376–378 MH^+; mp: 70 °C.

4.3.4. Diethyl 2-(4-nitrobenzoyl)succinate (4a). To a solution of ethyl 4-nitrobenzoylacetate (2.0 g, 8.4 mmol), NaH (202 mg, 8.4 mmol), and NaI (100 mg) in THF (100 mL) was added ethyl chloroacetate (2.8 g, 16.8 mmol). After stirring the mixture at 50 °C for 1 h it was cooled and diluted with ether (50 mL) and acidified with aqueous 5% HCl solution. After extraction with ether, drying over $MgSO_4$ and evaporation under reduced pressure, the product **4a** (1.6 g, 58%) was isolated as a yellow oil after column chromatography of the residue on silica gel (CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13–1.27 (m, 6H), 3.04 (dd, 1H, J=6.5 Hz, J=23.4 Hz), 3.22 (dd, 1H, J=9.2 Hz, J=26.0 Hz), 4.09–4.16 (m, 4H), 4.85 (q, 1H, J=9.1 Hz), 5.30 (s, 1H), 8.19 (d, 2H, J=8.8 Hz), 8.34 (d, 2H, J=8.8 Hz); LRMS (CI): 324 MH^+.

4.3.5. Diethyl 2-benzoylsuccinate (4b). A suspension of ethyl benzoylacetate **3b** (20.2 g, 18.3 mL, 105 mmol), K_2CO_3 (15.2 g, 110 mmol), NaI (2.0 g), and ethyl chloroacetate (13.2 g, 11.6 mL, 108 mmol) in acetone/DME 120 mL: 80 mL was heated under reflux for 24 h. After cooling to room temperature the salts were filtered and washed with acetone. The combined filtrates were evaporated to dryness under reduced pressure affording **4b** (9.40 g, 71%) as a red brown oil with sufficient purity. A sample was extra purified by column chromatography on silica gel (CH_2Cl_2) affording **4b** as a colorless to green oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.2 (m, 6H), 3.13–3.16 (m, 2H), 4.12–4.17 (m, 4H), 4.84 (t, 1H, J=7.7 Hz), 7.51 (t, 2H, J=7.7 Hz), 7.60 (t, 1H, J=7.7 Hz), 8.04 (d, 2H, J=8.4 Hz); LRMS (CI): 279 MH^+.

4.4. General procedure B: synthesis of 4-carbethoxy-2,3-dioxopyrrolidines 5 in acetic acid

To a solution of sodium diethyl oxalacetate (1 equiv) in acetic acid was added portionwise with constant stirring, amine (1 equiv) followed by aldehyde (1 equiv). After heating the mixture until everything dissolved, it was kept overnight at room temperature. On dilution with water and stirring, a yellow solid separated, which was filtered, washed with water, dried under reduced pressure, and recrystallized from toluene. After drying under reduced pressure the 2,3-dioxopyrrolidines **5** were obtained with sufficient purity.

4.4.1. 1,5-Bis-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5a). Product **5a** was prepared as described in the GP B and was obtained as a white powder (2.79 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.20 (t, 3H, J=7.3 Hz), 4.20 (q, 2H, J=7.3 Hz), 5.68 (s, 1H), 7.19 (m, 6H), 7.41 (d, 2H, J=8.8 Hz), 8.99 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 61.2, 61.9, 113.3, 123.6, 129.2, 129.4, 129.6, 131.8, 133.8, 134.9, 156.7, 163.1, 165.2; LRMS (CI): 392 MH^+; mp: 172 °C.

4.4.2. 1-Benzyl-5-(4-chlorophenyl)-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5b). Product **5b** (1.190 g, 32%) was prepared as described in the GP B and was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.10 (t, 3H, J=7.3 Hz), 4.10 (q, 2H, J=7.3 Hz), 4.38 (dd, 2H), 4.86 (s, 1H), 7.03–7.35 (m, 9H), 8.71 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8, 44.0, 59.0, 61.1, 112.9, 128.0, 128.4, 128.9, 129.1, 129.2, 133.2, 134.6, 136.0, 157.4, 163.5, 165.0; LRMS (CI): 372 MH^+; mp: 195 °C.

4.4.3. 5-(4-Chlorophenyl)-1-cyclohexyl-3-hydroxy-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5c). Product **5c** (671 mg, 31%) was prepared as described in the GP B and was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.20 (t, 3H), 1.40 (m, 10H), 3.71 (m, 1H), 4.11 (q, 2H), 5.13 (s, 1H), 7.18 (d, 2H, J=6.6 Hz), 7.31 (d, 2H, J=7.3 Hz), 8.30 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.9, 25.1, 25.7, 30.9, 54.3, 59.5, 60.9, 112.8, 128.6, 129.0, 134.2, 134.9, 156.9, 163.9, 164.6; LRMS (CI): 364 MH^+; mp: >350 °C.

4.4.4. 3-Hydroxy-1-(4-methoxybenzyl)-5-(4-methoxyphenyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5d). Product **5d** (1.59 g, 40%) was prepared as described in the GP B and was obtained as a white

powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.07 (t, 3H, J=7.3 Hz), 3.48 (d, 1H, J=14.6 Hz), 3.80 (s, 3H), 3.82 (s, 3H), 4.06 (q, 2H, J=7.3 Hz), 4.82 (s, 1H), 5.12 (d, 1H, J=14.6 Hz), 6.82 (d, 2H, J=8.8 Hz), 6.86 (d, 2H, J=8.8 Hz), 7.02 (d, 2H, J=8.1 Hz), 7.04 (d, 2H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 43.6, 55.6, 59.4, 60.9, 114.3, 114.4, 128.9, 129.4, 130.1, 130.2, 159.5, 160.0, 165.8; LRMS (CI): 398 MH^+; mp: 174 °C.

4.4.5. 5-(4-Chlorophenyl)-3-hydroxy-1-(4-methoxybenzyl)-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5e). Product **5e** (2.58 g, 64%) was prepared as described in the GP B and was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, 3H, J=7.3 Hz), 3.66 (d, 1H, J=15.3 Hz), 3.83 (s, 3H), 3.90–4.06 (m, 2H), 4.76 (d, 1H, J=15.3 Hz), 4.91 (s, 1H), 6.83 (d, 2H, J=8.8 Hz), 6.98 (d, 2H, J=8.1 Hz), 7.11 (d, 2H, J=8.1 Hz), 7.37 (d, 2H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.9, 44.1, 56.0, 60.2, 60.5, 112.2, 115.0, 129.2, 129.5, 130.1, 133.7, 136.0, 154.8, 159.5, 162.8, 165.6; LRMS (CI): 402 MH^+; mp: 180–181 °C.

4.4.6. 3-Hydroxy-5-(3-hydroxyphenyl)-2-oxo-1-(3,4,5-trimethoxyphenyl)-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5f). Product **5e** (851 mg, 38%) was prepared as described in the GP B and was obtained as a white powder. ^{1}H NMR (300 MHz, DMSO): δ=1.07 (t, 3H, J=7.3 Hz), 3.57 (s, 3H), 3.69 (s, 6H), 3.99–4.06 (m, 2H), 5.99 (s, 1H), 6.56 (d, 2H, J=8.1 Hz), 6.63 (s, 1H), 6.74 (d, 2H, J=8.1 Hz), 6.93 (s, 2H), 7.03 (t, 1H, J=8.1 Hz), 9.38 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ=14.9, 56.8, 60.6, 60.9, 61.6, 101.2, 112.7, 115.1, 115.9, 119.6, 130.1, 133.3, 135.7, 139.1, 153.4, 153.6, 158.0, 162.9, 164.9; LRMS (CI): 430 MH^+; mp: 205 °C.

4.5. General procedure C: synthesis of 2,3-dioxopyrrolidines 5 in ethanol

A suspension of sodium diethyl oxalacetate (1 equiv), amine (1 equiv), and aldehyde (1 equiv) in ethanol was heated at reflux toward complete solution (30 min) or until completion (TLC). After cooling the mixture was added on ice-water and then acidified with H_2SO_4 or H_3PO_4 until pH 2. The precipitate was filtered, washed with water, and dried under reduced pressure. The powder was washed with petroleum ether in order to remove traces of aldehyde or if necessary recrystallized with toluene. After drying under reduced pressure the 2,3-dioxopyrrolidines **5** were obtained with sufficient purity.

4.5.1. 5-(4-Dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid ethyl ester (5i). Product **5i** (7.4 g, 48%) was prepared as described in the GP C and was obtained as a white powder. Heating at reflux for 3 days was necessary and acidification was unnecessary. ^{1}H NMR (300 MHz, DMSO): δ=0.95 (s, 3H), 2.56 (s, 3H), 2.84 (s, 6H), 3.80 (q, 2H, J=7.3 Hz), 4.78 (s, 1H), 6.63 (d, 2H, J=8.8 Hz), 6.94 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, DMSO): δ=15.3, 28.0, 41.1, 57.8, 62.5, 99.9, 112.9, 128.9, 129.1, 129.8, 150.5, 166.1, 169.9, 170.6; LRMS (CI): 305 MH^+; mp: 186 °C.

4.5.2. 3-Hydroxy-1-methyl-2-oxo-5-phenyl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5j). Product **5j** (7.7 g, 59%) was prepared as described in the GP C and was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=corresponding with data literature;[31] LRMS (CI): 262 MH^+; mp: 133 °C (lit. 164–165 °C).

4.5.3. 3-Hydroxy-5-(2-hydroxy-phenyl)-1-methyl-2-oxo-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5k). Product **5k** (3.58 g, 52%) was prepared as described in the GP C and was obtained as a white powder. ^{1}H NMR (300 MHz, DMSO): δ=1.02 (t, 3H, J=7.3 Hz), 2.63 (s, 3H), 3.94–3.99 (m, 2H), 5.43 (s, 1H), 6.73 (t, 1H, J=7.3 Hz), 6.82 (d, 2H, J=7.3 Hz), 7.10 (t, 1H, J=8.8 Hz), 9.58 (s, 1H), 11.31 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ=14.9, 28.0, 60.1, 111.5, 116.6, 120.1, 122.7, 129.9, 155.2, 157.0, 163.1, 165.6; LRMS (CI): 305 MH^+; mp: 196–197 °C.

4.5.4. 1-Allyl-3-hydroxy-2-oxo-5-thiophen-2-yl-2,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (5l). Product **5l** (17.3 g, 62%) was prepared as described in the GP C and was obtained as a white powder. ^{1}H NMR (300 MHz, DMSO): δ=1.12 (t, 3H, J=7.3 Hz), 3.49 (s, 2H), 4.02–4.11 (m, 4H), 5.00 (d, 1H, J=16.4 Hz), 5.10 (d, 1H, J=10.1 Hz), 5.62–5.75 (m, 1H), 7.11 (t, 1H, J=5.49 Hz), 7.17 (d, 1H, J=3.7 Hz), 7.52 (d, 1H, J=6.4 Hz); ^{13}C NMR (75 MHz, DMSO): δ=14.3, 43.0, 55.6, 61.4, 112.9, 119.2, 126.5, 127.1, 128.3, 132.4, 138.5, 157.6, 163.1, 165.3; LRMS (CI): 294 MH^+; mp: 119 °C.

4.6. General procedure D: synthesis of alcohols 9

A suspension of enol **5** (1 equiv), zinc powder (6 equiv), and a few drops of sulfuric acid in acetic acid 150 mL was vigorously stirred at 100 °C for 2 h. A second portion of zinc powder (6 equiv) was added and the reaction mixture was then stirred at 100 °C until completion of the reaction (followed by TLC). After cooling to room temperature the excess of zinc and the inorganic salts were filtered off. The filtrate was then diluted with water (300 mL). The aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were washed with saturated $NaHCO_3$ solution until neutral and finally dried with magnesium sulfate. The solvents were evaporated under reduced pressure and the residue used directly in the next step or was chromatographed on silica gel (EtOAc) to furnish the pure alcohol **9**.

4.6.1. (3*S*,4*R*,5*S*)-5-(4-Dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9c*trans–trans*) and (3*R*,4*S*,5*S*)-5-(4-dimethylamino-phenyl)-3-hydroxy-1-methyl-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9c*trans–cis*). Products **9c***trans–trans* and **9c***trans–cis* were prepared as described in the GP D. Product **9c***trans–trans* (560 mg, 36%) was obtained as a white powder and **9c***trans–cis* (83 mg, 5.4%) was obtained as a viscous colorless oil. Product **9c***trans–trans* ^{1}H NMR (400 MHz, $CDCl_3$): δ=1.22 (t, 3H, J=7.3 Hz), 2.62 (s, 3H), 2.96 (s, 6H), 3.06 (t, 1H, $2\times{}^3J$=8.4 Hz), 4.18 (q, 2H, J=7.3 Hz), 4.53 (d, 1H, J=8.1 Hz), 4.66 (d, 1H, J=8.8 Hz), 6.71 (d, 2H, J=8.8 Hz), 7.13 (d, 2H, J=8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ=14.1, 28.1, 40.3, 56.1, 61.3, 62.9, 72.6, 112.5, 124.6, 128.3, 150.8, 171.5, 173.0; LRMS (CI): 307 MH^+; mp: 45 °C.

Product **9c***trans–cis* ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.94 (t, 3H, J=7.3 Hz), 2.74 (s, 3H), 2.94 (s, 6H), 3.59 (t, 1H, 2×^3J=7.4 Hz), 3.78–3.88 (m, 2H), 4.08–4.17 (m, 1H), 4.55 (d, 1H, J=7.3 Hz), 4.68 (d, 1H, J=7.3 Hz), 6.67 (d, 2H, J=8.8 Hz), 7.11 (d, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.6, 28.6, 40.2, 49.4, 60.7, 62.7, 70.4, 112.0, 121.8, 128.6, 151.0, 169.6, 173.2; LRMS (CI): 307 MH^+.

4.6.2. (3*S*,4*R*,5*S*)-1-Benzyl-5-(4-chloro-phenyl)-3-hydroxy-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9d*trans–trans*) and (3*R*,4*S*,5*S*)-1-benzyl-5-(4-chlorophenyl)-3-hydroxy-2-oxo-pyrrolidine-3-carboxylic acid ethyl ester (9d*trans–cis*). Products **9d***trans–trans* (6.4 g, 64%) and **9d***trans–cis* (520 mg, 5.2%) were prepared as described in the GP D and were obtained as white powders. Product **9d***trans–trans* ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.15 (t, 3H, J=7.3 Hz), 3.06 (t, 1H, J=8.1 Hz), 3.52 (d, 1H, J=14.6 Hz), 4.13 (q, 2H, J=7.3 Hz), 4.44 (d, 1H, J=7.3 Hz), 4.71 (d, 1H, J=8.1 Hz), 5.05 (d, 2H, J=14.6 Hz), 6.95–6.99 (m, 2H), 7.15 (d, 2H, J=8.8 Hz), 7.25–7.27 (m, 3H), 7.36 (d, 2H, J=8.8 Hz); LRMS (CI): 374–376 MH^+; mp: 99 °C.

Product **9d***trans–cis* ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.92 (t, 3H, J=7.3 Hz), 3.50 (t, 1H, J=8.1 Hz), 3.61 (d, 1H, J=14.6 Hz), 3.67–3.81 (m, 3H), 4.56 (t, 2H, J=6.6 Hz), 5.16 (d, 1H, J=14.6 Hz), 6.98–7.02 (m, 2H), 7.23 (d, 2H, J=8.8 Hz), 7.26–7.28 (m, 3H), 7.30 (s, 2H, J=8.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 45.2, 48.7, 60.2, 61.6, 70.9, 128.4, 128.9, 129.2, 129.3, 130.1, 133.9, 135.2, 135.6, 169.7, 173.1; LRMS (CI): 374–376 MH^+; mp: 117–118 °C.

4.7. General procedure E: synthesis of benzylidene-5-aryl-2-oxopyrroles 10

To a solution of oxopyrrole **2** (1 equiv) in ethanol was added aromatic aldehyde (1 equiv). A catalytic amount of concentrated HCl was added and the mixture was heated under reflux for 2 h. During cooling to room temperature orange crystals precipitated. The solid was filtered and washed with cold ethanol. After drying under reduced pressure, compound **10** was obtained as orange powder.

4.7.1. 4-(4-Carboxy-benzylidene)-2-(4-methoxy-phenyl)-5-oxo-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (10a). Product **10a** (1.09 g, 69%) was prepared as described in the GP E and was obtained as an orange powder. ^{1}H NMR (300 MHz, DMSO): δ=1.1 (t, 3H), 3.8 (s, 1H), 4.1 (q, 2H), 7.0 (d, 2H, J=8.8 Hz), 7.5 (d, 2H, J=8.8 Hz), 7.9 (d, 2H, J=8.1 Hz), 8.0 (s, 1H), 8.1 (d, 2H, J=8.8 Hz), 10.9 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ=14.6, 56.2, 60.3, 102.9, 114.1, 122.7, 129.6, 131.6, 131.8, 131.9, 137.9, 139.3, 152.6, 161.8, 164.3, 167.3, 167.7; LRMS (CI): 394 MH^+; mp: 282 °C.

4.7.2. 4-(4-Methoxy-benzylidene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (10b). Product **10b** (1.24 g, 89%) was prepared as described in the GP E and was obtained as a yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.3 Hz), 3.90 (s, 3H), 4.23 (q, 2H, J=7.3 Hz), 6.94 (dd, 2H, J=8.8 Hz), 7.45–7.49 (m, 3H), 7.55–7.59 (m, 2H), 8.21 (s, 1H), 8.31 (d, 2H, J=8.78 Hz), 8.61 (br s, 1H); LRMS (CI): 350 MH^+; mp: 188 °C.

4.7.3. 4-(Ethoxycarbonyl-hydroxy-methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (16). To a suspension of **2c** (462 mg, 2.00 mmol) in (5 mL) was added diethyl oxalate (0.55 mL, 4.00 mmol) and sodium ethoxide (5 mmol from sodium (115 mg) dissolved in 3 mL ethanol). The mixture was heated at reflux for 2 h, partially concentrated under reduced pressure, diluted with water and acidified with acetic acid affording a white precipitate. After filtering and drying under reduced pressure compound **16** (250 mg, 40%) was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (t, 3H, J=6.9 Hz), 1.37 (t, 3H, J=7.3 Hz), 4.17 (q, 2H, J=7.3 Hz), 4.39 (t, 3H, J=7.3 Hz), 7.45 (s, 5H), 9.75 (br s, 1H), 14.41 (br s, 1H); LRMS (CI): 332 MH^+; mp: 178 °C.

4.7.4. 3-(4-Methoxyphenyl)-2*H*-pyrrolo[3,4-*c*]benzoxepine-1,4-dione (13) and 2-(4-methoxyphenyl)chromeno[2,3-*b*]pyrrole-3-carboxylic acid ethyl ester (14). A solution of methoxyphenylpyrrolinone **2d** (512 mg, 2.00 mmol), salicylaldehyde (244 mg, 2.00 mmol) in acetic acid (2 mL) was stirred and heated in a monomode microwave oven at 120 °C for 30 min. After cooling to room temperature the mixture was poured on water and extracted with ether. The organic phase was washed with water and finally dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel (CH_2Cl_2/EtOAc 95:5) to furnish the pure **14** (87 mg, 13%) as an orange powder. Washing the slightly impure fractions containing product **13** with CH_2Cl_2 furnished pure **13** (50 mg, 8%) as yellow-orange powder. Compound **13** ^{1}H NMR (300 MHz, DMSO): δ=3.85 (s, 3H), 7.04 (d, 2H, J=8.8 Hz), 7.16 (d, 1H, J=8.8 Hz), 7.28 (t, 1H, J=7.3 Hz), 7.39 (s, 1H), 7.48 (t, 1H, J=7.3 Hz), 7.64 (d, 1H, J=7.3 Hz), 7.74 (d, 2H, J=8.8 Hz), 11.41 (br s, 1H); ^{13}C NMR (75 MHz, DMSO): δ=56.3, 99.0, 114.2, 120.3, 122.8, 124.9, 126.3, 128.5, 130.7, 132.8, 133.7, 134.1, 150.7, 156.5, 159.0, 162.3, 166.7; UV (CH_2Cl_2): λ_{max} (log ε)=427 nm (4.230), 310 (4.072); LRMS (CI): 320 MH^+; mp: 287 °C.

Compound **14** ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.42 (t, 3H, J=7.3 Hz), 3.88 (s, 3H), 4.41 (q, 2H, J=7.3 Hz), 6.99 (d, 2H, J=8.8 Hz), 7.48 (t, 1H, J=7.3 Hz), 7.69 (t, 1H, J=7.3 Hz), 7.76 (d, 1H, J=7.3 Hz), 7.85 (d, 1H, J=7.3 Hz), 8.25 (d, 1H, J=8.8 Hz), 8.65 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.8, 55.7, 60.3, 103.4, 113.5, 118.2, 120.9, 125.4, 127.5, 128.8, 129.7, 132.0, 133.3, 136.4, 151.3, 161.8, 163.4, 164.5, 164.9; LRMS (CI): 348 MH^+; mp: 134 °C.

4.7.5. 5-Oxo-2-phenyl-4-(phenyl-hydrazono)-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (18). To a suspension of **2c** (924 mg, 4.00 mmol) in ethanol (10 mL) was added freshly prepared phenyldiazonium chloride (560 mg, 4.00 mmol). The mixture was refluxed for 1 h. After 5–6 min compound **18** started to precipitate. After cooling, the precipitate was filtered and dried affording **18** (804 mg, 60%) as bright orange crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.98 (t, 3H, J=6.9 Hz), 4.11 (q, 2H, J=6.6 Hz), 7.01–7.57 (m, 10H), 9.04 (br s, 1H), 13.34 (br s, 1H); LRMS (CI): 366 MH^+; mp: 199 °C.

4.7.6. 4-(Bis(methylthio)methylene)-5-oxo-2-phenyl-4,5-dihydro-1*H*-pyrrole-3-carboxylic acid ethyl ester (19). To a solution of **2c** (462 mg, 2.00 mmol) in DMSO (10 mL) was added triethylamine (0.55 mL, 4.00 mmol). After 3 min, CS_2 (0.132 mL, 2.00 mmol) was added and methyl iodide was added after the color change. The reaction mixture was stirred at room temperature for 4 h and then poured on ice-water and acidified with acetic acid (1 mL). The aqueous mixture was extracted with ethyl acetate. The organic phase was washed with water and brine and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the viscous residue was chromatographed on silica gel (CH_2Cl_2/EtOAC 4:1) to furnish the pure **19** (400 mg, 60%) as yellow crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.25 (t, 3H, J=7.3 Hz), 2.50 (s, 3H), 2.63 (s, 3H), 4.23 (q, 2H, J=7.0 Hz), 7.38–7.43 (m, 3H), 7.58–7.62 (m, 2H), 9.17 (br s, 1H); LRMS (CI): 336 MH^+; mp: 118 °C.

4.7.7. 5-Chloro-4-formyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20a). To pyrrolinone **2c** (5.00 g, 21.0 mmol) in DMF (3.40 mL, 43.0 mmol) was added $POCl_3$ (16.1 mL, 173 mmol) in a dropswise manner at T<10 °C. The mixture was heated overnight at 100 °C and then poured on ice (800 mL). After 2 h stirring the suspension was extracted with ethyl acetate (4×100 mL). The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was filtered over silica gel (CH_2Cl_2) to furnish the pure **20a** (4.82 g, 80%) as brownish powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.20 (t, 3H, J=7.1 Hz), 4.23 (q, 2H, J=7.2 Hz), 7.40 (m, 5H), 9.17 (s, 1H), 10.32 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 60.9, 112.8, 119.6, 122.0, 128.4, 128.9, 129.3, 130.1, 136.4, 163.8, 186.9; LRMS (CI): 278: MH^+; mp: 160 °C.

4.8. General procedure F: synthesis of *N*-substituted pyrroles 20 via alkylation

To pyrrole aldehyde **20a** (1 equiv) in acetonitrile was added alkylating agent (1.4 equiv) and K_2CO_3 (1.6 equiv). The mixture was heated overnight at 60 °C and then poured on ice. The suspension was extracted with ethyl acetate. The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was chromatographed over silica gel (CH_2Cl_2/EtOAc) to furnish the pure *N*-substituted pyrroles **20**.

4.9. General procedure G: synthesis of *N*-substituted pyrroles 20 via chloroformylation

To *N*-substituted oxopyrrole **2** (1 equiv) in DMF (2 equiv) was added $POCl_3$ (8 equiv) in a dropswise manner at T<10 °C. The mixture was heated overnight at 120 °C and then poured on ice. After 2 h stirring the suspension was extracted with ethyl acetate. The organic phase was washed with brine and water and finally dried with magnesium sulfate. The solvents were evaporated in vacuo and the residue was filtered over silica gel (CH_2Cl_2) to furnish the pure *N*-substituted pyrrole **20**.

4.9.1. 1-Benzyl-5-chloro-4-formyl-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20b). Product **20b** (3.97 g, 99%) was prepared as described in the GP F and was obtained as an orange-brown powder.

The same product **20b** (76 mg, 66%) was also prepared as described in the GP G. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.01 (t, 3H, J=7.1 Hz), 4.10 (q, 2H, J=7.2 Hz), 5.05 (s, 2H), 6.82 (m, 2H), 7.26 (m, 8H), 10.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.7, 48.0, 60.3, 114.3, 119.1, 123.3, 126.1, 127.8, 128.1, 128.7, 129.3, 130.2, 130.5, 135.4, 139.2, 163.3, 186.7; LRMS (CI): 368: MH^+; mp: 82–84 °C.

4.9.2. 5-Chloro-4-formyl-1-(2-oxo-2-phenyl-ethyl)-2-phenyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20c). Product **20c** (300 mg, 76%) was prepared as described in the GP F and was obtained as an orange-brown powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.03 (t, 3H, J=7.1 Hz), 4.11 (q, 2H, J=7.1 Hz), 5.18 (s, 2H), 7.40–7.53 (m, 10H), 10.50 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=13.8, 50.8, 60.4, 114.0, 119.1, 123.4, 127.3, 128.4, 129.1, 129.5, 130.2, 130.4, 133.8, 134.5, 139.5, 163.2, 187.0, 190.8; LRMS (CI): 396: MH^+; mp: 79–81 °C.

4.9.3. 5-Chloro-1,2-bis-(4-chlorophenyl)-4-formyl-1*H*-pyrrole-3-carboxylic acid ethyl ester (20d). Product **20d** (740 mg, 66%) was prepared as described in the GP G and was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.13 (t, 3H, J=7.3 Hz), 4.19 (q, 2H, J=7.3 Hz), 7.03 (d, 2H, J=8.2 Hz), 7.08 (d, 2H, J=8.2 Hz), 7.22 (d, 2H, J=9.1 Hz), 7.34 (d, 2H, J=9.1 Hz), 10.43 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 61.2, 115.1, 119.7, 124.8, 128.4, 128.6, 130.0, 130.1, 133.4, 135.5, 136.1, 138.1, 163.5, 186.8; LRMS (CI): 422 MH^+; mp: 199 °C.

4.9.4. 6-Benzyl-5-chloro-7-phenyl-2,6-dihydro-pyrrolo[3,4-*d*]pyridazin-1-one (21a). To a solution of **20b** (183 mg, 0.50 mmol) in ethanol (10 mL) was added hydrazine monohydrate (50 μL, 1.00 mmol). The reaction mixture was heated at reflux for 4 h. On cooling **21a** precipitated. The precipitate was filtered and washed with cold ethanol furnishing **21a** (108 mg, 64%) as yellow crystals. ^{1}H NMR (300 MHz, DMSO): δ=5.35 (s, 2H), 6.84 (d, 2H, J=6.6 Hz), 7.23–7.28 (m, 3H), 7.40–7.46 (m, 5H), 8.09 (s, 1H); ^{13}C NMR (75 MHz, DMSO): δ=48.5, 111.3, 112.1, 115.9, 126.1, 127.9, 128.4, 129.1, 129.3, 129.4, 131.2, 132.7, 136.3, 157.9; LRMS (CI): 336 MH^+; mp: 249–251 °C.

4.9.5. 6-Benzyl-5-chloro-2-methyl-7-phenyl-2,6-dihydro-pyrrolo[3,4-*d*]pyridazin-1-one (21b). To a solution of **20b** (877 mg, 2.40 mmol) in ethanol (40 mL) was added methyl hydrazine (190 μL, 3.60 mmol). The reaction mixture was heated at reflux overnight. The solvent was evaporated in vacuo and the residue was chromatographed over silica gel (CH_2Cl_2/EtOAc 9:1) to furnish the pure **21b** (352 mg, 42%) as orange crystals. ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.69 (s, 3H), 5.31 (s, 2H), 6.86 (m, 2H), 7.26 (m, 3H), 7.37 (m, 5H), 8.00 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=38.1, 48.7, 111.2, 112.4, 116.2, 126.0, 127.9, 128.2, 128.9, 129.2, 130.9, 132.9, 135.8, 157.6; LRMS (CI): 350 MH^+; mp: 77 °C.

4.9.6. Diethyl 6-benzyl-5-phenyl-6*H*-thieno[2,3-*b*]pyrrole-2,4-dicarboxylate (24). To a solution of **20b** (741 mg, 2.00 mmol) in ethanol (20 mL) was added mercapto ethyl

acetate (0.333 mL, 3.00 mmol). The reaction mixture was refluxed overnight. On standing **24** precipitated. The precipitate was filtered and washed with water. After drying under reduced pressure product **24** (323 mg, 37%) was obtained as a white powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.24 (t, 3H, J=7.1 Hz), 1.36 (t, 3H, J=7.1 Hz), 4.22 (q, 2H, J=7.1 Hz), 4.33 (q, 2H, J=7.1 Hz), 5.01 (s, 2H), 7.05 (m, 2H), 7.29 (m, 3H), 7.45 (m, 5H), 8.06 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.3, 14.4, 59.8, 61.1, 77.2, 126.3, 127.1, 127.5, 128.2, 128.4, 128.6, 128.9, 129.3, 129.5, 130.6, 130.7, 134.4, 139.5, 146.4, 163.4, 163.8; LRMS (CI): 434: (MH^+); mp: 137 °C.

4.10. General procedure H: synthesis of azepines 25, 26, and 27

To *N*-benzylated pyrrole aldehyde **20b** (1 equiv) in ethanol was added the *ortho* functionalized aniline (1 equiv) and a few drops of piperidine. The reaction mixture was heated at reflux for 4 h. After partial evaporation of the solvent under reduced pressure the mixture was diluted with diethyl ether. The precipitated piperidine salts were filtered. The filtrate was evaporated in vacuo. The residue was chromatographed over silica gel (CH_2Cl_2/EtOAc) to furnish the pure azepines as brown viscous oils.

4.10.1. 8-Benzyl-10-ethoxycarbonyl-9-phenylpyrrolo[7,6-*b*]-1,4-benzoxazepine (25). Product **25** (81 mg, 38%) was prepared as described in the GP H and was obtained as a brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.12 (t, 3H, J=7.1 Hz), 4.13 (q, 2H, J=7.1 Hz), 7.26 (m, 14H), 4.96 (s, 2H), 8.75 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 46.3, 59.9, 103.9, 108.6, 120.3, 126.2, 126.3, 127.7, 128.0, 128.1, 128.8, 128.9, 130.2, 130.5, 134.5, 136.4, 140.7, 148.0, 151.7, 157.3, 163.6; LRMS (CI): 423 MH^+.

4.10.2. 8-Benzyl-10-ethoxycarbonyl-9-phenylpyrrolo[7,6-*b*]-1,4-benzothiazepine (26). Product **26** (100 mg, 45%) was prepared as described in the GP H and was obtained as a brown viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.09 (t, 3H, J=7.1 Hz), 4.10 (q, 2H, J=7.1 Hz), 6.79 (m, 2H), 5.08 (s, 2H), 7.09 (m, 4H), 7.22 (m, 3H), 7.32 (m, 5H), 9.12 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ=14.0, 48.3, 60.0, 112.3, 121.7, 126.2, 126.8, 127.3, 127.4, 127.6, 128.0, 128.7, 128.8, 129.0, 129.3, 130.4, 130.8, 132.1, 136.8, 141.4, 150.8, 158.5, 163.3; LRMS (CI): 439 MH^+.

4.10.3. 1-Benzyl-2-phenyl-1,10-dihydro-benzo[*b*]pyrrolo[2,3-*e*][1,4]diazepine-3-carboxylic acid ethyl ester (27). Product **27** (67 mg, 36%) was prepared as described in the GP H and was obtained as a brown viscous oil. ^{1}H NMR (300 MHz, DMSO): δ=1.17 (t, 3H, J=7.1 Hz), 4.02 (q, 2H, J=7.1 Hz), 5.15 (s, 2H), 7.32 (m, 14H); ^{13}C NMR (75 MHz, DMSO): δ=14.2, 53.1, 60.9, 93.1, 113.9, 116.3, 123.3, 123.8, 126.7, 127.0, 127.7, 128.0, 129.0, 131.4, 136.3, 136.9, 139.2, 153.5, 157.5; LRMS (CI): 422 MH^+.

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Stereoselective carbonyl reductions of chloro-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones

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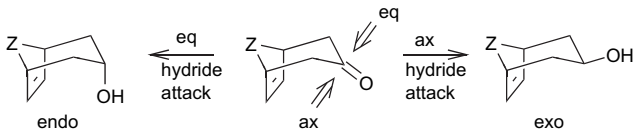
Abstract—The lithium aluminium hydride reduction of 2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-one (**8**) was reinvestigated. In contrast to most halogeno-substituted oxabicyclic ketones, which give predominantly the corresponding *endo* alcohols, the expected (3*endo*)-2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**9n**) is formed in a minute proportion. An X-ray structure analysis of the dominating product gave proof of the *exo*-alcohol, i.e., (3*exo*)-2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (**9x**). On the other hand, reduction of trichloroketone **11**, 2,2,*endo*-4-trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one, and the methoxy-substituted chloroketones **13** and **14** provided the corresponding *endo* alcohols (**12** and **15**).

1. Introduction

It is long known that bicyclo[3.2.1]oct-6-en-3-one (**1**) is reduced by sodium borohydride or lithium aluminium hydride to form a mixture of the corresponding *endo*- and *exo*-alcohols (**2n** and **2x**).[1] The proportion obtained with lithium aluminium hydride (LAH) in ether was 39:61, whereas with $NaBH_4$ in methanol the *endo* alcohol predominated (75:25).[1]

The bicyclic ketone **1** may be regarded as a bridged cyclohexanone, and thus the reductions can be put within the well-known framework of axial versus equatorial attack of nucleophiles at the carbonyl group. Provided that the reactive conformation is a chair-like one, axial attack will lead to the equatorial alcohol, i.e., *exo* hydroxy-bicycle. While this approach will be influenced by the neighboured etheno-bridge, the less hindered equatorial attack produces the *endo*-, or *axial* alcohol.

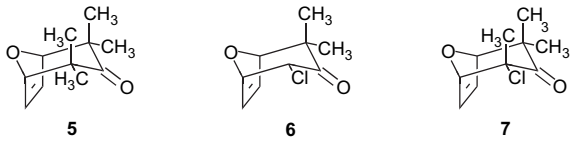


2n **4n** | **1: Z = CH_2** **3: Z = O** | **2x** **4x**

In recent years, oxabicyclic analogues of ketone **1** have found widespread applications in organic synthesis and, hence, several researchers directed their attention to the stereoselective reduction of the carbonyl group.[2–5] Reduction of the parent oxabicyclic ketone, 8-oxabicyclo[3.2.1]oct-6-en-3-one (**3**), with LAH in THF affords almost equal amounts of *endo*- and *exo*-alcohols (**4n** and **4x**) (46:54).[6] With sodium borohydride a diastereoselectivity of ca. 67:33 was determined by analysis via the corresponding *O*-benzyl ethers.[7] Bulkier complex hydrides, i.e., DIBAL-H or K-Selectride® produces increasing proportions of the *endo* alcohol (88:12 and 97:3, respectively).[7] For the selective preparation of these alcohols, L-Selectride®, and samarium diiodide have been recommended.[4,5]

In contrast to **3**, the α,α′-tetramethylderivative (**5**) with LAH in diethyl ether gives a high *exo*-selectivity (5:1).[5]

In another context we have found that the introduction of chloro (and bromo) substituents at the α-position leads to an enhanced proportion of the *endo* alcohols, as has been demonstrated with several oxabicycles.[8] For example, *endo*-2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**6**) furnished the *endo* alcohol with a 72% yield.[8] Similarly, the $\Delta^{6,7}$-saturated *endo*-2,*endo*-4-dichloro-8-oxabicyclo[3.2.1]octan-3-one was found to form the corresponding *endo* alcohol on LAH reduction in THF.[9] However, the more crowded trimethyl chloroketone **7** gave a 78:22 mixture of the *endo*/*exo* diastereomers.[8]



5 **6** **7**

Keywords: Haloketones; Halohydrines; Reduction; Hydrides; Diastereoselectivity; Heterocycles; X-ray diffraction.
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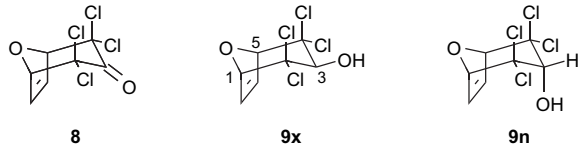
2. Results and discussion

Some years ago we investigated the LAH reduction of the oxabicyclic tetrachloroketone **8** and obtained a single tetrachloro alcohol.[9] However, we were unable at that time to determine its configuration. So we felt worth repeating this experiment and clarifying the problem.



The reaction of ketone **8** with LAH under standard conditions followed by acidic work-up led to a solid product that was sublimed. A capillary gas chromatogram showed two peaks in the ratio of 97:3. The ^{1}H and ^{13}C NMR spectra of the mixture were in accordance with the spectra obtained earlier.[9] Additional weak signals (see Section 4) were obviously produced by the minor product. Recrystallization of the solid from ethanol yielded crystals with mp 164–165.5 °C that were suitable for an X-ray structure analysis. The result from this was that the tetrachlorohydrin has the *exo* configuration at C-3 (**9x**, Fig. 1). It follows that the minor reduction product (3%) is the *endo* alcohol. As shown in Figure 2, in the solid state the molecules of the *exo* tetrachloro alcohol are associated with neighbours by hydrogen bonds to the ether oxygen.[10]

It is well known that the chair conformation of cyclohexanes becomes flattened by poly-substitution, especially with geminal methyl groups ('reflex effect'), and by spanning with a two-carbon bridge between positions 1 and 3 ('inverse reflex effect').[11] The above-mentioned molecules correspond to this situation, and the X-ray parameters of **9x** reveal these effects.

The carbon atoms C-1, C-2, C-4 and C-5 form a plane and may define the 'seat of the chair'. The plane of the triangle

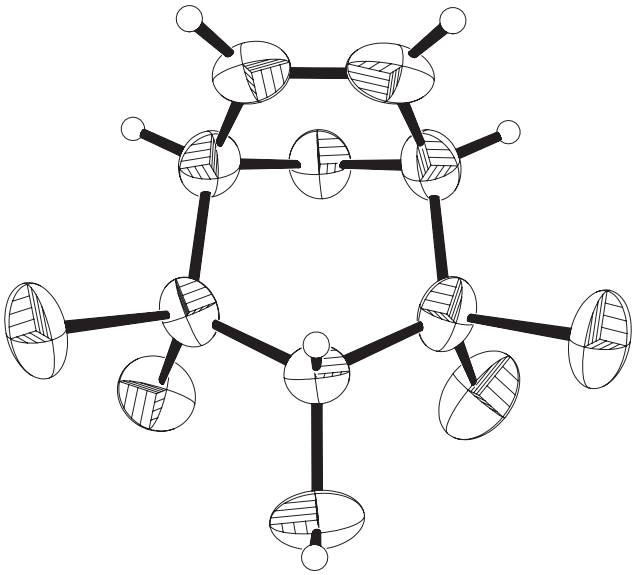


Figure 1. X-ray structure of (3*exo*)-2,2,4,4-tetrachloro-8-oxabicyclo-[3.2.1]oct-6-en-3-ol (*exo*-**9x**).

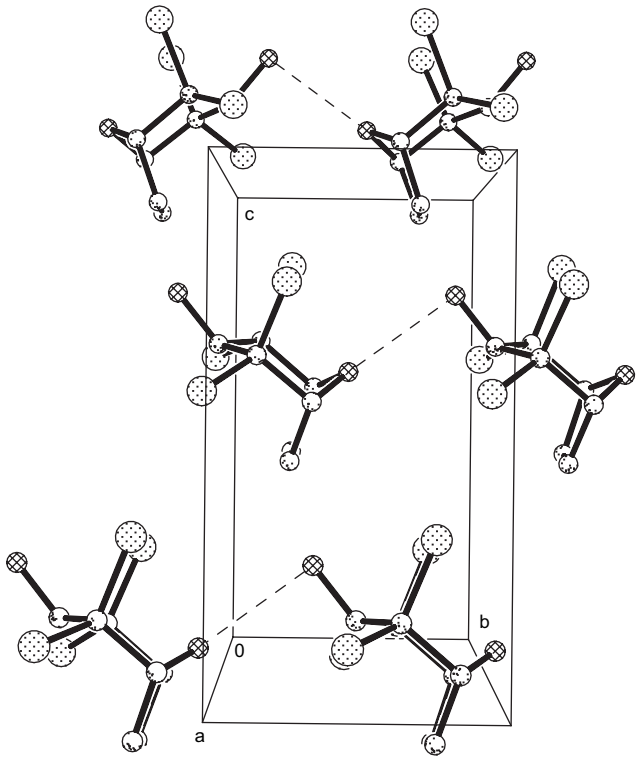


Figure 2. Unit cell of **9x**.

formed by the atoms C-2, C-3 and C-4 is inclined with a 35.5° angle. In contrast, the 'back of the chair' (C-1, O-8 and C-5) is more steep forming an angle of inclination with 73.5° (or 106.5° for the supplementary angle). The deviation of the tetrahydropyran-oxygen atom from the main plane is 86 pm (0.86 Å), whereas the opposite carbon atom (C-3) is only 50 pm (0.50 Å) below the C-1/C-2/C-4/C-5 plane (Fig. 3).

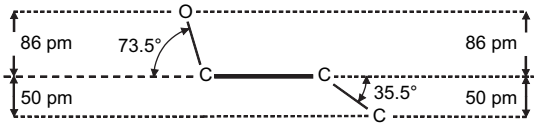
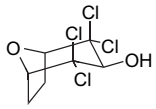


Figure 3. Side view of the oxacyclohexane skeleton of the tetrachloro-alcohol-hydrin **9x**.

In contrast to the tetrachloroketone **8**, which was partially, but selectively bis-dechlorinated on hydrogenation over palladium–carbon catalyst in methanol,[9] the double bond of tetrachlorohydrin **9x** was saturated to give **10** without affecting the chloro substituents.

As mentioned above, this almost perfect *exo*-selectivity is in contrast to the analogous tetramethylketone **5**, and trimethyl chloroketone **7**, that gave mixtures of the *endo*/*exo* diastereomers,[5,8] though the substituents have similar van der Waals radii.

Hence we looked at the behaviour of the trichloroketone **11**, 2,2,*endo*-4-trichloro-8-oxabicyclo[3.2.1]oct-6-en-3-one, which proved to give also only one product on reduction. However, in this case the NMR spectra (vide infra) indicate that the *endo* alcohol **12** is formed.



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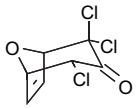
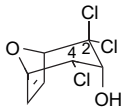
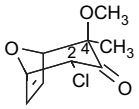


11



12



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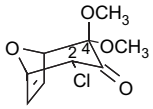
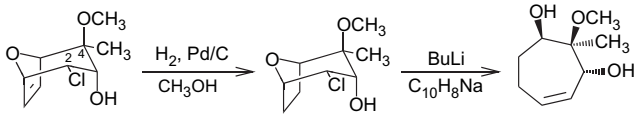


14

Recently we reported on an easy access to the methoxy-substituted chloroketones **13** and **14**.[12,13] LAH reduction of both **13** and **14** afforded again the corresponding *endo* alcohols (for the latter, please see Ref. 6). Hydrogenation of the unsaturated chlorohydrin **15** gave the oxabicycle **16**. The lithium alkoxide generated from alcohol **16** was subjected to a reductive elimination (Boord reaction) induced by sodium naphthalenide,[8] which led to the cycloheptenediol **17**.



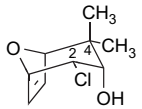
15 16 17

As mentioned above, the LAH reduction of 2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**6**) was reported to furnish also the *endo* alcohol.[8] However, it should be noted that the product alcohol was isolated by crystallization, and the mother liquor was not examined for other products.[8,14]

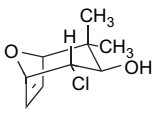
Years before, we investigated reductions of **6** with sodium borohydride.[15] Indeed, reduction did occur using a standard protocol in isopropyl alcohol, but the result was an oily product after 5 h reaction time, and TLC indicated that reaction was unselective.

A more satisfying outcome was obtained performing the reduction in presence of aqueous sodium hydrogencarbonate ($NaHCO_3$) in ethanol.[16] After 1 h reaction time at room temperature work-up afforded a mixture of the *endo*- and *exo*-alcohol **18n** and **18x**, respectively, in >80% yield. However, a small amount of unreacted **6**, which was recovered, indicated that the reduction needs a longer time. Though it remains to be proved that this result would be of value in synthesis, it furnished us a sample of the *exo*-epimer (**18x**), useful for the assignment of configurations by NMR spectroscopy.

Finally, we performed the reduction of **6** with sodium borohydride in presence of cerium trichloride (Luche reagent),[17] which gave an *endo*-selectivity of ca. 99%.



18n



18x

2.1. Assignment and configuration of the alcohols 12, 15 and 18

Arguments for the assignment of *endo*- and *exo*-alcohols by NMR spectroscopy were stated by Treu and Hoffmann,[5] and us,[8] and the assignments in the present work are based on these.

Though the data of the *endo* alcohol produced from **8** could only be determined from the mixture of isomers, the difference in the HO and H-3 resonances is clearly discernible.

Whilst **9x** shows a doublet at δ=4.44 ($^3J_{3,OH}$=12.9 Hz) for H-3, the corresponding resonance for **9n** appears as a dt at 4.62 with $J_{3,OH}$=7.2 Hz and J=1.6 Hz. The splitting of the *exo*-H-3 is due to a W coupling pathway with the bridgehead protons; the lines of the latter are also split. The comparatively strong coupling between the HO-proton and H-3 ($^3J_{3,OH}$= 12.9 Hz) of **9x** is consistent with an *anti*- or *synperiplanar* partial conformation at the HO–C(3)H bond; the latter conformation exists in the solid state, according to the X-ray structure analysis.

For Treu's *exo*-alcohol derived from tetramethylketone **5**, a coupling constant of 8 Hz ($^3J_{3,OH}$) was reported.[5] From this one can conclude that rather electronic than steric effects of the four neighboured chloro substituents hamper rotation about the C(3)–O-bond and enforce population of a favoured conformation. Likewise, a coupling constant $^3J_{3,OH}$= 12.0 Hz is seen with the saturated tetrachlorohydrin **10** (δ_{OH}= 3.15 ppm).

The alcohols derived from ketone **6** showed also characteristic differences. The H-3 signal of the *exo*-alcohol **18x** appears at δ=3.45 as a dd with $J_{3,OH}$=4.7 Hz and $J_{2,3}$=8.5 Hz; the smaller coupling constant may indicate that torsion about the C(3)–O-bond is less hindered than with **9x**. The magnitude of the larger J clearly points to a nearly *antiperiplanar*, i.e., *axial–axial* (*exo–endo*) relationship of protons H-2 and H-3, which is supported by comparison with the corresponding value of the *endo* alcohol (**18n**) ($J_{2,3}$=4.8 Hz, δ=3.60).[8]

Concerning the trichlorohydrin **12** (derived from **11**)—which is structurally equivalent to **18n**—the multiplet (9 lines), centred at δ=4.32, cannot be analyzed for certain by first-order rules. However, from the signal of the proton bound to the chloro-substituted carbon atom (here C-4, according to IUPAC nomenclature rules!)—a dd with J=4.6 and J=3.6 Hz at δ=4.70—the larger coupling constant (J=4.6 Hz) is in line with an *axial–equatorial* relationship of H-3 and H-4, i.e., the *endo* alcohol (**12n**). Presumably the complex multiplet with **12** results from a W coupling of H-3 with the bridgehead protons (H-1 and H-5).

The coupling constants $^3J_{2,3}$ with **15** and the alcohol produced from **14**[6] (5.0 Hz each) correspond to that of **18n** ($^3J_{2,3}$= 4.8 Hz)[8], and thus give proof of their *endo*-configuration.

3. Conclusions

Hydride reductions of 8-oxabicyclo[3.2.1]oct-6-en-3-ones represent examples of π-facial diastereoselective addition

reactions to carbonyl groups, that have turned out to be phenomena of complex origin, still in dispute.[18–25] Comparing the hydride reductions of methyl-substituted 8-oxabicyclo-[3.2.1]oct-6-en-3-ones with those of chloro- (and bromo) substituted oxabicyclic ketones it becomes apparent that the observed *endo*-selectivity results from an electronic effect induced by the halogeno substituents. Recently, Rosenberg et al. investigated hydride reductions of 2-substituted 4-*tert*-butylcyclohexanones, which are well-known models for the chair conformation.[25] They compared the stereoselectivities with current models of theory and came to the conclusion that selectivity is controlled by electrostatic interactions between the nucleophile and substituent.

Apart from a stimulus for chemical theorists, the stereoselective reduction of halogeno-substituted oxabicyclic ketones might open the door for following transformations. The reader should remember that halogeno-substituted 8-oxabicyclo[3.2.1]oct-6-en-3-ones, obtained by [4+3] cycloaddition routes, are usually dehalogenated immediately before further synthesis steps are tackled. In contrast, utilization of the halogeno substituents is a general goal for further research.

4. Experimental

4.1. Reduction of 2,2,4,4-tetrachloro-8-oxabicyclo-[3.2.1]oct-6-en-3-one (8) with LAH: (3*exo*)-2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (9x) and (3*endo*)-2,2,4,4-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-ol (9n)

To a magnetically stirred suspension of LAH (0.19 g, 5 mmol) in dry THF (10 mL), a solution of **8** (2.62 g, 10 mmol) in dry THF (10 mL) was added dropwise and with cooling in an ice bath. The ice bath was removed, and the mixture was stirred at room temperature for 2 h. Then the mixture was chilled again with an ice bath, and water (10 mL) was added dropwise, cautiously and with vigorous magnetic stirring. The precipitate formed was dissolved by adding dilute sulfuric acid (10%, ca. 8.5 mL). The layers formed were separated, and the aqueous layer extracted with diethyl ether (3×10 mL). The THF and ether extracts were combined, washed with saturated aqueous $NaHCO_3$ solution followed by brine, and dried with sodium sulfate. The organic solution was filtrated and concentrated in a rotary evaporator to give 2.55 g of a colourless solid (**9**, 97% yield) that was purified by sublimation at 80 °C/10^{-2} Torr; mp 160–162 °C. A capillary GLC (20 m PSO 86, on column injection, 1 min isotherm at 40 °C, then temperature program from 40 to 300 °C with 5 K/min) showed two peaks with a 97 (**9x**):3 (**9n**) ratio.

The ^{1}H NMR spectrum (250 MHz, $CDCl_3$) showed, in addition to the resonances from **9x**,[9] weak signals at δ=3.12 (d, $^3J_{3,OH}$=7.2 Hz, 1H, OH), 4.62 (dt, $^3J_{3,OH}$=7.2 Hz, $^4J_{13}$=$^4J_{35}$=1.6 Hz, 1H, 3-H), 5.01 (d, J=0.9 Hz, 2H, 1-H and 5-H), 6.51 (s, 2H, 6-H and 7-H), which can be assigned to **9n**.

9n: ^{1}H NMR (250 MHz, $CDCl_3$): δ=3.23 (d, $^3J_{3,OH}$=12.9 Hz, 1H, OH), 4.44 (d, $^3J_{3,OH}$=12.9 Hz, 1H, 3-H), 5.10 (s, 2H, 1-H and 5-H), 6.58 (m, appearing as a d, line distance 0.5 Hz, 2H, 6-H and 7-H).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ=80.1 (C-3), 87.3 (C-2, C-4), 87.5 (C-l, C-5), 132.7 (C-6, C-7).

For the X-ray analysis,[10] a small sample was allowed to crystallize from a little ethanol. The crystals obtained showed mp 164–165.5 °C.

4.2. (3*exo*)-2,2,4,4-Tetrachloro-8-oxabicyclo[3.2.1]-octan-3-ol (10)

A solution of **9x** (0.79 g, 3 mmol) in methanol (30 mL) was shaken with 10% palladium/carbon catalyst (30 mg) under a hydrogen atmosphere. When the uptake of hydrogen gas had stopped, the catalyst was filtered off and repeatedly washed with methanol. The filtrate and washings were concentrated in a rotary evaporator, and the remaining solid sublimed at 100 °C/10^{-2} Torr. Yield 0.78 g (98%) with mp 157–158 °C.

^{1}H NMR (250 MHz, $CDC1_3$): δ=2.15–2.42 (m, 4H, 6-H and 7-H), 3.15 (d, $^3J_{3,OH}$=12.0 Hz, 1H, OH), 4.19 (d, $^3J_{3,OH}$=12.0 Hz, 1H, 3-H), 4.72 (dd, $^3J_{1,7exo}$=$^3J_{5,6exo}$=5.1 Hz, $^3J_{1,7endo}$=$^3J_{5,6endo}$=2.9 Hz, 2H, 1-H and 5-H).

^{13}C NMR (62.9 MHz, $CDC1_3$): δ=25.9 (C-6, C-7), 78.1 (C-3), 85.25 (C-l, C-5), 90.3 (C-2, C-4).

IR (KBr, cm^{-1}): 3400 (O–H), 2980, 2960, 2900, 2880 (C–H).

$C_7H_6Cl_4O_2$ (263.9): Calcd C 31.61, H 3.03, Cl 53.32; found C 31.72, H 3.00, Cl 53.55.

4.3. 3*endo*, 4*endo*-2,2,4-Trichloro-8-oxabicyclo[3.2.1]-oct-6-en-3-ol (12)

A solution of **11** (1.14 g, 5 mmol) in THF (10 mL) was treated with LAH (95 mg, 2.5 mmol) and worked-up as described for **9**. The colourless residue was sublimed at 70 °C/10^{-2} Torr to give 1.05 g (97%) of *endo*-**12**. The ^{1}H NMR indicated only a single product. A sample for analysis was recrystallized from *n*-hexane/diethyl ether (1:1, 5 mL) to yield 0.96 g (84%) of *endo*-**12** with mp 96–97 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ=2.72 (d, $^3J_{3,OH}$=6.4 Hz, 1H, OH), 4.32 (m with 9 lines, 1H, 3-H), 4.70 (dd, J=4.6 Hz, J=3.4–3.8 Hz, 1H, 4-H), 4.80 (m with 3 lines, line distance 1.6–1.8 Hz, 1H, 1-H), 4.87 (t, $^4J_{13}$=$^3J_{17}$=1.7 Hz, 1H, 5-H), AB sub-spectrum centred at δ=6.53, with δ_A=6.61, δ_B=6.46, J_{AB}=6.0 Hz (7-H and 6-H), the lines of the A and B part are split into doublets with 1.7 Hz each ($J_{1,7}$=$J_{5,6}$).

^{13}C NMR (125.8 MHz, $CDCl_3$): δ=55.7 (C-4), 77.4 (C-3), 81.4, 86.3 (C-1, C-5), 87.55 (C-2), 132.9, 135.0 (C-6, C-7).

IR (KBr, cm^{-1}): 3390 (O–H), 3085 (=C–H), 2940, 2900 (C–H), 1590 (C=C).

$C_7H_7Cl_3O_2$ (229.5): Calcd C 36.64, H 3.08, Cl 46.35; found C 36.87, H 3.10, Cl 46.23.

4.4. 2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]-oct-6-en-3-ol (15)

A solution of **13** (497 mg, 2.45 mmol) in THF (5 mL) was treated with LAH (95 mg, 2.5 mmol) and worked-up as described for **9**. The colourless residue was chromatographed on silica 60 (25 g) eluting with PE/EA (4:1). After a fore-run (50 mL), fractions with 15 mL were taken. Evaporation of fractions 10–21 gave 404 mg (81%) of **15**, a colourless solid with mp 104–105 °C. A sample for analysis was recrystallized from a little toluene; mp 106–107.5 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.20 (s, 3H, 4-CH_3), 2.09 (d, $^3J_{3,OH}$=6.0 Hz, 1H, OH), 3.32 (s, 3H, OCH_3), 3.80 (m with 7 lines, 1H, 3-H), 4.54 (dd, $^3J_{1,2}$=3.6 Hz, $^3J_{2,3}$=5.0 Hz, 1H, 2-H), 4.67 (t, $^3J_{5,6}$=$^4J_{3,5}$=1.7 Hz, 1H, 5-H), 4.70 (dt, $^3J_{1,2}$=3.6 Hz, $^3J_{1,7}$=$^4J_{1,3}$=1.7 Hz, 1H, 1-H), AB sub-spectrum with δ_A=6.48, δ_B=6.33 and J_{AB}= 6.1 Hz, the lines of the A and B part are finely split (6-H and 7-H).

^{13}C NMR (62.9 MHz, $CDCl_3$,): δ=17.2 (4-CH_3), 49.6 (OCH_3), 58.2 (C-2), 72.8, 80.5, 82.0 (C-5, C-3, C-1), 133.3, 134.3 (C-6, C-7). The signal of the quaternary C-4 could not be observed.

IR (KBr, cm^{-1}): 3440 (O–H), 3080, 3070 (=C–H), 2990, 2980, 2960, 2950, 2940, 2020, 2880, 2810 (C–H), 1590 (C=C).

$C_{10}H_{15}C1O_2$ (204.65): Calcd C 52.82, H 6.40, Cl 17.32; found C 52.93, H 6.44, Cl 17.45.

4.5. (2*endo*,3*endo*,4*exo*)-2-Chloro-4-methoxy-4-methyl-8-oxabicyclo[3.2.1]octan-3-ol (16)

A solution of **15** (307 mg, 1.5 mmol) in methanol (15 mL) was shaken with palladium on carbon catalyst (10% Pd) in an atmosphere of hydrogen gas, at normal pressure and room temperature. When the uptake of hydrogen had stopped, the catalyst was removed by filtration and washed with methanol. The filtrates were concentrated in a rotary evaporator and the remaining solid purified by sublimation at 60 °C/0.01 Torr. The colourless solid (299 mg, 97%) showed mp 106–107 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ=1.25 (s, 3H, 4-CH_3), 1.73–1.98 (m, 2H, *exo*-6-H and *exo*-7-H), 2.14–2.34 (m, 2H, *endo*-6-H and *endo*-7H), 2.37 (d, $^3J_{3,OH}$=2.0 Hz, 1H, OH), 3.29 (s, 3H, OCH_3), 3.71 (m, 1H, 3-H), 4.20 (d, J=8.4 Hz, 1H, 5-H), 4.29 (m, 1H, 2-H), 4.46 (m, appearing as a t, line distance 3.9 Hz, 1H, 1-H).

^{13}C NMR/DEPT (62.9 MHz, $CDCl_3$): δ=16.7 (−, 4-CH_3), 24.4 (+), 24.8 (+, C-6, C-7), 49.2 (−, OCH_3), 60.7 (−, C-2), 72.2 (−), 76.8 (−), 77.75 (−), C-1, C-3, C-5), 78.1 (C_q, C-4).

IR (KBr, cm^{-1}): 3420 (O–H), 2985, 2950, 2940, 2930, 2915, 2890, 2860, 2815 (C–H).

Anal. calcd for $C_9H_{15}ClO_3$ (206.7): C 52.31, H 7.32, Cl 17.15; found C 52.20, H 7.33, Cl 17.28.

4.6. (1α, 2α, 3β)-2-Methoxy-2-methylcyclohept-4-en-1,3-diol (17)

(a) A 100 mL two-necked flask, equipped with a gas inlet and septum was thoroughly dried (heat gun) and charged with naphthalene (641 mg, 5 mmol). Under a nitrogen atmosphere, THF (10 mL) was added. With magnetic stirring small pieces of clean sodium (140 mg, 6 mmol) were added, maintaining a nitrogen stream. Stirring was continued for 3 h at room temperature.

(b) Chloroalcohol **16** (see above) (207 mg, 1 mmol) was dissolved under nitrogen in THF (5 mL) using a thoroughly dried 25 mL two-necked flask, equipped with a gas inlet, septum and magnetic stirring bar. BuLi solution (0.63 mL, 1 mmol) was added dropwise by syringe with magnetic stirring at −40 °C. After 30 min stirring at −40→−35 °C, 6 mL of the sodium naphthalenide solution (3 mmol, see Section (a)) was added dropwise by syringe. Stirring was continued for 30 min at −35→−30 °C. The reaction mixture was quenched by adding water (10 mL), and the layers separated (at room temperature). The aqueous layer was extracted with diethyl ether, and the combined organic solutions dried with sodium sulfate. The solvent was evaporated and the residue was purified by chromatography on silica (20 g), eluting with PE/EA (1:1) to give 119 mg (69%) **17** with mp 74–75 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ=1.18 (s, 3H, 2-CH_3), 1.58 (m, appearing as a t, 1H, 7-H), 1.82 (m, 1H, 7-H), 1.94 (m, 1H, 6-H), 2.53 (m, 1H, 6-H), 2.65 (s, 1H, 3-OH), 2.76 (d, $^3J_{1,OH}$=1.8 Hz, 1H, 1-OH), 3.32 (s, 3H, OCH_3), 4.06 (dd, $^3J_{1,7}$=5.3 Hz, $^3J_{1,OH}$=1.8 Hz, 1H, 1-H), 4.74 (s, 1H, 3-H), 5.54 (m, 1H, 5-H), 5.84 (m, 1H, 4-H).

^{1}H NMR (500 MHz, CD_3CN): δ=1.10 (s, 3H, 2-CH_3), 1.57 (m, appearing as a t, 1H, 7-H), 1.79 (m, 2H, 6-H and 7-H), 2.44 (m, 1H, 6-H), 2.83 (s, 1H, OH), 3.01 (s, 1H, OH), 3.26 (s, 3H, OCH_3), 4.01 (d, $^3J_{1,7}$=3.6 Hz, 1H, 1-H), 4.61 (s, 1H, 3-H), 5.44 (m, 1H, 5-H), 5.77 (m, 1H, 4-H).

^{13}C NMR/DEPT (125.8 MHz, $CDCl_3$): δ=13.0 (+, 2-CH_3), 19.7 (−), 28.1 (−, C-6, C-7), 49.3 (+, OCH_3), 70.5 (+), 70.6 (+, C-1, C-3), 79.5 (C_q, C-2), 130.0 (+), 133.8 (+, C-4, C-5).

^{13}C NMR/DEPT (125.8 MHz, CD_3CN): δ=13.7 (+, 2-CH_3), 20.6 (−), 29.4 (−, C-6, C-7), 49.7 (+, OCH_3), 71.2 (+), 71.5 (+, C-1, C-3), 80.0 (C_q, C-2), 130.5 (+), 135.45 (+, C-4, C-5).

IR (KBr, cm^{-1}): 3400 (O–H), 3005 (=C–H), 2965, 2945, 2915, 2875, 2880, 2835, 2815 (C–H).

Anal. calcd for $C_9H_{16}O_3$ (172.2): C 62.77, H 9.36; found C 62.82, H 9.37.

4.7. Reaction of *endo*-2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (6) with sodium borohydride: (2*endo*,3*endo*)- and (2*endo*,3*exo*)-2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (18n and 18x)[15]

4.7.1. Procedure a. *endo*-2-Chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**6**) (932.5 mg, 5 mmol) was dissolved in 20 mL of ethanol and mixed with 5 mL of saturated

aqueous $NaHCO_3$ solution. A solution of sodium borohydride (200 mg, 5 mmol) in water (5 mL) was added dropwise to the suspension formed, with magnetic stirring at room temperature. Progress of the reaction, which was accompanied with gas evolution, was indicated by dissolution of the suspension forming a clear solution, and monitored by TLC (alumina sheet, PE/EA 4:1, spraying with vanillin/sulfuric acid reagent). After 1 h no starting ketone **6** could be detected.

Then the mixture was acidified with sulfuric acid (5 mL of concd H_2SO_4 diluted with 10 mL of water) and extracted with diethyl ether (5×15 mL). The ether extracts were combined, washed with brine (30 mL) and dried with magnesium sulfate. Evaporation of the solvent gave 906 mg of colourless crystals.

A GLC (Carbowax column) showed two product peaks in the ratio of 13:1:1 (87:6:7), in addition to the peak of unreacted ketone **6** (relative intensity 1 or 6%).

Analysis by GLC–CIMS (20 m SE 54 column, 50→250 °C, 10 K/min) showed a strong peak at t_R=17.9 min, in addition to minor ones at t_R=18.1 (ketone **6**) and 19.9 min. The first and the third one resulted from isomeric alcohols $C_9H_{13}ClO_2$, **18n** and **18x**, respectively (see below).

The mixture was combined with the products from another preparation and chromatographed on silica (gravity column), eluting with PE/EA (6:1), whereupon unreacted starting ketone **6** (106 mg) was recovered from the mixture of alcohols (1386 mg), which were not separated. The fraction containing the isomeric alcohols was subjected to MPLC on silica (Lichroprep™ Si60, Merck, Darmstadt). Elution with dichloromethane resulted in two fractions. From the first fraction 1060 mg of **18n** was isolated. For analysis a sample was sublimed, which showed mp 96 °C. The IR, ^{1}H NMR and ^{13}C NMR spectra were in accordance with those from a former preparation.[8]

The second fraction gave 90 mg of **18x** with mp 83 °C.

18x: EIMS (70 eV): *m/z* (%)=190 (6) [$M^{\bullet+}$ from $C_9H_{13}^{37}ClO_2$], 188 (19) [$M^{\bullet+}$ from $C_9H_{13}^{35}ClO_2$], 153 (20), 135 (16), 120 (18), 118 (31), 116 (100), 110 (15), 109 (82), 105 (12), 95 (40), 85 (66), 81 (90).

CIMS (CH_4, 70 eV): *m/z* (%)=189 (<1) [MH^+ from $C_9H_{13}^{35}ClO_2$], 171 (2) [MH^+-H_2O], 153 (17) [MH^+-HCl], 125 (7), 113 (18), 111 (7), 109 (9), 107 (20), 105 (7), 103 (23), 95 (7), 85 (100), 81 (19).

IR ($CHCl_3$): broad absorption band at 3610–3250 surmounted by a sharp band at 3590 cm^{-1} (OH).

^{1}H NMR (300 MHz, $CDCl_3$): δ=0.93 (s, 3H, *endo*-CH_3), 1.12 (s, 3H, *exo*-CH_3), 2.22 (d, $^3J_{3,OH}$=4.7 Hz, 1H, OH), 3.45 (dd, $J_{2,3}$=8.5 Hz, $J_{3,OH}$=4.7 Hz, 1H, H-3), 3.86 (dd, $J_{2,3}$=8.5 Hz, $J_{1,2}$=4.0 Hz, 1H, H-2), 4.25 (d, $J_{5,6}$=1.7 Hz, 1H, H-5), 4.76 (dd, $J_{1,2}$=3.9 Hz, $J_{1,7}$=1.7 Hz, 1H, H-1); AB sub-spectrum with δ_A=6.38 and δ_B=6.32, $J_{AB}=J_{6,7}$= 6.0 Hz (6-H and 7-H), the A and B part is split into doublets with J=1.8 Hz each.

^{13}C NMR (75 MHz, $CDCl_3$): δ=19.8 (*endo*-CH_3), 23.3 (*exo*-CH_3), 40.2 (C-4), 60.1 (C-2), 78.3 (C-3), 81.3 (C-1), 87.9 (C-5), 129.7 (C-6), 132.8 (C-7).

18n: $C_9H_{13}ClO_2$ (188.65): Calcd C 57.30, H 6.945, Cl 18.79; found C 57.29, H 7.05, Cl 18.74.

EIMS (70 eV): *m/z* (%)=190 (12) [$M^{\bullet+}$ from $C_9H_{13}^{37}ClO_2$], 188 (35) [$M^{\bullet+}$ from $C_9H_{13}^{35}ClO_2$], 153 (63), 152 (25), 135 (33), 120 (23), 118 (29), 116 (91), 111 (15), 110 (13), 109 (50), 105 (17), 103 (11), 95 (58), 85 (96), 83 (11), 81 (100).

CIMS (CH_4, 70 eV): *m/z* (%)=191 (1) [MH^+ from $C_9H_{13}^{37}ClO_2$], 189 (2) [MH^+ from $C_9H_{13}^{35}ClO_2$], 171 (6) [MH^+-H_2O], 153 (15) [MH^+-HCl], 143 (9), 141 (14), 107 (26), 103 (20), 95 (18), 85 (30), 81 (100).

4.7.2. Procedure b. *endo*-2-Chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (**6**) (1.865 g, 10 mmol) was dissolved in 40 mL of ethanol, mixed with saturated aqueous $NaHCO_3$ solution (10 mL), and treated with sodium borohydride (500 mg, 13 mmol) in water (20 mL) as described above. After 1 h the reaction mixture was worked-up as described above to give 1.61 g of colourless crystals that were recrystallized from petroleum ether. The product (1.39 g, 73%) showed mp 92 °C. According to a GLC (Carbowax) it contained 3–4% of starting ketone **6**.

4.8. Reaction of *endo*-2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-one (6) with sodium borohydride/$CeCl_3$: (2*endo*,3*endo*)-2-chloro-4,4-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-3-ol (18n)[15]

To a stirred solution of chloroketone **6** (186.5 mg, 1 mmol) and cerium trichloride heptahydrate (372.5 mg, 1 mmol) in ethanol (10 mL) sodium borohydride (152 mg) was added in small portions. After 2.5 h stirring at room temperature no starting ketone **6** could be detected by GLC. The mixture was acidified with 10 mL of 2 N hydrochloric acid to give a clear solution. The organic solvent (ethanol) was removed with a rotary evaporator, and the remaining mixture was extracted with diethyl ether (5×10 mL). After drying ($MgSO_4$) the solvent was evaporated to give 152 mg of colourless crystals with mp 91 °C that contained >99% **18n** according to a capillary GLC.

The spectra (^{1}H NMR and IR) were in agreement with those of the substance described above.

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New efficient access to thieno[3,2-*b*]pyridine derivatives via regioselective lithiation of 3-methylthiopyridine

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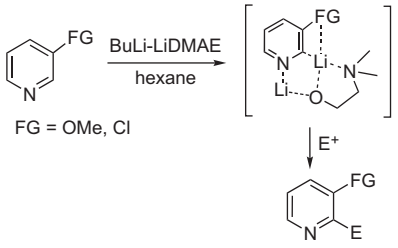
Abstract—The synthesis of thieno[3,2-*b*]pyridines was achieved using a three-step process allowing the construction of the thiophenic ring with 17–34% overall yields. The key step was the regioselective lithiation–bromination of the 3-methylthiopyridine induced by BuLi–LiDMAE superbase followed by Sonogashira coupling and halogenocyclization producing the fused heterocycles.

1. Introduction

Due to their isosterism with indolopyridines or isoquinolines, thienopyridines have attracted much attention because of their potential biological activity as antipsychotics,[1] antibacterians,[2] LH receptor agonists,[3] antitumoral agents[4] or Src kinase inhibitors.[5] Possessing a π-electron rich thiophene ring and a π-electron deficient pyridine ring, these annelated aromatic heterocycles are also of general interest for the chemistry of ligands and theoretical organic chemistry.[6]

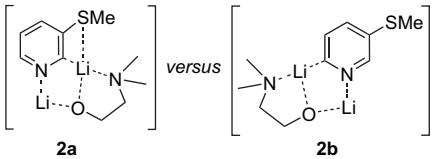
Generally, these fused heterocyclic compounds are prepared by the construction of the pyridinic ring from appropriate substituted thiophene derivatives. These methods suffer from disadvantage of limited access to starting materials, low-functional compatibility and/or long-multistep sequences.[7] In this context, our group is now interested in the development of short polycyclic syntheses[8] based on the selective functionalization of aza-π-deficient heterocycles, such as pyridines, allowing the opportune garlanding for subsequent cyclization.

Some of our previous investigations,[9,10] exhibited the usefulness of the monometallic BuLi–LiDMAE superbase (DMAE: 2-(dimethylamino)ethanol) in apolar solvents to perform regioselective C-2-lithiation of 3-chloro and 3-methoxypyridines. The exclusive C-2-metallation was explained by a strong complexation of lithium by heteroatom (Cl or O), pyridine nitrogen and dimethyl-aminoethoxide in a specific lithiated aggregate (Scheme 1).



Scheme 1. Selective functionalization of 3-methoxy and 3-chloropyridines induced by BuLi–LiDMAE superbase.

In this paper, we focused our attention on regioselective functionalization of 3-methylthiopyridine **1** to evaluate the potential cooperative effect of sulfur atom during the metallation step (Scheme 2). In a synthetic context, the introduction of functionalities at C-2 versus C-6 on the pyridine ring of sulfur containing derivatives could constitute the key step of an alternative and rapid route to functionalized thieno[3,2-*b*]pyridines (Scheme 3).



Scheme 2. Potential cooperative effect of sulfur atom during metallation.

Keywords: Thieno[3,2-*b*]pyridine; Regioselective lithiation; BuLi–LiDMAE superbase; Sonogashira coupling; Halogenocyclization.
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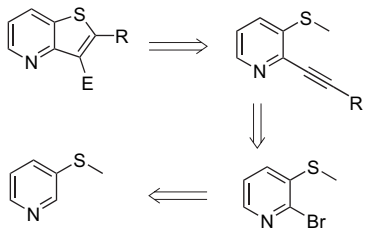


Scheme 3. Access to functional thieno[3,2-*b*]pyridines.

2. Results and discussion

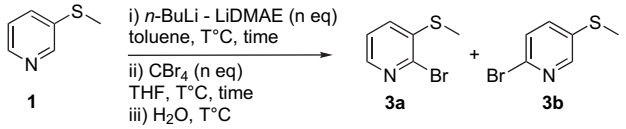
The reactivity of 3-methylthiopyridine **1** was first investigated under various metallation and condensation conditions to evaluate an efficient and regioselective functionalization (i.e., C-2 vs C-6). As mentioned in previous works,[9,10] apolar solvents such as hexane or toluene have to be used to allow a strong aggregation between BuLi–LiDMAE and pyridine substrates. Due to the lack of solubility of **1** in hexane we chose to use toluene as metallation solvent.[11] The expected 2- and 6-lithiopyridine intermediates (**2a** and **2b**) resulting from an α-lithiation process were trapped by tetrabromomethane (CBr_4) as electrophile in THF to produce the stable bromide derivatives **3a** and **3b**.[11]

In Table 1, we report the more significant results of this preliminary study. At first, it appeared to us that standard conditions used with 3-chloropyridine (3 equiv of superbase at −45 °C and hydrolysis at −20 °C, Entry 1) only conducted to poor yields (31%) due to some degradation. However, it was also noticed that the selectivity of **3a/3b** increased when hydrolysis was conducted at −45 °C (Entry 2). We then decided to focus our attention on temperatures of metallation, condensation and hydrolysis steps. At −80 °C, an interesting increase of yield was obtained (51%, Entry 3) showing that a lower temperature of metallation limited the degradation. However, in the same time, we observed a slight decrease in the selectivity. In contrast at −95 °C, the selectivity was increased to 90/10 and the conversion was limited to 65% (Entry 4). At this temperature the use of an excess (6 equiv) of superbase allowed us to combine a high regioselectivity and a yield (89/11 and 73%, respectively, Entry 6). In these conditions, we determined an optimal 1 h condensation time (condensation times up to 2 h led to degradation of lithiated species). Entries 7–10 finally confirmed that with the same excess of superbase, extended or shorter metallation times as well as a higher temperature conducted to a decrease in both yield and selectivity. In agreement with this preliminary study, we have set the best conditions for the regioselective functionalization of 3-methylthiopyridine **1** as follows: 6 equiv of base in non complexing toluene, a metallation time of 4 h and a condensation time of 1 h, all the protocol having to be conducted at −95 °C.

As the regioselectivity of this reaction is concerned, our results confirm the hypothesis of the sulfur atom chelating effect on the basic system, even if, as expected, the complexing influence appears less strong than in 3-chloro or 3-methoxypyridines.[9] It must be noted that no trace of 4-bromo-3-methylpyridine was detected so, this emphasizes the strong aggregation between BuLi–LiDMAE superbase and pyridine moieties, which dictate the selectivity of lithiation.

The versatility and the synthetic value of our methodology were next examined by the introduction of various representative electrophiles at C-2 and/or C-6 positions (Table 2). The expected compounds **4**–**8** were obtained in moderate to good isolated yields (45–68% overall). Chloride, sulfide and deuterium are selectively introduced in C-2 position due to the expected chelating effect of the sulfur atom on the basic system during the deprotonation step. In contrast, despite a good conversion rate, iodide derivatives were obtained in low 11% yield (not reported here) due to a great instability of the formed products. It can be assumed that the

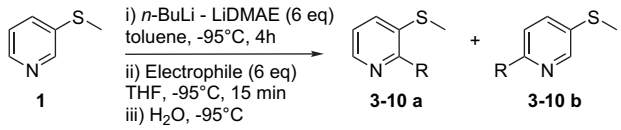
Table 1. Optimization of the functionalization of 3-methylthiopyridine **1**[a]



Entry	Metallation conditions			Halogenation conditions		Hydrolysis	Yields[b] (%)	Results[b,c] ratio
	Base (equiv)	*T* (°C)	*t* (h)	CBr_4 (equiv)	*T* (°C)	*T* (°C)	(**3a+3b**)	(**3a/3b**)
1	3	−45	1	3	−45	−20[a]	31	77/23
2	3	−45	1	3	−45	−45	29	86/14
3	3	−80	4	3	−80	−20[a]	51	82/18
4	3	−95	4	3	−95	−95	23[d]	90/10
5	4	−95	4	4	−95	−95	65	72/28
6	6	−95	4	6	−95	−95	73	89/11
7	6	−95	8	6	−95	−95	53	87/13
8	6	−95	2	6	−95	−95	44	84/16
9	6	−80	4	6	−80	−80	61	82/18
10	6	−80	1	6	−80	−80	48	83/17

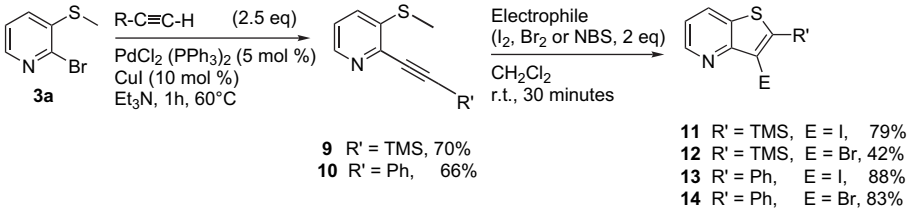
[a] Reaction temperature (−45 or −80 °C) was risen to −20 °C in 15 min.
[b] GC yields and selectivity ratio relative to an internal standard.
[c] Total conversion of **1** was observed.
[d] Conversion rate of reaction was limited to 65%.

Table 2. Scope and limitation of the electrophile[a]



Entry	Electrophile	R	Total isolated yields[b]	Ratio[c]	Isolated yields[b]	
			a+b (%)	**a/b**	Isomer **a** (%)	Isomer **b** (%)
1	CBr_4	Br	68	9/1	**3a** (59%)	**3b** (9%)
2	C_2Cl_6	Cl	65	8/2	**4a** (50%)	**4b** (15%)
3	I_2	I	11	8/2	**5a+5b**[c,d,e]	
4	Me_2S_2	SMe	49	7/3[c]	**6a+6b**[c,e]	
5	Ph_2S_2	SPh	63	9/1	**7a** (57%)	**7b** (6%)
6	TESCl	$Si(Et)_3$	52	1/9	**8a+8b**[b,c]	
7	DCl/D_2O	D	—	8/2	**9a**[c] (80%)	**9b**[c](20%)
8	PhCHO	CH(OH)Ph	45	2/8	**10a** (8%)	**10b** (37%)

[a] Reactions performed on 1.33 mmol of **1**.
[b] Isolated yields after silica gel chromatography.
[c] GC or ^1H NMR yields.
[d] Rapid degradation of the products.
[e] Isolated as a mixture of regioisomers **a** and **b**.



Scheme 4. Synthesis of thieno[3,2-*b*]pyridine derivatives.

iodopyridines might be in situ formed and quickly attacked by remaining *n*-BuLi or lithium alkoxides. On an other hand, phenylmethanol or triethylsilyl moieties were introduced with a reverse regioselectivity (**7b** and **8b** formed as major products). This inverse selectivity showed the competition between a chelating effect and a steric hindrance of the electrophile moiety. Indeed, it may be postulated that the approach of the sterically hindered electrophile to the lithiated pyridine aggregate in C-2 position was more difficult than in C-6 one. This led us to conclude that the condensation step is strongly controlled by the formation of the product and that the complexation effect of sulfur part is slight.

In a synthetic context, the silyl product **8b** could have been involved in Hiyama coupling.[12] However, they are only obtained as a crude intractable and unstable mixture, which is rapidly degraded in the reaction medium not allowing further additional range of functionalization by this way of synthesis.

We next turned our efforts towards the functionalization of formed halogenated derivatives. Starting from the readily available 2-bromo-3-methylthiopyridine **3a**, a two step approach to functionalized thienopyridines has then been examined involving Sonogashira coupling with terminal acetylenes (trimethysilylacetylene or phenylacetylene) followed by an electrophilic cyclization.[13] This scheme of synthesis leads to particularly quite reaction times and very easy setting to access to thieno[3,2-*b*]pyridine derivatives (Scheme 4).

In a first step, acetylenic reagents were successfully coupled in Sonogashira reactions using $PdCl_2(PPh_3)_2$ (5 mol %) and CuI (10 mol %) in Et_3N as solvent and base. Electrophilic cyclization was next performed using iodine or bromine as electrophile. 2-Alkynyl-3-methylthiopyridines **9**–**10** reacted efficiently to produce **11**, **13** and **14** in excellent yields (79–88%). In most cases, reaction time did not exceed 30 min at room temperature. It is noteworthy that reactions with Br_2 gave different results from those obtained with I_2. Indeed, no trace of silyl bromide derivative **12** was detected using Br_2 as electrophile while **14** was obtained with good yield. When Br_2 was changed by NBS and the reaction mixture stirred overnight at room temperature, expected cyclization product **12** were obtained in acceptable 42% yield. This result could be explained by a rapid bromodesilylation producing an unstable 2,3-dibromothieno[3,2-*b*]pyridine. Thieno[3,2-*b*]pyridine derivatives **11**, **12**, **13** and **14** were then prepared with overall yields of 33, 17, 34 and 32%, respectively.

3. Conclusion

In summary, a new synthesis of thieno[3,2-*b*]pyridines have been prepared from 3-methylthiopyridine in moderate to good yields. We believe that the three steps approach based on the construction of thiophenic ring is a useful alternative to classical methods and should prove quite useful in heterocyclic synthesis. We are currently aiming to expand this methodology for the use of other functionalized fused polyheterocycles.

4. Experimental

4.1. General methods

^1H and ^{13}C NMR spectra were recorded at 400 or 250 and 100 MHz, respectively, with $CDCl_3$ as solvent and TMS as internal standard (for ^1H NMR). HRMS were determined at the Service Central d'Analyse of the CNRS at Vernaison (France).

4.2. Materials and solvents

All reagents were commercially available and were purified by distillation when necessary. *n*-BuLi was used as a commercial 1.6 M solution in hexanes. 2-(Dimethylamino) ethanol (DMAE) was distilled and stored over molecular sieves before use. Toluene and THF were distilled and stored on sodium wire before use.

4.3. Preparation of 3-methylthiopyridine (1)

A solution of anhydrous THF (80 mL) was cooled at −80 °C and *t*-BuLi (31 mL, 54 mmol) was added dropwise under a nitrogen atmosphere. Then, a solution of 3-bromopyridine (4.230 g, 27 mmol) in THF (5 mL) was added dropwise. After stirring for 30 min at −80 °C, the reaction medium was cooled at −95 °C and dimethyldisulfur (6 mL, 67 mmol) in THF (5 mL) was added. After stirring for 1 h at −95 °C, hydrolysis was performed at −20 °C with H_2O (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). After drying ($MgSO_4$), filtration and solvents evaporation, the crude product was purified by column chromatography on a silica gel (Geduran Si 60, 0.063–0.200 mm). The spectroscopic data are in conformity with literature.

4.4. General procedure for functionalization of 3-methylthiopyridine (1)

A solution of 2-(dimethylamino)ethanol (0.8 mL, 8 mmol) in anhydrous toluene (15 mL) was cooled at ca. −5 °C, and *n*-BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 15 min. at 0 °C, the reaction medium was cooled at −95 °C. 3-Methylthiopyridine **1** (166 mg, 1.33 mmol) in anhydrous toluene (5 mL) was added dropwise. After stirring for 4 h at −95 °C, a solution of the appropriate electrophile (8 mmol) in anhydrous THF (10 mL) was added dropwise. After stirring at −95 °C during the appropriate time, hydrolysis was performed at this temperature with H_2O (30 mL). The aqueous phase was extracted with ethyl acetate (20 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.4.1. 2-Bromo-3-methylthiopyridine (3a) and 6-bromo-3-methylthiopyridine (3b). Compounds **3a** and **3b** were prepared according to the general method described herein with CBr_4 (2.653 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **3a** (159 mg, 59%) and **3b** (24 mg, 9%), yield in **3a+3b** (183 mg, 68%) with a regioselectivity **3a/3b**: 9/1.

4.4.1.1. 2-Bromo-3-methylthiopyridine (3a). Brown gummy solid; ^1H NMR δ_H 2.50 (s, 3H), 7.40 (m, 2H), 8.24 (d, J=2 Hz, 1H); ^{13}C NMR δ_C 15.43, 123.16, 132.82, 140.69, 145.09, 161.80; IR (NaCl) ν 2920, 1542, 1447, 1349, 1113, 1078, 1011, 820, 754; MS (EI) *m/z* 205 (99), 203 (100), 190 (7), 124 (52), 109 (74), 97 (66), 82 (46), 76 (13), 57 (13), 51 (19); HRMS (ESI^+) Calculated for C_6H_6BrNS=202.9405, found $[M+H]^+$=203.9491.

4.4.1.2. 6-Bromo-3-methylthiopyridine (3b). White solid; mp 54–56 °C; ^1H NMR δ_H 2.50 (s, 3H), 7.27 (dt, J=4.5, 1.0 Hz, 1H), 7.39 (dd, J=7.9, 1.7 Hz, 1H), 8.13 (dd, J=4.8, 1.7 Hz, 1H); ^{13}C NMR δ_C 15.99, 127.97, 135.33, 136.95, 138.48, 147.90; IR (NaCl) ν 2920, 1542, 1447, 1349, 1113, 1078, 1011, 820, 754; MS (EI) *m/z* 205 (99), 203 (100), 190 (7), 124 (52), 109 (74), 97 (66), 82 (46), 76 (13), 57 (13), 51 (19).

4.4.2. 2-Chloro-3-methylthiopyridine (4a) and 6-chloro-3-methylthiopyridine (4b). Compounds **4a** and **4b** were prepared according to the general method described herein with C_2Cl_6 (1.896 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **4a** (106 mg, 50%) and **4b** (32 mg, 15%), yield in **4a+4b** (138 mg, 65%) with a regioselectivity **4a/4b**: 8/2.

4.4.2.1. 2-Chloro-3-methylthiopyridine (4a).[14] Pale yellow gummy solid; ^1H NMR δ_H 2.44 (s, 3H), 7.19 (dt, J=4.7 Hz, 1H), 7.42 (dd, J=7.8, 1.3 Hz, 1H), 8.11 (dd, J=4.7, 1.5 Hz, 1H); ^{13}C NMR δ_C 14.88, 122.90, 133.28, 136.13, 144.61, 147.96; IR (NaCl) ν 2924, 1547, 1449, 1354, 1120, 1014, 823, 726; MS (EI) *m/z* 162 (8), 161 (31), 159 (100), 146 (6), 144 (15), 123 (26), 122 (13), 117 (11), 97 (7), 96 (22), 83 (13), 82 (18), 78 (17), 76 (8), 69 (11), 64 (6), 60 (6), 51 (12).

4.4.2.2. 6-Chloro-3-methylthiopyridine (4b). Pale yellow gummy solid; ^1H NMR δ_H 2.51 (s, 3H), 7.25 (dd, J=8.0, 1H), 7.55 (dd, J=8.3, 2.6 Hz, 1H), 8.27 (d, J=2.4 Hz, 1H); ^{13}C NMR δ_C 16.18, 124.24, 134.64, 137.33, 147.58, 148.37; IR (NaCl) ν 2924, 1547, 1449, 1354, 1120, 1014, 823, 726; MS (EI) *m/z* 162 (8), 161 (31), 159 (100), 146 (6), 144 (15), 123 (26), 122 (13), 117 (11), 97 (7), 96 (22), 83 (13), 82 (18), 78 (17), 76 (8), 69 (11), 64 (6), 60 (6), 51 (12).

4.4.3. 3-Methylthio-2-phenylthiopyridine (5a) and 3-methylthio-6-phenylthiopyridine (5b). Compounds **5a** and **5b** were prepared according to the general method described herein with Ph_2S_2 (1.744 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **5a** (177 mg, 57%) and **5b** (18 mg, 6%), yield in **5a+5b** (195 mg, 63%) with a regioselectivity **5a/5b**: 9/1.

4.4.3.1. 3-Methylthio-2-phenylthiopyridine (5a). Pale yellow gummy solid; ^1H NMR δ_H 2.53 (s, 3H), 7.04 (dt, J=4.8 Hz, 1H), 7.41 (m, 3H), 7.49 (dd, J=7.8, 1.5 Hz, 1H), 7.55 (m, 2H), 8.20 (dd, J=4.7, 1.5 Hz, 1H); ^{13}C

NMR δ_C 16.16, 121.05, 128.50, 129.19, 134.14, 134.32, 146.33, 151.90, 157.10; IR (NaCl) ν 2921, 1561, 1439, 1352, 1131, 747, 690; MS (EI) *m/z* 234 (14), 233 (M^+, 56), 232 (74), 218 (100), 217 (32), 186 (47), 172 (12), 115 (12), 82 (39), 69 (35), 65 (38), 51 (10); HRMS (ESI^+) Calculated for $C_{12}H_{11}NS_2$=233.0334, found $[M+H]^+$= 234.0405.

4.4.3.2. 3-Methylthio-6-phenylthiopyridine (5b). Pale yellow gummy solid; ^1H NMR δ_H 2.48 (s, 3H), 6.89 (dd, *J*=8.4 Hz, 1H), 7.42 (m, 4H), 7.59 (m, 2H), 8.37 (d, *J*=2.1 Hz, 1H); ^{13}C NMR δ_C 16.19, 121.46, 128.52, 129.17, 134.10, 135.74, 147.93, 151.30, 158.64; IR (NaCl) ν 2921, 1561, 1439, 1352, 1131, 747, 690; MS (EI) *m/z* 234 (14), 233 (M^+, 56), 232 (74), 218 (100), 217 (32), 186 (47), 172 (12), 115 (12), 82 (39), 69 (35), 65 (38), 51 (10).

4.4.4. Procedure for C-2 and C-6 functionalization of 3-methylthiopyridine (1) with deuterium. A solution of DMAE (0.8 mL, 8 mmol) in toluene (15 mL) was cooled at ca. −5 °C, and *n*-BuLi (10 mL, 16 mmol) was added dropwise under a nitrogen atmosphere. After 15 min at 0 °C, the reaction medium was cooled at −95 °C. 3-Methylthiopyridine **1** (166 mg, 1.33 mmol) in toluene (5 mL) was added dropwise. After 4 h of stirring at −95 °C, a solution MeOD (2 mL, 49 mmol) in THF (10 mL) was added dropwise. After 1 h of stirring at −95 °C the solution was dried ($MgSO_4$), filtrated and solvents were evaporated. The ^1H NMR data of the crude mixture allowed to determine a regioselectivity **6a/6b**: 8/2.

4.4.5. (3-Methylthiopyridin-2-yl)phenylmethanol (7a) and (3-methylthiopyridin-6-yl)phenylmethanol (7b). Compounds **7a** and **7b** were prepared according to the general method described herein with PhCHO (1.744 g, 8 mmol) as electrophile. Purification of crude product was performed by column chromatography (eluent: hexane/AcOEt 90/10) and led to the separation of regioisomers **7a** (25 mg, 8%) and **7b** (114 mg, 37%), yield in **7a+7b** (139 mg, 45%) with a regioselectivity **7a/7b**: 2/8.

4.4.5.1. (3-Methylthiopyridin-2-yl)phenylmethanol (7a). White solid; mp 60–62 °C; ^1H NMR δ_H 2.31 (s, 3H), 5.91 (s, 1H), 7.28 (m, 6H), 7.50 (dd, *J*=8.1 Hz, 1H), 8.40 (dd, *J*=4.6 Hz, 1H); ^{13}C NMR δ_C 29.82, 74.75, 121.49, 127.10, 128.07, 128.37, 128.76, 128.92, 134.63, 136.07, 145.50, 157.89; IR (NaCl) ν 3391, 2921, 1421, 1393, 1038, 699, 607; MS (EI) *m/z* 233 (5), 232 (15), 231 (M^+, 80), 216 (29), 182 (25), 155 (54), 154 (50), 124 (33), 110 (27), 105 (28), 79 (83), 77 (100), 51 (45); HRMS (ESI^+) Calculated for $C_{13}H_{13}NOS$=231.0719, found $[M+H]^+$= 232.0791.

4.4.5.2. (3-Methylthiopyridin-6-yl)phenylmethanol (7b). White solid; mp 70–72 °C; ^1H NMR δ_H 2.50 (s, 3H), 5.75 (s, 1H), 7.10 (dd, *J*=8.2 Hz, 1H), 7.28 (m, 5H), 7.52 (dd, *J*=8.3, 2.2 Hz, 1H), 8.45 (d, *J*=1.9 Hz, 1H); ^{13}C NMR δ_C 15.80, 72.40, 123.25, 127.09, 127.71, 127.90, 128.12, 128.49, 128.67, 134.44, 142.15, 143.87, 157.58; IR (NaCl) ν 3391, 2921, 1421, 1393, 1038, 699, 607; MS (EI) *m/z* 233 (5), 232 (15), 231 (M^+, 80), 216 (29), 182 (25), 155 (54), 154 (50), 124 (33), 110 (27), 105 (28), 79 (83), 77 (100), 51 (45).

4.5. Procedure for the palladium-catalyzed formation of 2-(1-alkynyl)-3-methylthiopyridines (9–10)

To a solution of Et_3N (10 mL), $PdCl_2(PPh_3)_2$ (0.070 g, 5 mol %), 2-bromo-3-methylthiopyridine **3a** (0.408 g, 2 mmol) and the appropriate terminal acetylene (5 mmol) (stirring for 5 min beforehand) was added CuI (0.038 mg, 10 mol %) and stirring was continued for another 15 min before flushing with N_2. The mixture was heated to Et_3N reflux and stirred for 1 h. The resulting solution was rapidly washed with a saturated aqueous NH_4Cl solution, and extracted with dichloromethane (2×10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.5.1. 2-(2-Trimethylsilylethyn-1-yl)-3-methylthiopyridine (9). Compound **9** was prepared according to the method described herein with trimethylsilylacetylene (0.246 g, 5 mmol) as terminal acetylene. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **9** (0.310 g, 70%) as a brown gummy solid. ^1H NMR δ_H 0.30 (s, 9H), 2.47 (s, 3H), 7.19 (dt, *J*=4.7 Hz, 1H), 7.46 (dd, *J*=8.1, 1.3 Hz, 1H), 8.3 (dd, *J*=4.1 Hz, 1H); ^{13}C NMR δ_C −0.18, 14.69, 101.03, 112.13, 123.24, 128.71, 131.49, 145.30; IR (NaCl) ν 2952, 2157, 1558, 1398, 1247, 1079, 1037, 850, 758, 703; MS (EI) *m/z* 221 (M^+, 55), 206 (97), 190 (17), 176 (29), 130 (14), 84 (100), 51 (14).

4.5.2. 2-(2-Phenylethyn-1-yl)-3-methylthiopyridine (10). Compound **10** was prepared according to the method described herein with phenylacetylene (0.255 g, 5 mmol) as terminal acetylene. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **10** (0.300 g, 66%) as a brown powder; mp 75–77 °C; ^1H NMR δ_H 2.51 (s, 3H), 7.23 (dt, *J*=4.8 Hz, 1H), 7.38 (m, 3H), 7.48 (dd, *J*=8.0 Hz, 1H), 7.65 (m, 2H), 8.36 (dd, *J*=4.6 Hz, 1H); ^{13}C NMR δ_C 14.82, 86.55, 122.35, 123.02, 128.51, 129.26, 131.57, 132.21, 145.51; IR (NaCl) ν 3058, 2918, 2214, 1490, 1410, 1218, 1139, 756, 691; MS (EI) *m/z* 227 (4), 226 (15), 225 (M^+, 65), 224 (100), 223 (53), 222 (11), 209 (8), 191 (8), 180 (8), 150 (11), 148 (39), 139 (13), 111 (13), 77 (13), 51 (13); HRMS (ESI^+) Calculated for $C_{14}H_{11}NS$= 225.0613, found $[M+H]^+$=226.0690.

4.6. Procedure for the iodo- and bromocyclizations

To a solution of 0.25 mmol of the 2-(1-alkynyl)-3-methylthiopyridines **9**–**10** and 3 mL of CH_2Cl_2 was added gradually I_2 or Br_2 (0.5 mmol) in 2 mL of CH_2Cl_2. The reaction mixture was flushed with N_2 and stirred at room temperature for 30 min. The excess of I_2 or Br_2 was removed by washing with a saturated aqueous solution of $Na_2S_2O_3$. The aqueous solution was then extracted by CH_2Cl_2 (2×10 mL). After drying ($MgSO_4$), filtration and solvent evaporation, the crude product was purified by column chromatography on a silica gel (0.063–0.200 mm) with hexane/ethyl acetate mixtures as eluent.

4.6.1. 3-Iodo-2-trimethylsilylthieno[3,2-*b*]pyridine (11). Compound **11** was prepared according to the method described herein with I_2 (127 mg, 0.5 mmol). Column

chromatography (eluent: hexane/AcOEt 70/30) yielded **11** (66 mg, 79%) as a yellow pale solid; mp 79–81 °C; ^{1}H NMR δ_H 0.20 (s, 9H), 6.95 (dt, J=4.5, 1.3 Hz, 1H), 7.81 (dd, J=8.1, 1.4 Hz, 1H), 8.47 (dd, J=4.6, 1.4 Hz, 1H); ^{13}C NMR δ_C 0.05, 91.81, 119.95, 130.73, 148.69; IR (KBr) ν 2924, 1384, 1246, 981, 889, 842, 759, 632; MS (EI) m/z 334 (12), 333 (M^+, 67), 318 (100), 190 (44), 176 (60), 162 (13), 148 (19), 130 (15), 116 (19), 89 (30), 69 (24), 57 (37); HRMS (ESI$^+$) Calculated for $C_{10}H_{12}INSSi$=332.9506, found $[M+H]^+$=333.9580.

4.6.2. 3-Bromo-2-trimethylsilylthieno[3,2-*b*]pyridine (12). Compound **12** was prepared according to the method described herein with NBS (89 mg, 0.5 mmol). The mixture stirred at room temperature overnight. Column chromatography (eluent: hexane/AcOEt 70/30) yielded **12** (30 mg, 42%) as yellow gummy solid; ^{1}H NMR δ_H 0.050 (s, 9H), 7.30 (dt, J=4.5 Hz, 1H), 8.17 (dd, J=8.1 Hz, 1H), 8.80 (dd, J=4.5 Hz, 1H); ^{13}C NMR δ_C 1.64, 29.18, 116.65, 118.81, 129.86, 140.19, 147.58, 153.16; IR (NaCl) ν 2955, 2923, 1389, 1250, 994, 893, 842, 759; MS (EI) m/z 287 (70), 285 (M^+, 70), 272 (98), 270 (100), 190 (67), 176 (28), 148 (40), 130 (20), 89 (20); HRMS (ESI$^+$) Calculated for $C_{10}H_{12}BrNSSi$=284.9644, found $[M+H]^+$= 285.9716.

4.6.3. 3-Iodo-2-phenylthieno[3,2-*b*]pyridine (13). Compound **13** was prepared according to the method described herein with I_2 (127 mg, 0.5 mmol). Column chromatography (eluent: hexane/AcOEt 70/30) yielded **13** (74 mg, 88%) as a yellow gummy solid. ^{1}H NMR δ_H 7.31 (dt, J=4.7 Hz, 1H), 7.50 (m, 3H), 7.73 (m, 2H), 8.12 (dd, J= 8.1, 1.2 Hz, 1H), 8.82 (dd, J=4.6, 1.2 Hz, 1H); ^{13}C NMR δ_C 83.42, 120.06, 128.81, 129.56, 129.94, 130.42, 134.32, 148.50; IR (NaCl) ν 3040, 2924, 2852, 1542, 1479, 1389, 1148, 1073, 785, 750, 694; MS (EI) m/z 338 (13), 337 (M^+, 100), 210 (51), 166 (12), 139 (20), 127 (11), 105 (27), 91 (15), 83 (12), 69 (9), 57 (12); HRMS (ESI$^+$) Calculated for $C_{13}H_8INS$=336.9423, found $[M+H]^+$= 337.9517.

4.6.4. 3-Bromo-2-phenylthieno[3,2-*b*]pyridine (14). Compound **14** was prepared according to the method described herein with Br_2 (0.26 mL, 0.5 mmol). Column chromatography (eluent: hexane/AcOEt 70/30) yielded **14** (60 mg, 83%) as a white solid; mp 110–112 °C; ^{1}H NMR δ_H 7.30 (dt, J=4.6 Hz, 1H), 7.50 (m, 3H), 7.80 (m, 2H), 8.12 (dd, J=8.1, 1.3 Hz, 1H), 8.80 (dd, J=4.6, 1.3 Hz, 1H); ^{13}C NMR δ_C 107.51, 120.01, 128.87, 129.58, 130.47, 132.16, 148.36, 153.27; IR (NaCl) ν 3052, 2926, 1393, 1276, 1074, 894, 754; MS (EI) m/z 291 (85), 289 (M^+, 100), 210 (39), 166 (16), 139 (24), 105 (16); HRMS (ESI$^+$) Calculated for $C_{13}H_8BrNS$=288.9561, found $[M+H]^+$= 289.9647.

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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.2006.04.008.

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A general and efficient method for the copper-catalyzed cross-coupling of amides and thiophenols with 6-halogenoimidazo[1,2-*a*]pyridines

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Abstract—Convenient and efficient methods for the preparation of novel 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridine derivatives that utilize copper-catalyzed methodologies are reported. These methods are particularly noteworthy because of their experimental simplicity and the low cost of the catalyst system.

1. Introduction

During the course of our work to evaluate the applicability of metallo-catalyzed cross-coupling reactions in the imidazo[1,2-*a*]pyridine series, we previously reported on the reactivity of this nucleus towards Suzuki type cross-coupling,[1] and copper- or palladium-catalyzed coupling reactions with amines and azoles.[2] From a diversity-targeting perspective, we were then interested in developing the 6-amido or 6-phenylsulfanylimidazo[1,2-*a*]pyridine series since no broadly applicable methods for the synthesis of these classes of compounds exist in the literature. To the best of our knowledge, few examples of 6-amidoimidazo[1,2-*a*]pyridines have been described in the literature and were prepared starting from 6-nitroimidazo[1,2-*a*]pyridines in two steps: reduction of the nitro group and reaction with an isocyanate or a carboxylate derivative.[3] Concerning the thioether compounds, two recent publications have related their preparation on the 6-position of the imidazo[1,2-*a*]pyridine through nucleophilic substitution with sodium thiolate or halogen–metal exchange and addition of a thiophenol.[4] Nevertheless, no experimental data were given and these procedures are incompatible with sensitive functionalities.

The formation of aryl C–X bonds (X=N, S, O, etc.) via copper-catalyzed coupling between aryl halides and hetero-centered nucleophiles has drawn a great deal of attention in the past few years.[5] The high stability and low costs of copper catalysts enable these transformations to be a useful complement to the more extensively investigated palladium-catalyzed processes. Concerning the Goldberg reaction,[6] recent developments dramatically simplified this classical amidation reaction. The enhanced version of the Goldberg coupling was reported using CuI and chelating 1,2-diamine in combination with K_3PO_4, K_2CO_3, or Cs_2CO_3.[7] Application of this methodology to various heteroaromatic compounds is still a relatively unexplored process. Only a few examples of copper-catalyzed *N*-arylations of amides with furan, thiophene, quinoline, and pyrimidine were reported in the literature.[7,8]

New methods for the copper-catalyzed formation of aryl–sulfur bonds, which are analogous to the Ullmann biaryl ether synthesis,[9] were recently reported by Palomo and co-workers in 2000,[10] and concomitantly by Venkataraman et al.,[11] and Buchwald and Kwong[12] in 2002. The Buchwald methodology is the most attractive from an economic standpoint using CuI in the presence of ethylene glycol and K_2CO_3. Only two examples of application to heterocycles were given in this publication. The Venkataraman methodology using neocuproine as ligand was extended to 8-mercaptoadenine.[13]

Because of the lack of a general protocol for their synthesis, we felt that the copper-based protocols may be readily extended to the synthesis of 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridines. Herein, we detail our copper-catalyzed C–N cross-coupling results using 6-halogeno-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridines with a broad

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selection of useful amido substrates, and we report the copper-based protocol for the cross-coupling of 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine with thiophenols.

2. Results and discussion

2.1. Copper-catalyzed carbon–nitrogen bond formation

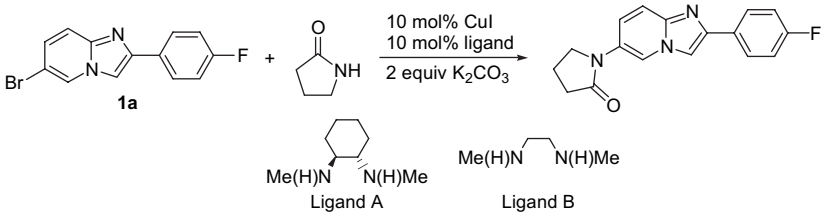
In our initial screening experiments, 6-bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a** and pyrrolidinone were used as model substrates to evaluate suitable reaction conditions for the lactam cross-coupling (Table 1). Indeed, compound **1** is a very convenient starting material as it is very stable and easily obtained in one-step through condensation of commercially available 5-halogenopyridin-2-amine with α-bromo-4-fluoroacetophenone.

Two commercially available ligands were evaluated for the coupling reaction: *trans*-*N*,*N*′-dimethyl-1,2-cyclohexyldiamine (ligand A, entries 1 and 2) and *N*,*N*′-dimethylethylenediamine (ligand B, entries 3 and 4). Reactions were performed in two different solvents, toluene (entries 1 and 3) and dioxane (entries 2 and 4). In all cases, the coupling product was obtained in good yields (75–92%). Optimized reaction conditions utilized 10 mol % CuI, K_2CO_3 (2 equiv), and 10 mol % ligand B in toluene at 110 °C.

In the first part of this study, these reaction conditions were applied to the coupling of various lactams. As shown in Table 2, the process is also efficient when the size of the lactam ring is varied. Of particular interest is the result in entry 2, in which it appears that steric hindrance has no adverse effect on the success of the couplings.

The scope of this copper-catalyzed *N*-arylation of lactams was then extended to the use of amides, carbamate, and urea (Table 3). The heteroarylation of acetamide proved to be successful, starting from the iodinated substrate **1b** (85% yield, entry 2). *N*-Benzylformamide could also be coupled to **1a** and **1b** but in only 48% yield in both cases (entries 3 and 4). The use of ligand A in the presence of K_2CO_3 or K_3PO_4 was then evaluated. As can be seen, the reaction of *N*-benzylformamide with **1b** proceeded in 71% yield using ligand A and K_3PO_4 (entry 6). These modified conditions were also efficient in the *N*-arylation of benzamide (99% yield, entry 8) and to a lesser extent, phenylurea (58% yield, entry 10). The *N*-(*tert*-butyloxycarbonyl)aniline remained a problematic substrate in the catalyst systems evaluated, resulting in only poor yields.

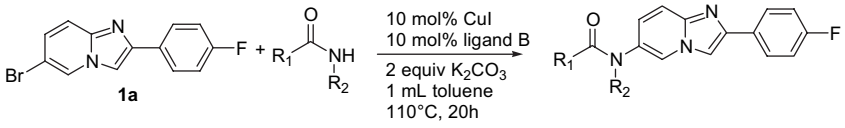
Table 1. Optimization studies on the copper-catalyzed cross-coupling of **1a** with pyrrolidinone[a]

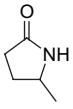
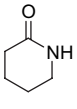


Entry	Ligand	Solvent, temperature	Yield, %[b]
1	A	Toluene, 110 °C	88
2	A	Dioxane, 100 °C	83
3	B	Toluene, 110 °C	92
4	B	Dioxane, 100 °C	75

[a] Reaction conditions: 1 mmol **1a**, 1.2 mmol lactam, 10 mol % CuI, 10 mol % ligand, 2 mmol K_2CO_3, 1 mL solvent, and 20 h.
[b] Isolated yields.

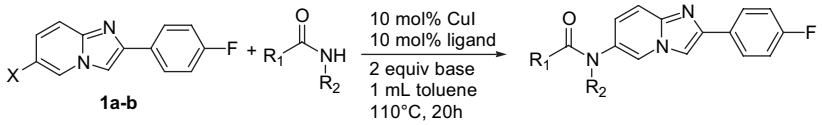
Table 2. Copper-catalyzed cross-coupling of **1a** with various lactams[a]



Entry	Lactam	Yield, %[b]	Entry	Lactam	Yield, %[b]
1		83	3		80
2		87	4		75

[a] Reaction conditions: 1 mmol **1a**, 1.2 mmol lactam, 10 mol % CuI, 10 mol % ligand B, 2 mmol K_2CO_3, 1 mL toluene, and 20 h at 110 °C.
[b] Isolated yields.

Table 3. Copper-catalyzed cross-coupling of **1a–b** with various amides, carbamate, and urea[a]



Entry	Amido substrate	X	Ligand	Base	Yield, %[b]
1	CH_3CONH_2	Br	B	K_2CO_3	NI[c]
2		I	B	K_2CO_3	85
3		Br	B	K_2CO_3	48
4	CH_2NHCHO	I	B	K_2CO_3	48
5		I	A	K_2CO_3	43
6		I	A	K_3PO_4	71
7	$CONH_2$	I	B	K_2CO_3	NI[c]
8		I	A	K_3PO_4	99
9	$NHCONH_2$	I	B	K_2CO_3	NI[c]
10		I	A	K_3PO_4	58
11	$NHCO_2C(CH_3)_3$	Br	B	K_2CO_3	5
12		I	B	K_2CO_3	27
13		I	A	K_2CO_3	Traces
14		I	A	K_3PO_4	23

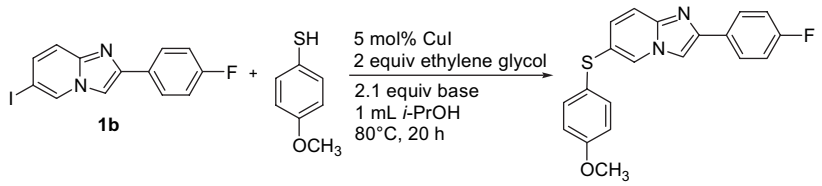
[a] Reaction conditions: 1 mmol **1a–b**, 1.2 mmol amides, carbamate, and urea, 10 mol % CuI, 10 mol % ligand, 2 mmol base, 1 mL toluene, and 20 h at 110 °C.
[b] Isolated yields.
[c] NI=not isolated.

2.2. Copper-catalyzed carbon–sulfur bond formation

The reaction conditions for the C–S couplings were optimized using 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine and 4-methoxythiophenol as substrates (Table 4). Attempts to use brominated starting materials were unsuccessful. The conditions developed by Buchwald and Kwong[12] were applied using 5 mol % CuI and ethylene glycol (2 equiv) in isopropanol. From the different bases evaluated, the use of K_2CO_3 resulted in the best coupling yields (94%, entry 3). The coupling also proceeded in good yield using the procedure described for the *N*-arylation of amide: 5 mol % CuI, 15 mol % ligand A, and K_3PO_4 (2.1 equiv) in toluene (entry 1).

To investigate the scope of the reaction, various substituted thiophenols were included in this study (Table 5). From the results obtained with different methoxythiophenols, the substituent position appears to influence the coupling efficacy, with the *ortho*-methoxythiophenol the least reactive reagent. In this case, attempts to use increased catalyst loading met with good success. However, traces of starting material in the coupling product were very difficult to remove. We were not able to isolate the product. We then introduced a higher amount of thiophenol in order to consume all the starting material. The excess thiophenol present at the end of the reaction was easily eliminated by washing with aqueous sodium hydroxide solution. Using these modified conditions, the 2-methoxythiophenol could be coupled in 67% yield (entry 6), while the coupling of 3-methoxythiophenol took place in 98% yield (entry 2). The 4-aminothiophenol also necessitated the use of an excess of thiophenol and led to the 4-aminophenylsulfanylderivative in 95% yield (entry 9). To the best of our knowledge, the aminothiophenol counterpart has never been previously evaluated in copper-based coupling reaction. Finally, the reaction of **1b** with

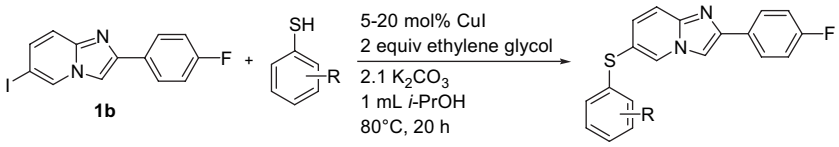
Table 4. Optimization studies on the copper-catalyzed cross-coupling of **1b** with 4-methoxythiophenol[a]



Entry	Base	Yield, %[b]
1	K_3PO_4	88[c]
2	K_3PO_4	83
3	K_2CO_3	94
4	Cs_2CO_3	84

[a] Reaction conditions: 1 mmol **1b**, 1 mmol thiol, 5 mol % CuI, 2 mmol ethylene glycol, 2.1 mmol base, 1 mL isopropanol, and 20 h at 80 °C.
[b] Isolated yields.
[c] Reaction was carried out in the presence of ligand A (15 mol %) in toluene at 110 °C.

Table 5. Copper-catalyzed cross-coupling of **1b** with various thiophenols[a]



Entry	R	CuI (mol %)	Yield, %[b]
1	3-OCH_3	5	NI[c]
2		20	98[d]
3	2-OCH_3	5	NI
4		15	NI
5		20	NI
6		20	67[e]
7	4-Cl	5	83
8	4-NH_2	5	22
9		20	95[d]
10	4-OH	5	96

[a] Reaction conditions: 1 mmol **1b**, 1 mmol thiol, 5–20 mol % CuI, 2 mmol ethylene glycol, 2.1 mmol base, 1 mL isopropanol, and 20 h at 80 °C.
[b] Isolated yields.
[c] Not isolated.
[d] Thiol (1.5 mmol) was used.
[e] Thiol (2 mmol) was used.

4-chlorothiophenol proceeded in 83% yield (entry 7) and in 96% yield with 4-hydroxythiophenol (entry 10).

3. Conclusion

In summary, we have developed a mild and efficient copper-catalyzed system for the amidation of 6-halogeno-imidazo[1,2-*a*]pyridines. Lactams of different sizes, amides, urea, and *N*-BOC aniline were thus introduced in the 6-position of this nucleus using the inexpensive and air-stable copper(I) iodide along with commercially available *N*,*N*′-dimethylated 1,2-diamine ligands in the presence of potassium carbonate or potassium phosphate. The best results were obtained with lactams that could be introduced on the 6-bromoimidazo[1,2-*a*]pyridine. In the other cases, the iodinated starting material was required.

We have also reported a general synthetic protocol for the cross-coupling of various thiophenols with 6-iodoimidazo[1,2-*a*]pyridine using copper(I) iodide, ethylene glycol, and potassium carbonate in isopropanol. In some cases, an excess of thiophenol was required but was easily eliminated at the end of the reaction via a basic treatment.

In both cases, our protocols are palladium-free and avoid the use of expensive and air sensitive ligands. They constitute the first convenient and flexible routes to new 6-amido and 6-phenylsulfanylimidazo[1,2-*a*]pyridines.

4. Experimental

4.1. General

Unless otherwise noted, all chemicals were used as received. 6-Bromo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1a**[1b] and 6-iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1b**[2a] were prepared according to literature procedures. All new compounds were fully characterized by ^1H, ^{13}C, and elemental analysis. NMR spectra were run at 200 or 300 MHz (^1H) and 50, 75 or 125 MHz (^{13}C) in $CDCl_3$ with chemical shifts reported relative to residual deuterated solvent peaks. Possible inversion of two values in the ^{13}C NMR spectra is expressed by an asterisk. Mps were determined in a capillary apparatus and are uncorrected.

4.2. General procedure for copper-catalyzed carbon–nitrogen bond formation

6-Halogeno-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1** (1 mmol), copper(I) iodide (19 mg, 0.1 mmol), amide when solid (1.2 mmol), and base (2 mmol) were added to a screw-capped test tube. The tube was evacuated and back filled with argon. *N*,*N*′-Dimethylethylenediamine (11 μL, 0.1 mmol) or racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), amide when liquid (1.2 mmol), and solvent (1 mL) were added successively by syringe at room temperature. The tube was sealed with a Teflon-lined cap and the reaction mixture was heated at 110 °C for 20 h. After cooling to room temperature, the suspension was diluted with dichloromethane (15 mL), and was filtered through Celite®. The solvent was removed with the aid of a rotary evaporator to give a brown residue, which was purified by column chromatography to give pure product.

4.2.1. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-pyrrolidinone (Table 1, entry 3). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-pyrrolidinone (91 μL, 1.2 mmol) in toluene. Column chromatography on alumina, eluting with ethyl acetate afforded 270 mg (92% yield) of the title compound, mp 235 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.89 (dd, 1H, J=2.1–0.8 Hz, H-5), 7.90 (dd, 2H, J=9–5.4 Hz, F–Ph-2,6), 7.81 (s, 1H, H-3), 7.58 (d, 1H, J=9.6 Hz, H-8), 7.27 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.12

(t, 2H, J=9 Hz, F–Ph-3,5), 3.88 (t, 2H, J=7.2 Hz, CH_2), 2.64 (t, 2H, J=7.8 Hz, CH_2), 2.22 (m, 2H, CH_2). ^{13}C NMR (75 MHz) δ 174.6 (CO), 162.9 (F–Ph-4), 145.8 (C-2*), 143.6 (C-8a*), 130.1 (F–Ph-1), 127.8 (F–Ph-2,6), 127.2 (C-6), 119.4 (C-7), 118.1 (C-5), 117.2 (C-8), 115.9 (F–Ph-3,5), 108.9 (C-3), 48.8 (CH_2), 32.5 (CH_2), 18.2 (CH_2). Anal. Calcd for $C_{17}H_{14}FN_3O$: C, 69.14; H, 4.78. Found: C, 69.05; H, 5.16.

4.2.2. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-3-methyl-2-pyrrolidinone (Table 2, entry 1). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 3-methyl-2-pyrrolidinone (88 μL, 120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 258 mg (83% yield) of the title compound, mp 223 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.96 (d, 1H, J=2.1 Hz, H-5), 7.89 (dd, 2H, J=9–5.7 Hz, F–Ph-2,6), 7.78 (s, 1H, H-3), 7.62 (d, 1H, J=9.6 Hz, H-8), 7.28 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.10 (t, 2H, J=9 Hz, F–Ph-3,5), 3.81 (dd, 2H, J=9–5.4 Hz, CH_2), 2.71 (m, 1H, CH), 2.44 (m, 1H, CH), 1.83 (m, 1H, CH), 1.33 (d, 3H, J=7.2 Hz, CH_3). ^{13}C NMR (75 MHz) δ 177.6 (CO), 163.4 (F–Ph-4), 146.1 (C-2*), 144.0 (C-8a*), 130.4 (F–Ph-1), 128.5 (F–Ph-2,6), 128.0 (C-6), 119.8 (C-7), 118.3 (C-5), 117.7 (C-8), 116.3 (F–Ph-3,5), 109.5 (C-3), 47.1 (CH_2), 38.6 (CH_3), 27.7 (CH), 16.8 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.66; H, 5.34.

4.2.3. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-5-methyl-2-pyrrolidinone (Table 2, entry 2). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 5-methyl-2-pyrrolidinone (106 μL, 120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 268 mg (87% yield) of the title compound, mp 179 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.46 (s, 1H, H-5), 7.86 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.61 (d, 1H, J=9.6 Hz, H-8), 7.07 (t, 2H, J=8.7 Hz, F–Ph-3,5), 4.24 (m, 1H, CH), 2.58 (m, 2H, CH_2), 2.37 (m, 1H, CH), 1.75 (m, 1H, CH), 1.21 (d, 3H, J=6.3 Hz, CH_3). ^{13}C NMR (75 MHz) δ 174.6 (CO), 162.8 (F–Ph-4), 145.7 (C-2*), 143.9 (C-8a*), 129.9 (F–Ph-1), 127.8 (F–Ph-2,6), 124.7 (C-6), 122.2 (C-7*), 122.1 (C-5*), 117.4 (C-8), 115.7 (F–Ph-3,5), 108.8 (C-3), 55.7 (CH_2), 31.1 (CH_2), 26.7 (CH_3), 20.4 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.57; H, 5.46.

4.2.4. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-azetidinone (Table 2, entry 3). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-azetidinone (85 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 235 mg (80% yield) of the title compound, mp 238 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (m, 1H, H-5), 7.88 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.75 (s, 1H, H-3), 7.63 (d, 1H, J=9.6 Hz, H-8), 7.16 (dd, 1H, J=9.6–2.1 Hz, H-7), 7.10 (t, 2H, J=8.8 Hz, F–Ph-3,5), 3.68 (t, 2H, J=4.5 Hz, CH_2), 3.18 (t, 2H, J=4.5 Hz, CH_2). ^{13}C NMR (125 MHz) δ 165.1 (CO), 163.4 (F–Ph-4), 146.2 (C-2*), 144.0 (C-8a*), 130.4 (F–Ph-1), 128.3 (F–Ph-2,6), 127.5 (C-6), 118.5 (C-7), 117.0 (C-8), 116.4 (F–Ph-3,5), 114.3 (C-5), 109.3 (C-3), 39.3 (CH_2), 37.4 (CH_2). Anal. Calcd for $C_{16}H_{12}FN_3O$: C, 68.32; H, 4.30. Found: C, 68.23; H, 4.66.

4.2.5. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-2-piperidinone (Table 2, entry 4). The general procedure was followed using compound **1a** (291 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and 2-piperidinone (120 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 233 mg (75% yield) of the title compound, mp 233 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (m, 1H, H-5), 7.89 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.62 (d, 1H, J=9.3 Hz, H-8), 7.10 (t, 2H, J=8.7 Hz, F–Ph-3,5), 7.09 (dd, 1H, J=9.3–2.1 Hz, H-7), 3.67 (m, 2H, CH_2), 2.59 (m, 2H, CH_2), 1.97 (m, 4H, $2CH_2$). ^{13}C NMR (125 MHz) δ 170.8 (CO), 162.9 (F–Ph-4), 146.0 (C-2*), 144.5 (C-8a*), 130.4 (C-6), 130.0 (F–Ph-1), 127.9 (F–Ph-2,6), 124.9 (C-7), 123.8 (C-5), 117.7 (C-8), 115.8 (F–Ph-3,5), 108.7 (C-3), 52.3 (CH_2), 33.0 (CH_2), 23.7 (CH_2), 21.5 (CH_2). Anal. Calcd for $C_{18}H_{16}FN_3O$: C, 69.89; H, 5.21. Found: C, 69.78; H, 4.91.

4.2.6. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]acetamide (Table 3, entry 2). The general procedure was followed using compound **1b** (338 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and acetamide (71 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (90/10) afforded 229 mg (85% yield) of the title compound, mp 233 °C. ^1H NMR (200 MHz, DMSO-d_6) δ 9.22 (m, 1H, H-5), 8.47 (s, 1H, H-3), 7.97 (dd, 2H, J=8.7–5.4 Hz, F–Ph-2,6), 7.58 (d, 1H, J=9.5 Hz, H-8), 7.28 (t, 2H, J=8.7 Hz, F–Ph-3,5), 7.17 (dd, 1H, J=9.5–1.6 Hz, H-7), 2.11 (s, 3H, CH_3), NH not found. ^{13}C NMR (50 MHz, DMSO-d_6) δ 170.7 (CO), 163.1 (F–Ph-4), 130.2 (F–Ph-1), 127.9 (F–Ph-2,6), 127.1 (C-6), 121.7 (C-7), 117.5 (C-5), 115.9 (C-8), 115.6 (F–Ph-3,5), 110.2 (C-3), 22.5 (CH_3). Anal. Calcd for $C_{15}H_{12}FN_3O$: C, 66.91; H, 4.49. Found: C, 66.77; H, 4.57.

4.2.7. *N*-Benzyl-*N*-[2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridin-6-yl]formamide (Table 3, entry 6). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and *N*-benzylformamide (162 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5 to 99/1) afforded 245 mg (71% yield) of the title compound, mp 132 °C. ^1H NMR (300 MHz, $CDCl_3$) δ rotamer A 8.43 (s, 1H, CHO), 7.87 (dd, 2H, J=8.8–5.5 Hz, F–Ph-2,6), 7.81 (d, 1H, J=1.8 Hz, H-5), 7.74 (s, 1H, H-3), 7.60 (d, 1H, J=9.5 Hz, H-8), 7.27 (m, 5H, Ph), 7.11 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.01 (dd, 1H, J=9.5–1.8 Hz, H-7);

rotamer B 8.59 (s, 1H, CHO), 7.87 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.85 (d, 1H, *J*=1.8 Hz, H-5), 7.70 (s, 1H, H-3), 7.57 (d, 1H, *J*=9.5 Hz, H-8), 7.27 (m, 5H, Ph), 7.11 (t, 2H, *J*=8.8 Hz, F–Ph-3,5), 7.01 (dd, 1H, *J*=9.5–1.8 Hz, H-7). ^{13}C NMR (125 MHz) δ 163.1 (F–Ph-4), 162.2 (CO), 146.5 (C-2*), 144.4 (C-8a*), 136.1 (C-6), 129.6 (F–Ph-1), 129.1 (Ph), 128.7 (Ph), 128.3 (Ph-1), 128.2 (Ph-4), 128.0 (F–Ph-2,6), 123.9 (C-7), 122.8 (C-5), 118.3 (C-8), 116.0 (F–Ph-3,5), 108.9 (C-3), 49.6 (CH_2). Anal. Calcd for $C_{21}H_{16}FN_3O$: C, 73.03; H, 4.67. Found: C, 73.28; H, 4.46.

4.2.8. *N*-[2-(4-Fluorophenyl)imidazo[1,2-*a*]pyridin-6-yl]-benzamide (Table 3, entry 8). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and benzamide (145 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99/1) afforded 327 mg (99% yield) of the title compound, mp 262 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.47 (s, 1H, NH), 9.39 (s, 1H, H-5), 8.55 (s, 1H, H-3), 7.97 (m, 4H, F–Ph-2,6, Ph-2,6,), 7.66 (d, 1H, *J*=9.3 Hz, H-8), 7.57 (m, 5H, Ph-3,4,5, H-7, H-8), 7.30 (t, 2H, *J*=8.8 Hz, F–Ph-3,5). ^{13}C NMR (125 MHz) δ 166.9 (CO), 162.9 (F–Ph-4), 144.7 (C-2*), 143.7 (C-8a*), 135.4 (Ph-1), 133.0 (Ph-4), 131.6 (F–Ph-1), 129.6 (Ph-3,5), 128.8 (Ph-2,6), 128.5 (F–Ph-2,6), 127.7 (C-6), 122.8 (C-7), 118.4 (C-5), 117.5 (C-8), 116.8 (F–Ph-3,5), 111.3 (C-3). Anal. Calcd for $C_{20}H_{16}FN_3O$: C, 72.50; H, 4.26. Found: C, 72.72; H, 4.56.

4.2.9. *N*-Phenyl-*N*′-[2-(4-fluorophenyl)imidazo[1,2-*a*]-pyridin-6-yl]urea (Table 3, entry 10). The general procedure was followed using compound **1b** (338 mg, 1 mmol), racemic *trans*-*N*,*N*′-dimethyl-1,2-cyclohexanediamine (16 μL, 0.1 mmol), potassium phosphate (425 mg, 2 mmol), and phenylurea (163 mg, 1.2 mmol). Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (90/10) afforded 200 mg (58% yield) of the title compound, mp>260 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.94 (s, 1H, H-5), 8.76 (s, 1H, NH), 8.71 (s, 1H, NH), 8.39 (s, 1H, H-3), 7.94 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.51 (d, 1H, *J*=9.6 Hz, H-8), 7.45 (d, 2H, *J*=8.1 Hz, Ph-2,6), 7.29–7.21 (m, 4H, F–Ph-3,5, Ph-3,5), 7.07 (dd, 1H, *J*=9.6–2.1 Hz, H-7), 6.96 (t, 1H, *J*=7.5 Hz, Ph-4). ^{13}C NMR (50 MHz) δ 161.7 (F–Ph-4), 152.7 (CO), 143.5 (C-2*), 142.3 (C-8a*), 139.5 (Ph-1), 130.6 (F–Ph-1), 128.8 (Ph-3,5), 127.2 (F–Ph-2,6), 126.9 (C-6), 122.0 (Ph-4), 121.0 (C-7), 118.3 (Ph-2,6), 116.5 (C-5), 115.6 (F–Ph-3,5), 114.9 (C-8), 109.8 (C-3). Anal. Calcd for $C_{20}H_{15}FN_4O$: C, 69.35; H, 4.37. Found: C, 69.62; H, 4.14.

4.2.10. 6-[*N*-(*tert*-Butyloxycarbonyl)-*N*-phenylamino]-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine (Table 3, entry 12). The general procedure was followed using compound **1b** (338 mg, 1 mmol), *N*,*N*′-dimethylethylenediamine (11 μL, 0.1 mmol), potassium carbonate (276 mg, 2 mmol), and *N*-(*tert*-butyloxycarbonyl)aniline (232 mg, 1.2 mmol) in toluene. Column chromatography on silica gel eluting with dichloromethane and then with a mixture of dichloromethane–methanol (99.5/0.5) afforded 118 mg (27% yield) of the title compound, mp 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20 (m, 1H, H-5), 7.91 (dd, 2H, *J*=9–5.4 Hz, F–Ph-2,6), 7.76 (s, 1H, H-3), 7.65 (d, 1H, *J*=9.6 Hz, H-8), 7.37 (m, 2H, Ph-2,6), 7.25 (m, 3H, Ph-3,4,5), 7.18 (dd, 1H, *J*=9.6–2.1 Hz, H-7), 7.12 (t, 2H, *J*=9 Hz, F–Ph-3,5), 1.50 (s, 6H, *t*-Bu). ^{13}C NMR (125 MHz) δ 163.2 (F–Ph-4), 154.0 (CO), 145.9 (C-2*), 144.1 (C-8a*), 142.7 (Ph-1*), 131.2 (C-6*), 129.9 (F–Ph-1), 129.5 (Ph-2,6), 128.2 (F–Ph-2,6), 127.1 (Ph-3,5), 126.7 (Ph-4*), 126.6 (C-7*), 124.1 (C-5), 117.1 (C-8), 116.1 (F–Ph-3,5), 108.9 (C-3), 82.5 ($C(CH_3)_3$), 28.6 ($3CH_3$). Anal. Calcd for $C_{24}H_{22}FN_3O_2$: C, 71.45; H, 5.50. Found: C, 71.48; H, 5.71.

4.3. General procedure for copper-catalyzed carbon–sulfur bond formation

6-Iodo-2-(4-fluorophenyl)imidazo[1,2-*a*]pyridine **1b** (338 mg, 1 mmol), copper(I) iodide (9.5 mg, 0.05 mmol to 38 mg, 0.2 mmol), potassium carbonate (290 mg, 2.1 mmol), and thiophenol when solid, were added to a screw-capped test tube. The tube was evacuated and back filled with argon. Ethylene glycol (111 μL, 2 mmol), thiophenol when liquid, and isopropanol (1 mL) were added successively by syringe at room temperature. The tube was sealed with a Teflon-lined cap and the reaction mixture was heated at 80 °C for 20 h. After cooling to room temperature, the suspension was diluted with ethyl acetate (15 mL) and washed three times with 10 N aqueous sodium hydroxide. After drying ($MgSO_4$), the solvent was removed with the aid of a rotary evaporator to give a brown residue that was purified by column chromatography to give pure product.

4.3.1. 2-(4-Fluorophenyl)-6-(4-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 4, entry 3). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-methoxythiophenol (123 μL, 1 mmol). Column chromatography on silica gel eluting with dichloromethane afforded 327 mg (94% yield) of the title compound, mp 134 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dd, 1H, *J*=1.8–0.6 Hz, H-5), 7.89 (dd, 2H, *J*=8.7–5.4 Hz, F–Ph-2,6), 7.72 (s, 1H, H-3), 7.51 (d, 1H, *J*=9.3 Hz, H-8), 7.37 (d, 2H, *J*=8.8 Hz, CH_3O–Ph-2,6), 7.12 (t, 2H, *J*=8.7 Hz, F–Ph-3,5), 7.09 (dd, 1H, *J*=9.3–1.8 Hz, H-7), 6.89 (d, 2H, *J*=8.8 Hz, CH_3O–Ph-3,5), 3.81 (s, 3H, CH_3). ^{13}C NMR (125 MHz) δ 162.9 (F–Ph-4), 159.9 (CH_3O–Ph-4), 145.6 (C-2*), 144.7 (C-8a*), 133.8 (CH_3O–Ph-2,6), 129.9 (F–Ph-1), 128.6 (CH_3O–Ph-1), 127.8 (F–Ph-2,6), 126.2 (C-7), 125.0 (C-6), 122.3 (C-5), 117.7 (C-8), 115.9 (F–Ph-3,5), 115.3 (CH_3O–Ph-3,5), 108.1 (C-3), 55.6 (CH_3O). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 68.57; H, 4.45.

4.3.2. 2-(4-Fluorophenyl)-6-(3-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 2). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 3-methoxythiophenol (185 μL, 1.5 mmol). After washing with 10 N aqueous sodium hydroxide, 347 mg (98% yield) of the title compound were obtained without further purification, mp 150 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.32 (m, 1H, H-5), 7.95 (dd, 2H, *J*=8.8–5.4 Hz, F–Ph-2,6), 7.82 (s, 1H, H-3), 7.62 (d, 1H, *J*=9.4 Hz, H-8), 7.30–7.13 (m, 4H, CH_3O–Ph-5, F–Ph-3,5, H-7), 6.90–6.78 (m, 3H, CH_3O–Ph-2,4,6), 3.79 (s, 1H, CH_3). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 160.6

(CH_3O–Ph-3), 146.1 (C-2*), 145.1 (C-8a*), 137.7 (CH_3O–Ph-1), 130.6 (CH_3O–Ph-5*), 130.5 (C-7*), 130.0 (F–Ph-1), 129.1 (C-5), 128.2 (F–Ph-2,6), 121.7 (CH_3O–Ph-6), 119.5 (C-6), 118.2 (C-8), 116.2 (F–Ph-3,5), 115.0 (CH_3O–Ph-2), 112.9 (CH_3O–Ph-4), 108.5 (C-3), 55.7 (OCH_3). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 68.59; H, 4.37.

4.3.3. 2-(4-Fluorophenyl)-6-(2-methoxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 6). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 2-methoxythiophenol (243 μL, 2 mmol). Column chromatography on silica gel eluting with a mixture of diethyl ether–petroleum ether (70/30) afforded 235 mg (67% yield) of the title compound, mp 149 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.29 (m, 1H, H-5), 7.98 (dd, 2H, J=8.8–5.3 Hz, F–Ph-2,6), 7.82 (s, 1H, H-3), 7.70 (d, 1H, J=9.4 Hz, H-8), 7.30 (m, 2H, CH_3O–Ph-6, H-7), 7.18 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.11 (dd, 1H, J=7.5–1.5 Hz, CH_3O–Ph-4), 6.94 (m, 2H, CH_3O–Ph-3,5), 3.94 (s, 1H, CH_3). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 157.1 (CH_3O–Ph-2), 145.8 (C-2*), 145.1 (C-8a*), 130.8 (CH_3O–Ph-6), 130.3 (CH_3O–Ph-4), 129.8 (F–Ph-1), 129.2 (C-5), 128.7 (C-7), 128.2 (F–Ph-2,6), 124.6 (C-6), 121.8 (CH_3O–Ph-5), 119.0 (CH_3O–Ph-1), 117.9 (C-8), 116.2 (F–Ph-3,5), 111.3 (CH_3O–Ph-3), 108.4 (C-3), 56.3 (OCH_3). Anal. Calcd for $C_{20}H_{15}FN_2OS$: C, 68.55; H, 4.31. Found: C, 66.32; H, 4.51.

4.3.4. 2-(4-Fluorophenyl)-6-(4-chlorophenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 7). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-chlorothiophenol (145 μL, 1 mmol). Column chromatography on silica gel eluting with dichloromethane afforded 294 mg (83% yield) of the title compound, mp 181 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.28 (m, 1H, H-5), 7.91 (dd, 2H, J=9–5.4 Hz, F–Ph-2,6), 7.78 (s, 1H, H-3), 7.58 (d, 1H, J=9.3 Hz, H-8), 7.27 (d, 2H, J=8.9 Hz, Cl–Ph-2,6), 7.19 (d, 2H, J=8.9 Hz, Cl–Ph-3,5), 7.14 (dd, 1H, J=9.3–1.5 Hz, H-7), 7.13 (t, 2H, J=9 Hz, F–Ph-3,5). ^{13}C NMR (125 MHz) δ 162.8 (F–Ph-4), 145.9 (C-2*), 144.7 (C-8a*), 134.6 (Cl–Ph-1), 133.0 (Cl–Ph-4), 130.3 (Cl–Ph-2,6), 129.7 (C-7), 129.6 (F–Ph-1), 129.5 (Cl–Ph-3,5), 128.9 (C-5), 127.8 (F–Ph-2,6), 118.7 (C-6), 118.1 (C-8), 115.9 (F–Ph-3,5), 108.2 (C-3). Anal. Calcd for $C_{19}H_{12}ClFN_2S$: C, 64.31; H, 3.41. Found: C, 64.27; H, 3.64.

4.3.5. 2-(4-Fluorophenyl)-6-(4-aminophenylsulfanyl)imidazo[1,2-*a*]pyridine (Table 5, entry 9). The general procedure was followed using copper(I) iodide (38 mg, 0.2 mmol) and 4-aminothiophenol (188 mg, 1.5 mmol). Column chromatography on silica gel eluting with CH_2Cl_2 and then with ether, afforded 317 mg (95% yield) of the title compound, mp 154 °C. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.02 (m, 1H, H-5), 7.92 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.74 (s, 1H, H-3), 7.53 (d, 1H, J=9.4 Hz, H-8), 7.32 (d, 2H, J=8.7 Hz, NH_2–Ph-2,6), 7.15 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.12 (d, 1H, J=9.4 Hz, H-7), 6.70 (d, 2H, J=8.7 Hz, NH_2–Ph-3,5), 3.85 (s, 2H, NH_2). ^{13}C NMR (50 MHz) δ 163.3 (F–Ph-4), 147.5 (NH_2–Ph-4), 145.5 (C-2*), 144.8 (C-8a*), 135.1 (NH_2–Ph-2,6), 130.1 (F–Ph-1), 128.4 (C-7), 128.1 (F–Ph-2,6), 125.2 (C-5), 124.2 (NH_2–Ph-1*), 121.1 (C-6*), 117.6 (C-8), 116.3 (NH_2–Ph-3,5), 116.1 (F–Ph-3,5), 108.3 (C-3). Anal. Calcd for $C_{19}H_{14}FN_3S$: C, 68.04; H, 4.21. Found: C, 68.12; H, 4.33.

4.3.6. 2-(4-Fluorophenyl)-6-(4-hydroxyphenylsulfanyl)-imidazo[1,2-*a*]pyridine (Table 5, entry 10). The general procedure was followed using copper(I) iodide (9.5 mg, 0.05 mmol) and 4-hydroxythiophenol (121 μL, 1 mmol). After washing with 10 N aqueous sodium hydroxide, 312 mg (96% yield) of the title compound was obtained without further purification, mp>250 °C. ^{1}H NMR (200 MHz, CD_3OD) δ 8.05 (m, 1H, H-5), 8.03 (s, 1H, H-3), 7.92 (dd, 2H, J=8.8–5.4 Hz, F–Ph-2,6), 7.42 (d, 1H, J=9.4 Hz, H-8), 7.26 (d, 2H, J=8.6 Hz, HO–Ph-2,6), 7.17 (t, 2H, J=8.8 Hz, F–Ph-3,5), 7.16 (dd, 1H, J=9.4–1.9 Hz, H-7), 6.70 (d, 2H, J=8.6 Hz, HO–Ph-3,5), 4.91 (s, 1H, OH). ^{13}C NMR (50 MHz) δ 169.1 (HO–Ph-4), 163.1 (F–Ph-4), 144.6 (C-2*), 144.4 (C-8a*), 136.4 (HO–Ph-2,6), 130.1 (F–Ph-1), 127.9 (F–Ph-2,6), 127.7 (C-7), 127.4 (C-6), 123.4 (C-5), 120.4 (HO–Ph-3,5), 115.6 (C-8), 115.5 (F–Ph-3,5), 113.2 (HO–Ph-1), 109.3 (C-3). Anal. Calcd for $C_{19}H_{13}FN_2OS$: C, 67.84; H, 3.90. Found: C, 67.98; H, 3.89.

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Derivatives of arylhydrazonic acids. Part 3: Stereochemical rearrangement of *Z*-oxanilo-*N*1-dialkyl-*N*2-arylamidrazones☆

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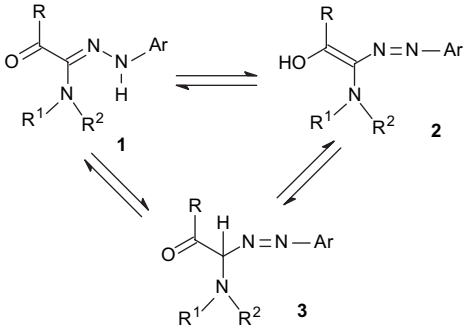
Abstract—Oxanilo-N^1-dialkyl-N^2-arylamidrazones have been prepared by nucleophilic substitution of the chloride function of appropriate hydrazonoyl chlorides. Relative stabilities of *Z*- and *E*-isomers, calculated with the RHF/6-31G* ab initio method, range between 0.7 and 2.1 kcal/mol. The *Z*-isomer is detected to be thermodynamically more stable for studied compounds. X-ray structure determination of 2-dimethylamino-*N*-phenyl-2-phenylhydrazonoacetamide revealed *E*- and *Z*-isomers (ratio 1:1) in the crystal. The different intra- and intermolecular hydrogen bond interactions, which are identified in solid state of compounds, are dissolved in polar solvents. All compounds were found to form *E*/*Z*-equilibrium in solution. In some cases *E*-isomers could be separated and fully characterized.

1. Introduction

Compounds with an open-chain or cyclic amidrazone structure represent a class of substances with various interesting biological activities. They have been found to be effective towards cholinesterase,[2] nucleoside hydrolase[3] or glycosidase.[4] Their antiinflammatory[5] and lipoxygenase or cyclooxygenase inhibiting properties[6] are already known.

Recently we reported about the synthesis of α-carbonyl substituted, open-chain amidrazones, which demonstrate inhibitory activity against soybean lipoxygenase-1 and human 5-lipoxygenase.[7] To correlate the biological activity with the structure of amidrazones, their exact structural elucidation is required. N^2-Arylsubstituted amidrazones with an α-carbonyl function can exist in the hydrazono (**1**), azo–enol (**2**) or azo (**3**) tautomeric form (see Scheme 1), each of which exhibits geometric isomerism. In literature, structure **1** is indicated to predominate.

Nearly all structures of N^2-arylamidrazones determined by X-ray diffraction analysis were found to be *Z*-configured.[8–10] The structure of *Z*- and *E*-isomers of *C*-phosphoryl substituted formamidrazones was reported by Buzykin.[11] Cunningham et al.[12] describe *E*/*Z*-N^2-aryl-N^1-dimethylethaneamidrazones, which bear at N^2 an additional methyl group. It was observed that uncatalyzed isomerization could be slowed by the presence of a disubstituted N^2-nitrogen. Since amidines are configurationally less stable, more attention has yet been given to isomerism of corresponding amidoximes,[13] imidates[14] and hydrazonates.[15]



Scheme 1. Tautomeric forms of α-carbonyl substituted amidrazones.

Starting from hydrazonoyl chlorides **4**, we have synthesized further derivatives of N^1-dialkyl-N^2-aryl substituted oxanilo-amidrazones **5**–**8**.

In the presence of a base in aprotic solvents hydrazonoyl chlorides react to form 1,3-dipolar ions. Kinetic studies demonstrated that base catalyzed dehydrochlorination of hydrazonoyl chlorides like **4** proceed in a fast step to the anion, which is followed by the slow abstraction of chloride to form nitrilimine. Studies referred to solvent mixture dioxane/water and triethylamine as base.[16] Furthermore, the nucleophile can substitute the chloride function. To explain

☆ See Ref. 1 for Part 2.
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mechanism of substitution at the carbon–nitrogen double bond, extensive investigations were undertaken by Rowe and Hegarty.[17–20] Preferably, *N*-disubstituted hydrazonoyl halides Aryl–C(X)=N–N(Me)Aryl **9** were studied, which cannot form nitrilimines under base conditions. Modes of reaction of the halide with a nucleophile are conceivable:

- S_N1 type slow scission of the carbon–halogen bond to yield an intermediate azocarbenium ion;
- direct (S_N2) displacement of halogen by a nucleophile.

Reaction in polar solvents like acetone/water or dioxane/water proceeds following the dissociative mechanism (S_N1, D_N+A_N).[18] In less polar solvents, an addition–elimination mechanism (S_N2, A_N+D_N) predominates. The rate determining step of S_N2 varies depending on solvent and base. With a strong base, the addition is discussed to be rate determining ($A_N^{\#}$)[14] whereas in most nonpolar solvent like benzene with secondary amines the elimination was noted to be the rate determining step ($S_N^{\#}$).[17]

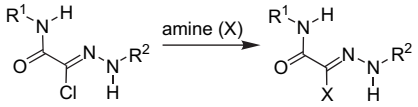
Considering that amidrazones **5–8** were prepared using dioxane as solvent, first step of reaction is assumed to lead to the abstraction of proton by base followed by an addition–elimination pathway. The stereospecifical formation of *Z*-isomers is explainable with both mechanisms. In case of S_N1, the nucleophile attacks the carbenium ion in trans position to the imino lone pair.[12] On the other hand following S_N2, the lone pair has such a configuration in the transition state that the stereospecifically trans elimination can occur.[18] All these data indicate, that the reaction of **4** with amines leads to *Z*-configured amidrazones.

Here we report for the first time on the separation and fully characterization of *E*-isomers besides *Z*-isomers of N^2-aryl-amidrazones.

2. Results and discussion

The preparation of hydrazonoyl chlorides **4** is well known because of their extensive use in 1,3-dipolar cycloaddition reactions. The synthesis of derivatives **4a–4j**, **4l**, **4m** and **4o–4q** is described in literature (lit. see Section 3). According to the reported procedures hydrazonoyl chlorides **4k** and **4n** were additionally prepared. The substitution pattern of compound **4** is shown in Table 1.

The structural assignment of **4** in solid state and in solution was reported.[21] Amidrazones **5–8** were obtained by reaction of oxanilo-1-arylhydrazono-1-chlorides **4** with dimethylamine, diisopropylamine, piperidine or morpholine (see Scheme 2). The substitution pattern of known (**5b**, **5d** and **7a**) and newly synthesized N^1-dialkyl-N^2-aryl substituted oxaniloamidrazones is summarized in Table 5. In accordance to literature data, the reaction of hydrazonoyl chlorides **4** with secondary amines results in isolation of *Z*-isomers. X-ray diffraction analysis of **7g** confirmed that the amidrazone moiety is *Z*-configured, see Figure 1. Essential bond lengths of **7g** are listed in Table 2. The N1–N2 bond length of 1.342(4) Å as well as C1–N2 and C1–N3 distances of 1.291(4) and 1.405(4) are well within the range that typically occurs in other amidrazone derivatives (1.30–1.37 Å for N1–N2, 1.28–1.30 Å for C1–N2 and 1.36–1.47 Å for C1–N3).[8–11] Two intramolecular hydrogen bonds N1–H1···N3 and N4–H2···N2 but no intermolecular hydrogen interactions were detected. The structure of the molecule in the crystal of **7g** with intramolecular hydrogen bonding is outlined in Figure 1.



4 **5-8**

Scheme 2. Synthesis of amidrazones.

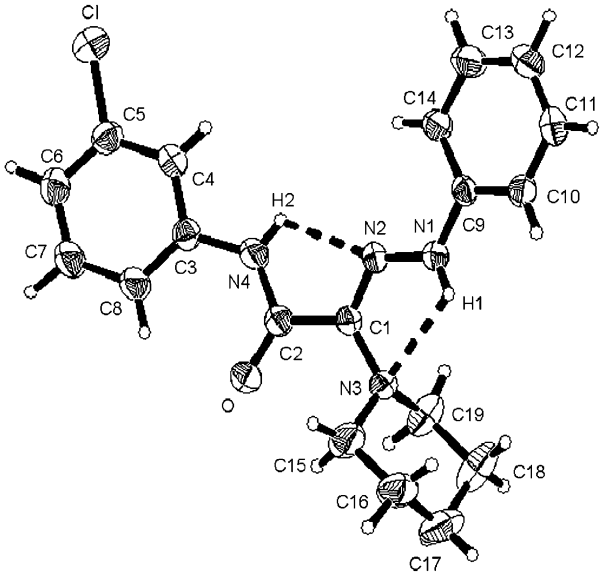


Figure 1. Molecular structure, atom numbering scheme (displacement ellipsoids with 50% probability) and intramolecular hydrogen bonds (dashed lines) of **7g**.

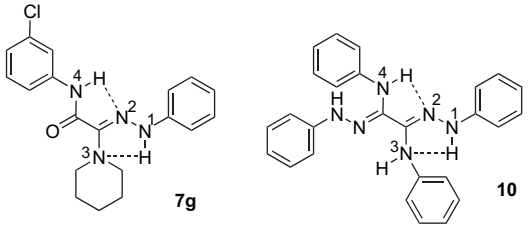
Table 1. Substitution pattern of starting hydrazonoyl chlorides $R^1NHCOC{=}N(Cl)NHR^2$ (**4**)

	R^1	R^2		R^1	R^2
4a	Ph	Ph	**4j**	3-Cl–C_6H_4	Ph
4b	Ph	3-CF_3–C_6H_4	**4k**	4-Cl–C_6H_4	Ph
4c	Ph	2-Cl–C_6H_4	**4l**	2-Cl–C_6H_4	2-Cl–C_6H_4
4d	Ph	4-Cl–C_6H_4	**4m**	2-Cl–C_6H_4	3-Cl–C_6H_4
4e	Ph	2-F–C_6H_4	**4n**	2-Cl–C_6H_4	4-Cl–C_6H_4
4f	Ph	3-F–C_6H_4	**4o**	3-Cl–C_6H_4	2-Cl–C_6H_4
4g	Ph	4-F–C_6H_4	**4p**	3-Cl–C_6H_4	3-Cl–C_6H_4
4h	3-CF_3–C_6H_4	Ph	**4q**	4-Cl–C_6H_4	4-Cl–C_6H_4
4i	2-Cl–C_6H_4	Ph			

Table 2. Characteristic bond length [Å] of the molecule structure of (*E*/*Z*)-**5a** and (*Z*)-**7g**

	(*Z*)-**5a**	(*E*)-**5a**	**7g**
	Molecule A	Molecule B	
N(1)–N(2)	1.351(2)	1.390(3)	1.342(4)
C(1)–N(2)	1.294(2)	1.286(3)	1.291(4)
C(1)–N(3)	1.395(2)	1.373(3)	1.405(4)
C(9)–N(1)	1.391(2)	1.396(3)	1.391(4)
C(1)–C(2)	1.496(3)	1.511(3)	1.491(4)

The formation of possible intramolecular hydrogen bonds as a result of very weak interactions is discussed for amidrazone derivative **10** by Harlow[10] as well (Scheme 3). The distances are comparable in both structures for N1–H1···N3 **7g**: 2.25(3) Å, **10**: 2.37(2) Å for N4–H2···N2 **7g**: 2.23(3) Å, **10**: 2.48(2) Å.



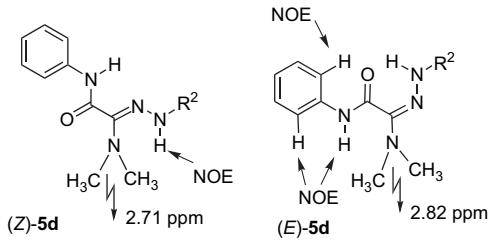
Scheme 3. Structures of *Z*-configured amidrazones **7g** and **10**.

However, purification of crude product of **7a** by careful recrystallization only from heptane led to isolation of different crystal forms. First nearly white crystals were obtained with melting point of 136–138 °C. Besides mixed crystals with melting points of nearly 125 °C, deep yellow, long and thin needles were collected (mp: 118–120 °C). All attempts to get crystals for X-ray diffraction analysis failed. Using TLC with solvent hexane/ether 7:3, two different compounds could be detected. The doubling of signals in ^{1}H and ^{13}C NMR spectra of mixed crystals and the adjustment of equilibrium in solution starting from one form point to the existence of tautomeric or isomeric forms of compound **7a**, see Scheme 1. From further amidrazone derivatives **5c** and **5d**, two different crystal forms could be isolated as well. It was observed by NMR that these different forms occur as pure isomer with less than 10% impurity of the other isomer.

The formation of different tautomeric forms according to Scheme 1 could be ruled out. Besides the signal of anilide proton, an additional lowfield signal was observed in ^{1}H NMR spectrum, which points to NH or OH moiety. Therefore, the azo form (structure **3** in Scheme 1, R=NHAryl) has been excluded. On the other hand, NOE was not observed between both lowfield signals, which is in contrast to enolic structure. In addition, ^{1}H NMR signal of enolic protons is usually found in the region of 13–14 ppm. However, all ^{1}H NMR studies were complicated by the presence of the two signals in the range of 8–10 ppm. Furthermore, mixtures of isomeric forms exhibit four signals. The assignment of different NH signals could only be realized with nearly pure isomers and from experience of appropriate hydrazonoyl chlorides.[21] All routine NMR experiments were run in DMSO, because in chloroform the isomers equilibrated fast.

NOE experiments with derivative **5d** revealed that the compound exists in (*Z*)-**5d** and (*E*)-**5d**, see Scheme 4. The irradiation in frequency of the methyl protons causes in *Z*-isomer an NOE to the hydrazone proton, whereas in the *E*-isomer an NOE was observed not only to the anilide proton but also to the aromatic *ortho*-protons.

Unfortunately, pure *E*-isomers form quiet long and extremely thin needles, which were not suitable for X-ray analysis. All effort to get crystals of *E*-isomer finished at most in isolation of crystals of *E*/*Z*-isomer mixture. X-ray structure determination of amidrazone derivative **5a** revealed *E*- and *Z*-isomer in the crystal ratio of 1:1. The molecular structure of *E*-isomer (molecule B) in the crystal of **5a** is shown in Figure 2. Besides the known intramolecular interactions in the *Z*-isomer, a hydrogen bond between the amide oxygen and the hydrazone proton is present in *E*-isomer (Fig. 3, molecule B). An additional intermolecular hydrogen bond is formed in the crystal of (*E*/*Z*)-**5a** between the carbonyl oxygen of *Z*-isomer (molecule A) and the amide proton of *E*-isomer (molecule B). Distances and angles of hydrogen bonds are listed in Table 3.



Scheme 4. Results of NOE experiments for *E*- and *Z*-isomer of amidrazone **5d**.

To prove the origin of *E*-isomer, crude products of different reaction mixtures were investigated by ^{1}H NMR. It could be noted that the mixtures contained variable amounts of *E*-isomers but not more than 50%, see Table 4. In some cases, *Z*- and *E*-isomers of compounds could be separated

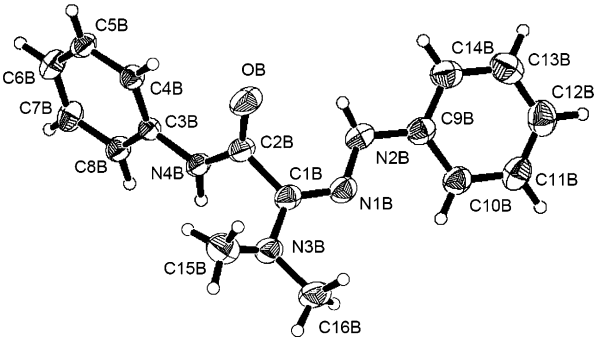


Figure 2. Molecular structure and atom numbering scheme of (*E*)-**5a** in molecule B (displacement ellipsoids with 50% probability).

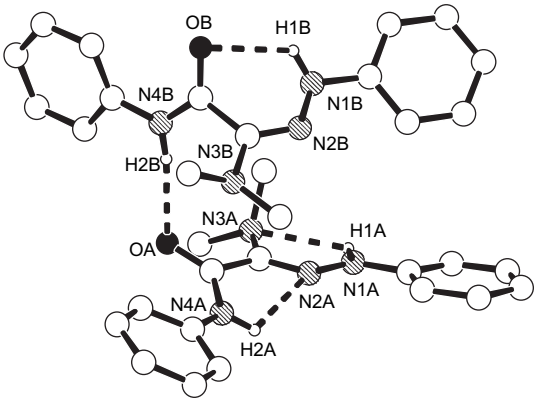


Figure 3. Intra- and intermolecular hydrogen bonding (dashed lines) in the crystal of (*E*/*Z*)-**5a**, molecule A: *Z*-isomer, molecule B: *E*-isomer.

Table 3. Potential intra- and intermolecular hydrogen bonds of the molecule structure of (*E*/*Z*)-**5a** and (*Z*)-**7g**

Type, D–H···A	D–H	H···A	D···A	D–H···A
Intramolecular				
(*Z*)-**5a** N1A–H1A···N3A	0.89(2)	2.34(2)	2.647(2)	100.4(15)
(*Z*)-**7g** N1–H1···N3	0.79(3)	2.25(3)	2.640(4)	111(3)
Intramolecular				
(*Z*)-**5a** N4A–H2A···N2A	0.87(2)	2.26(2)	2.670(2)	109.1(17)
(*Z*)-**7g** N4–H2···N2	0.81(4)	2.23(3)	2.634(4)	111(3)
Intramolecular				
(*E*)-**5a** N1B–H1B···OB	0.91(3)	2.37(3)	2.959(3)	122(2)
Intermolecular				
(*E*/*Z*)-**5a** N4B–H2B···OA	0.88(3)	2.08(3)	2.946(3)	171(2)

Distances (D–H, H···A, D···A) are given in Å, angles in °, D: donor, A: acceptor.

Table 4. Rate % of *E*-isomer of selected crude and recrystallized products of amidrazones $R^1NHCOC{=}N(X)NHR^2$ (**5–8**)

	R^1	R^2	Crude product	*Z*-Isomer	*E*-Isomer	Δ*E* (kcal/mol)
5a	H	H	38	21	50 (90[a])	1.269
5b	H	3-CF_3	16	5	70[a]	0.691
5e	H	4-F	46	<5	50	1.002
5h	2-Cl	2-Cl	<5	15	90	2.102
5l	3-Cl	3-Cl	<5	7	>95	0.879
5m	4-Cl	4-Cl	12	<5	85	1.084
7a	H	H	9	<5	85	1.189
7b	H	2-Cl	30	6	87	2.039
7f	2-Cl	H	<5	<5	n.i.[b]	1.313
8d	4-Cl	H	14	<5	n.i.[b]	1.102

[a] After SC-separation.
[b] Not isolated.

by fractionated crystallization or column chromatography, see Section 3. Besides the involved atoms and the substitution pattern at the phenyl rings the formation enthalpy depends on the specific configuration of the molecule. Ab initio calculations, carried out at the RHF 6-31G* level (see Section 3.1), demonstrate that the energy differences between the *Z*- and *E*-isomers range between 0.69 kcal/mol (compound **5b**) and 2.1 kcal/mol (compound **5h**). On the one hand, compounds with R^2=2-Cl (Table 4: **5h**, **7b**) were found to have higher energy differences between *Z*- and *E*-isomers, but on the other hand a relation of differences of the formation enthalpies and separation of isomers could not been detected. *Z*-Isomers are identified to be thermodynamically more stable for studied compounds. Melting points of *E*-isomer were observed at more than 10 °C lower temperatures like that of *Z*-isomers. Sometimes, *E*-isomers such as (*E*)-**7b** or (*E*)-**5a** transform to *Z*-isomer during heating process. Furthermore, separated *E*-isomers recrystallized from polar solvents as *E*/*Z*-mixtures.

In solution, intramolecular interactions seem to influence the stability of isomers. Maintaining and disrupting of intramolecular hydrogen bonding can be followed in ^{1}H NMR spectra. In accordance with earlier published data of hydrazonoyl chlorides **4**, the intra- and intermolecular interactions are disrupted in polar solvents. Compounds with NH···*ortho*-halogen hydrogen bonds display an independent NH signal.[21] In general, increasing polarity of solvent causes a downfield shift of NH signal of the more or less strong interactions N1–H1···N3 and N4–H2···N2 for about 1–2 ppm and an upfield shift of the strong intramolecular hydrogen bond N1–H1···O in *E*-isomer for about 3 ppm (cf.

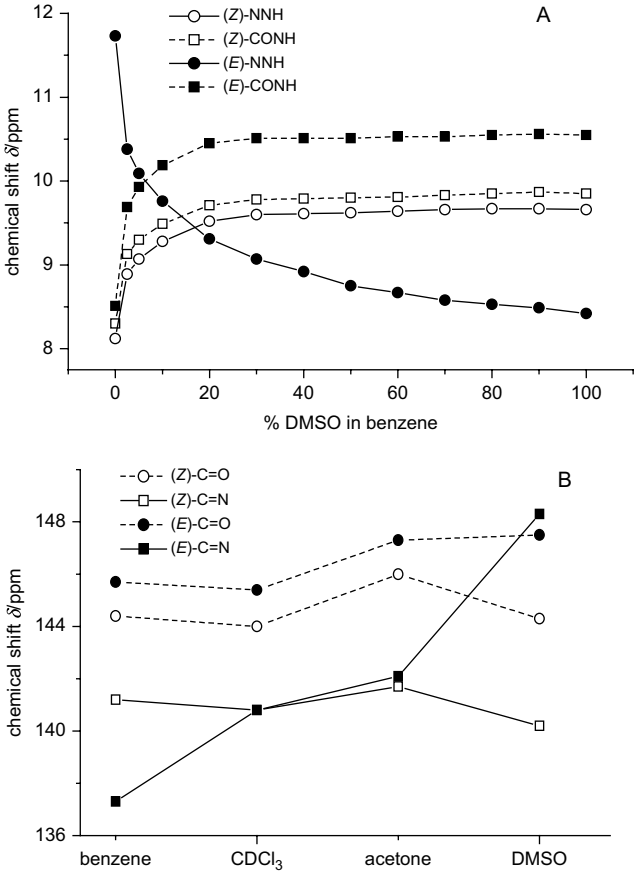


Figure 4. Dependence of the chemical shift δ **A**: of the NH of *Z*-isomer (open symbols) and NH of *E*-isomer (closed symbols) proton of compound **5d** on polarity of solvent; **B**: of C=O and C=N moiety of *Z*-isomer (open symbols) and NH of *E*-isomer (closed symbols) of compound **5d** on polarity of solvent.

Fig. 4A). The exceptional chemical shift of hydrazone proton in *E*-isomer indicates to an intensive intramolecular hydrogen bond in nonpolar solvent benzene.

The disruption of the strong intramolecular hydrogen bond N1–H1···O in *E*-isomer has a particular influence on the chemical environment of C atom of the amidrazone moiety, which is detected in ^{13}C NMR for C=N as well. The signal is shifted in dependence of polarity of solvent for about 10 ppm downfield. All the other signals remain unchanged (see Fig. 4B).

Intramolecular hydrogen bonds between NH proton and *ortho*-halogen substituent of appropriate phenyl ring were the only one, which could be detected in solution as well. In Table 5 compounds with *ortho*-substituted aryl moieties are highlighted. Signals in conjunction with amide structure (R^1) are profiled in bold character and with hydrazone moiety (R^2) in italic character. It is observed in ^{1}H NMR spectra that the *ortho*-halogen substituent of the aryl hydrazone structure (R^2) influences the chemical environment of corresponding proton but only in *Z*-isomer. On the other hand, *ortho*-chloro substituent of the arylamide function ($\mathbf{R^1}$) interacts with the amide proton in *Z*- and *E*-isomer as well, but it actually causes an interference with hydrazone proton in *E*-isomers. Even in ^{13}C NMR spectra the chemical shift of the signal of the hydrazone carbon reflects conspicuously the

Table 5. Substitution pattern of amidrazones $R^1NHCOC{=}N(X)NHR^2$ (**5**–**8**) and essential ^1H and ^{13}C NMR data of CONH and C=NNH moiety of *E*- and *Z*-isomers

No.	X	R^1	R^2	^1H NMR				^{13}C NMR			
				CONH		NNH		CO		C=N	
				Z	*E*	*Z*	*E*	*Z*	*E*	*Z*	*E*
5a	$N(CH_3)_2$	Ph	Ph	9.77	10.49	9.52	8.37	161.1	160.7	140.3	150.3
5b	$N(CH_3)_2$	Ph	3-CF_3–C_6H_4	9.96	10.60	9.81	8.56	160.5	160.7	141.5	153.0
5c	$N(CH_3)_2$	Ph	**2-Cl–C_6H_4**	10.00	10.70	**8.63**	8.46	160.1	160.1	**143.4**	150.8
5d	$N(CH_3)_2$	Ph	4-Cl–C_6H_4	9.84	10.55	9.65	8.41	161.0	161.0	140.9	152.2
5e	$N(CH_3)_2$	Ph	4-F–C_6H_4	9.78	10.47	9.56	8.20	160.6	160.4	141.0	151.4
5f	$N(CH_3)_2$	*2-Cl–C_6H_4*	Ph	9.84	*10.20*	9.56	*9.08*	160.2	n.d.	138.5	n.d.
5g	$N(CH_3)_2$	3-Cl–C_6H_4	Ph	9.94	10.70	9.62	8.44	161.2	n.d.	139.7	n.d.
5h	$N(CH_3)_2$	*2-Cl–C_6H_4*	**2-Cl–C_6H_4**	*9.63*	10.43	**8.74**	*9.01*	159.4	160.4	**141.8**	148.5
5i	$N(CH_3)_2$	*2-Cl–C_6H_4*	3-Cl–C_6H_4	9.93	*10.28*	9.63	*8.70*	160.0	n.d.	139.5	n.d.
5j	$N(CH_3)_2$	*2-Cl–C_6H_4*	4-Cl–C_6H_4	9.90	*10.25*	9.52	*8.83*	159.7	n.d.	138.9	n.d.
5k	$N(CH_3)_2$	3-Cl–C_6H_4	**2-Cl–C_6H_4**	10.13	10.83	**8.70**	8.51	160.2	n.d.	**143.5**	n.d.
5l	$N(CH_3)_2$	3-Cl–C_6H_4	3-Cl–C_6H_4	10.06	10.78	9.76	8.47	160.8	161.2	140.7	152.2
5m	$N(CH_3)_2$	4-Cl–C_6H_4	4-Cl–C_6H_4	9.97	10.69	9.70	8.42	160.8	160.9	140.4	151.6
6a	$N[CH_2CH(CH_3)_2]_2$	Ph	3-CF_3–C_6H_4	10.43	11.00	9.08	8.31	161.3	n.d.	141.1	n.d.
6b	$N[CH_2CH(CH_3)_2]_2$	*2-Cl–C_6H_4*	Ph	*9.66*	*9.94*	9.13	*8.91*	160.5	159.8	*138.0*	*140.6*
6c	$N[CH_2CH(CH_3)_2]_2$	4-Cl–C_6H_4	Ph	9.97	10.40	8.98	8.41	161.2	n.d.	139.5	n.d.
7a	$N(CH_2)_5$	Ph	Ph	9.79	10.35	9.05	8.73	161.1	160.7	140.2	148.2
7b	$N(CH_2)_5$	Ph	**2-Cl–C_6H_4**	9.96	10.46	**8.77**	8.81	160.1	160.2	**142.7**	148.8
7c	$N(CH_2)_5$	Ph	**2-F–C_6H_4**	9.93	10.41	**8.50**	8.41	160.0	160.2	**142.3**	150.1
7d	$N(CH_2)_5$	Ph	3-F–C_6H_4	9.88	10.47	9.21	8.67	160.5	160.4	140.7	149.8
7e	$N(CH_2)_5$	3-CF_3–C_6H_4	Ph	10.10	10.68	9.16	8.82	161.4	161.5	139.5	147.5
7f	$N(CH_2)_5$	*2-Cl–C_6H_4*	Ph	*9.52*	*10.00*	9.28	*10.42*	160.4	n.d.	*138.6*	n.d.
7g	$N(CH_2)_5$	3-Cl–C_6H_4	Ph	9.94	10.60	9.12	8.77	161.4	n.d.	139.7	n.d.
8a	$N(CH_2)_2O(CH_2)_2$	3-CF_3–C_6H_4	Ph	10.12	10.72	9.46	9.25	161.4	n.d.	137.7	n.d.
8b	$N(CH_2)_2O(CH_2)_2$	*2-Cl–C_6H_4*	Ph	*9.55*	*10.07*	9.59	*10.53*	160.3	159.5	*136.8*	*144.9*
8c	$N(CH_2)_2O(CH_2)_2$	3-Cl–C_6H_4	Ph	9.97	10.57	9.43	9.22	160.9	n.d.	137.6	n.d.
8d	$N(CH_2)_2O(CH_2)_2$	4-Cl–C_6H_4	Ph	9.94	10.53	9.39	9.14	161.1	n.d.	138.0	n.d.

δ (DMSO-d_6)/ppm; n.d.: not detected.

intramolecular association particularly between compounds **5h**, **6b** and **8b** (last two columns in Table 5).

In UV spectra the absorption with highest wavelength in both *Z*- and *E*-isomers is observed at about 350 nm with remarkably high intensity. This absorption is shifted to higher wavelength in the case of the *E*-isomer, possibly due to the different hydrogen bonding in both isomers, see Figure 5.

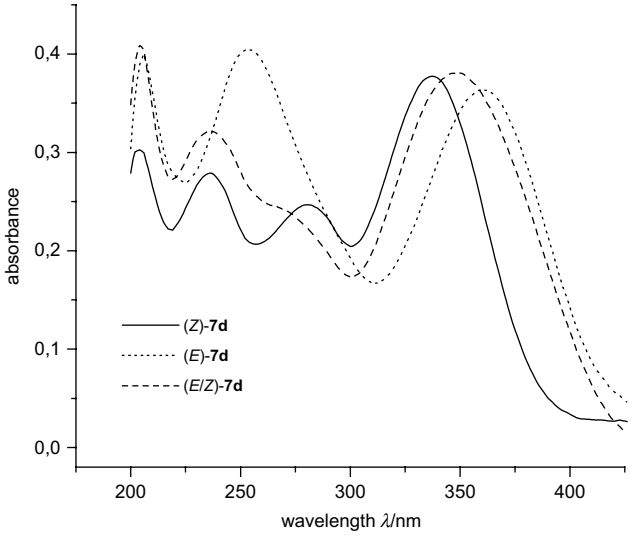


Figure 5. UV spectra of *Z*- and *E*-isomer of compound **7d** as well as of *E*/*Z*-isomer mixture.

In the case of the *E*-configuration, a further absorption band at about 250 nm with high intensity is observed. Due to the altered geometry in the *Z*-configuration, the energy differences between the excited singlet states diverge into two distinct values with higher distance, leading to the two observed absorption peaks at about 280 nm and 235 nm with lower intensity. In the experimentally measurable region up to the shortest wavelength of 200 nm yet another absorption band at about 215 nm is observed. The wavelength seems to be independent of the geometry of the molecule.

In conclusion, *E*-configured arylamidrazones **5**–**8** are formed from *Z*-isomers by rearrangement in solution. Presumably this process occurs whereas preparation and/or recrystallization from polar solvents. Nonpolar solvents like heptane favour the crystallization of *E*-isomers, the configuration of which is stabilized by intramolecular interaction N1–H1···O in such a nonpolar medium.

3. Experimental

3.1. General remarks

The quantum chemical calculations of the interesting compounds were carried out using the GAMESS program.[22] Optimized geometries and total energies of the *E*- and *Z*-isomers were calculated using the RHF/6-31G* ab initio method. The input structures for the individual compounds

were generated on the basis of the determined X-ray structures of **5a** and **7g** using the SYBYL6.9 program.[23]

Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Gemini 2000 and Gemini 200, operating at 399.96 MHz and 199.95 MHz for ^{1}H NMR and at 100.6 MHz and 50.3 MHz for ^{13}C NMR spectra. TMS was used as internal standard and routinely DMSO-d_6 as solvent. Chemical shifts are given in δ units and refer to the centre of the signal. Mass spectra were obtained with an AMD 402 of the firm AMD INTEDRA (70 eV); IR spectra were recorded on a Spectrum BX FT-IR from the firm Perkin Elmer. Probes were prepared in KBr. UV spectra were run on Spekol 1200 from the firm Carl Zeiss Jena GmbH using ethanol for solvent. TLC was routinely carried out with TLC aluminium sheets Silica gel 60 F_{254} of the firm Merck developed in the solvent chloroform/ether (7:3, v/v) and detected with ultraviolet light (254 nm). For separation of *E*/*Z*-isomers of amidrazones TLC sheets were developed in mixture of hexane/ether 7:3.

Crystallographic data (excluding structure factors) for the structures **5a** and **7g** in this paper have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 254724 (**5a**) and CCDC 254724 (**7g**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

3.2. Arylhydrazonoyl chlorides (4)

Compounds were obtained in accordance to Ref. 24 (**4a**), Ref. 21 (**4b**, **4e**, **4h**–**4j**, **4l**, **4m**, **4o** and **4p**), Ref. 25 (**4c** and **4d**), Ref. 1 (**4f** and **4g**) and Ref. 26 (**4q**).

3.2.1. *N*-Phenyl-2-[(4-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride (4k). According to lit.[21] **4k** is obtained from aniline (0.01 mol, 0.93 g) and 2-chloro-*N*-(4-chlorophenyl)-3-oxobutanamide (0.01 mol, 2.5 g) as yellow needles (2.1 g, 67%), mp 209–210 °C (from chloroform/heptane). IR (KBr) ν_{max}/cm^{-1}: 3380m, 3227m (NH ass.), 1865s (C=O, amide). ^{1}H NMR (DMSO-d_6) δ_H: 6.95–7.78 (9H, arom), 10.15 (1H, s, CONH, amide), 10.33 (1H, s, NNH, hydrazone). ^{13}C NMR (DMSO-d_6) δ_C: 114.9–143.0 (12C, arom), 118.0 (CN, hydrazone), 157.5 (CONH, amide); *m*/*z* 307 (M^+, 100%), 127 (100), 92 (55). Anal. Calcd for $C_{14}H_{11}Cl_2N_3O$ (308.2): C 54.6; H 3.6; Cl 23.0; N 13.6. Found: C 54.5; H 3.7; Cl 23.0; N 13.6.

3.2.2. *N*-(4-Chlorophenyl)-2-[(2-chlorophenyl)amino]-2-oxoethanehydrazonoyl chloride (4n). According to lit.[21] **4n** is obtained from 4-chloroaniline (0.01 mol, 1.3 g) and 2-chloro-*N*-(2-chlorophenyl)-3-oxobutanamide (0.01 mol, 2.5 g) (synthesized following lit.[27]) as pale yellow needles (1.2 g, 68%), mp 230–232 °C (from chloroform/ethyl acetate). IR (KBr) ν_{max}/cm^{-1}: 3358m, 3285m (NH ass.), 1793s (C=O, amide); ^{1}H NMR (DMSO-d_6) δ_H: 7.23–7.82 (8H, arom), 9.81 (1H, s, CONH, amide), 10.56 (1H, s, NNH, hydrazone). ^{13}C NMR (DMSO-d_6) δ_C: 116.1–141.6 (12C, arom), 118.1 (CN, hydrazone), 156.8 (CONH, amide). MS *m*/*z* 343 (M^+, 32%), 127 (100). Anal. Calcd for $C_{14}H_{10}Cl_3N_3O$ (342.6): C 49.1; H 2.9; Cl 31.0; N 12.3 Found: C 49.1; H 2.9; Cl 30.8; N 12.2.

3.3. Synthesis of substituted 2-amino-*N*-aryl-2-arylhydrazonoacetamides 5–8 (GP 1)

A solution of arylhydrazonoyl chloride **1** (5 mmol) in about 20 ml dioxane was added dropwise to 10 mmol dimethylamine (5 ml of 2 M solution in tetrahydrofuran), 5 mmol diisobutylamine (0.9 ml) and 5 mmol triethylamine (0.7 ml), 10 mmol piperidine (1.0 ml) or 10 mmol morpholine (0.9 ml), respectively, in a few millilitres of dioxane. After stirring at 40–45 °C for at least 12 h (control of reaction progress by TLC) the mixture was poured into 150 ml cold water. The solid was collected, washed with water, dried and recrystallized from the given solvent. The described *Z*-isomers as well as *E*-isomers are commonly impured with 1–15% of the corresponding isomer. Physical characteristics of prepared compounds are described in Table 6.

3.3.1. 2-Dimethylamino-*N*-phenyl-2-phenylhydrazonoacetamide (5a). The preparation from **4a** (1.4 g, 5 mmol) and dimethylamine following GP 1 gave the crude product **5a** as a mixture of 62% *Z*- and 38% *E*-isomer. Recrystallization from heptane led first to pale yellow crystals of *Z*-isomer (0.5 g, 35% yield) and then to yellow needles as an *E*/*Z*-mixture, which was recrystallized from heptane/chloroform and then from methanol to give yellow crystals as 1:1 mixture of (*Z*)- and (*E*)-**5a** for X-ray structure determination. Crystal structure analysis of **5a**: Crystal data. $C_{32}H_{36}N_8O_2$, M_r=564.69, monoclinic, a=11.770(4), b=15.400(4), c=17.362(6) Å, V=3077(2) Å^3, T=293(2) K, space group $P2_1/c$, Z=4, μ(Mo Kα)=0.080 mm^{-1}, =0.71073 Å, 28,673 reflections collected, 6001 unique (R_{int}=0.0943), which were used in all calculations. Final $wR(F^2)$ was 0.1382 (all data).

3.3.2. 2-Dimethylamino-*N*-phenyl-2-{[3-(trifluoromethyl)phenyl]hydrazono}acetamide (5b). The preparation from **4b** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave the crude product **5b** as a mixture of 84% *Z*- and 16% *E*-isomer. Recrystallization from heptane led to pale yellow needles of *Z*-isomer, which was rapidly transformed to the *E*/*Z*-mixture within one day at room temperature. The isomers could be separated by column chromatography (heptane, heptane/ether). After a fraction with 70% (*E*)-**5b** as yellow oil (0.5 g, 29% yield), fractions with *E*/*Z*-mixture and (*Z*)-**5b** (0.2 g, 12% yield) were obtained.

3.3.3. 2-[2-(Chlorophenyl)hydrazono]-2-dimethylamino-*N*-phenylacetamide (5c). The preparation from **4c** (1.5 g, 5 mmol) and dimethylamine following GP 1 gave from heptane first (*Z*)-**5c** as white needles (0.9 g, 55% yield). The second crystallization fraction gave (*E*)-**5c** as thin yellow needles (0.1 g, 5% yield).

3.3.4. 2-[4-(Chlorophenyl)hydrazono]-2-dimethylamino-*N*-phenylacetamide (5d). The preparation from **4d** (1.5 g, 5 mmol) and dimethylamine following GP 1 gave from heptane first (*Z*)-**5d** as pale yellow crystals (0.3 g, 19% yield). After crystals with *E*/*Z*-mixtures, long yellow needles were obtained as (*E*)-**5d** (0.5 g, 30% yield).

3.3.5. 2-[4-(Fluorophenyl)hydrazono]-2-dimethylamino-*N*-phenylacetamide (5e). The preparation from **4g** (1.5 g, 5 mmol) and dimethylamine following GP 1 gave the crude product **5e** as a mixture of 55% *Z*- and 45% *E*-isomer.

Table 6. Physical characteristics of amidrazones **5–8**

Mp		Anal.		MS	UV (log ε)	IR NH; CO	^{1}H NMR	^{13}C NMR
		C	H					
Calcd for $C_{16}H_{18}N_4O$		68.1	6.4	M, 282				
(*Z*)-**5a**	112–114	68.0	6.5	282 (M^+, 100), 92 (55)	347 (4.23)	3372, 3330, 3296, 3241; 1661, 1648	2.69 (6H, s, $2CH_3$), 6.80–7.75 (10H arom)	40.2 (2C, $2CH_3$), 113.9–144.7 (12C arom)
(*E*)/(*Z*)-**5a** (1:1)	107–109	67.9	6.5	282 (M^+, 100), 161 (30)	348 (4.23)	3372, 3330; 1661, 1648	(*E*): 2.80 (6H, s, $2CH_3$), 6.61–7.70 (10H arom)	(*E*): 38.2 (2C, $2CH_3$), 112.6–147.7 (12C arom)
Calcd for $C_{17}H_{11}F_3N_3O$		58.3	4.9	M, 350				
(*Z*)-**5b**	74–78	58.2	4.9	350 (M^+, 100), 229 (46), 186 (35)	340 (3.96)	3392, 3297; 1663, 1655(sh)	2.71 (6H, s, $2CH_3$), 7.01–7.73 (9H arom)	40.1 (2C, $2CH_3$), 109.7–145.1 (12C arom), 124.5 (q, J=295 Hz, CF_3)
(*E*)-**5b**	64–66	58.1	5.1	350 (M^+, 100), 229 (57), 186 (46)	342 (4.11)	3289; 1667	2.85 (6H, s, $2CH_3$), 6.87–7.69 (9H arom)	37.7 (2C, $2CH_3$), 108.3–148.7 (12C arom)
Calcd for $C_{16}H_{17}ClN_4O$		60.7	5.4	M, 316				
(*Z*)-**5c**	133–135	60.7	5.4	316 (M^+, 100), 195 (40)	335 (4.11)	3289; 1656	2.75 (6H, s, $2CH_3$), 6.84–7.76 (9H arom)	40.1 (2C, $2CH_3$), 115.2–143.4 (12C arom)
(*E*)-**5c**	125–135	60.4	5.4	316 (M^+, 100), 195 (30)	359 (3.87)	3333, 3251; 1653	2.87 (6H, s, $2CH_3$), 6.69–7.73 (9H arom)	38.4 (2C, $2CH_3$), 113.3–142.5 (12C arom)
(*Z*)-**5d**	128–129	60.5	5.3	316 (M^+, 100), 195 (42), 125 (42)	344 (3.95)	3301, 3244; 1654(sh), 1649	2.71 (6H, s, $2CH_3$), 7.04–7.76 (9H arom)	40.2 (2C, $2CH_3$), 115.3–143.7 (12C arom)
(*E*)-**5d**	125–135	60.7	5.3	316 (M^+, 100), 195 (55), 125 (50).	360 (3.96)	3322, 3263; 1654	2.82 (6H, s, $2CH_3$), 6.64–7.71 (9H arom)	38.0 (2C, $2CH_3$), 114.1–152.0 (12C arom)
(*Z*)-**5f**	144–146	60.7	5.4	316 (M^+, 100), 161 (38)	351 (3.77)	3343, 3218; 1669, 1658	2.77 (6H, s, $2CH_3$), 6.84–8.27 (9H arom)	40.2 (2C, $2CH_3$), 113.6–144.2 (12C arom)
(*Z*)-**5g**	118–120	60.6	5.3	316 (M^+, 100), 161 (50)	346 (4.21)	3286; 1654	2.69 (6H, s, $2CH_3$), 6.64–7.94 (9H arom)	40.2 (2C, $2CH_3$), 114.0–144.5 (12C arom)
Calcd for $C_{16}H_{17}FN_4O$		64.0	5.7	M, 300				
(*Z*)-**5e**	107–109	64.1	5.7	300 (M^+, 100), 179 (38)	342 (4.20)	3401(w), 3298, 3267; 1673, 1660	2.69 (6H, s, $2CH_3$), 7.03–7.73 (9H arom)	40.1 (2C, $2CH_3$), 114.6–141.0 (11 C arom), 156.4 (1 C, d, J=235 Hz, arom *C*F)
(*E*)/(*Z*)-**5e** (1:1)	97–100	63.8	5.7	300 (M^+, 100), 179 (38), 109 (37)	347 (4.09)	3374, 3324, 3288; 1661, 1647	(*E*): 2.81 (6H, s, $2CH_3$), 6.91–7.75 (9H arom)	(*E*): 38.1 (2C, $2CH_3$), 113.5–144.7 (11C arom), 155.1 (1 C, d, J=231 Hz, arom *C*F)
Calcd for $C_{16}H_{16}Cl_2N_4O$		54.7	4.6	M, 350				
(*Z*)-**5h**	79–81	54.7	4.5	350 (M^+, 100), 195 (62)	343 (4.10)	3354; 1693	2.78 (6H, s, $2CH_3$), 6.89–8.06 (8H arom)	40.1 (2C, $2CH_3$), 114.6–139.3 (12C arom)
(*E*)-**5h**	103–105	54.5	4.6	350 (M^+, 100), 195 (75)	364 (3.98)	3282; 1685, 1660	2.86 (6H, s, $2CH_3$), 6.70–7.61 (8H arom)	39.1 (2C, $2CH_3$), 114.8–143.9 (12C arom)
(*Z*)-**5i**	127–129	54.4	4.5	350 (M^+, 100), 195 (62), 152 (45)	349 (3.89)	3345, 3242; 1674, 1665(sh)	2.77 (6H, s, $2CH_3$), 6.85–8.19 (8H arom)	40.2 (2C, $2CH_3$), 112.2–145.8 (12C arom)
(*Z*)-**5j**	139–141	54.7	4.6	350 (M^+, 100), 195 (100), 160 (60), 125 (100)	353 (4.23)	3379, 3364, 3247; 1670	2.73 (6H, s, $2CH_3$), 7.12–8.17 (8H arom)	40.2 (2C, $2CH_3$), 114.8–143.0 (12C arom)
(*Z*)-**5k**	147–149	54.7	4.6	350 (M^+, 100), 195 (42)	336 (4.23)	3295, 1659	2.75 (6H, s, $2CH_3$), 6.88–7.93 (8H arom)	40.0 (2C, $2CH_3$), 115.3–142.7 (12C arom)
(*Z*)-**5l**	146–148	54.8	4.5	350 (M^+, 100), 195 (42)	342 (4.33)	3295, 1659	2.69 (6H, s, $2CH_3$), 6.79–7.93 (8H arom)	40.3 (2C, $2CH_3$), 112.3–146.1 (12C arom)
(*E*)-**5l**	107–110	54.6	4.4	350 (M^+, 60), 195 (100), 160 (60), 152 (100), 125 (60)	359 (3.91)	3170; 1652	2.83 (6H, s, $2CH_3$), 6.59–7.91 (8H arom)	37.8 (2C, $2CH_3$), 111.2–149.6 (12C arom)
(*Z*)-**5m**	125–129	54.5	4.8	350 (M^+, 100), 195 (76), 160 (40), 125 (58)	347 (4.18)	3384, 3283; 1665(sh), 1655	2.69 (6H, s, $2CH_3$), 7.22–7.81 (8H arom)	40.2 (2C, $2CH_3$), 115.3–143.4 (12C arom)

Table 6. (*continued*)

	Mp	Anal.		MS	UV (log ε)	IR NH; CO	^{1}H NMR	^{13}C NMR
		C	H					
(*E*)-**5m**	106–112	54.6	4.6	350 (M^+, 100), 195 (85), 160 (52), 125 (79)	355 (4.05)	3412(br), 3300(br), 1654	2.81 (6H, s, $2CH_3$), 6.90–7.72 (8H arom)	38.0 (2C, $2CH_3$), 114.0–146.9 (12C arom)
Calcd for $C_{23}H_{29}F_3N_4O$		63.6	6.7	M, 434				
(*Z*)-**6a**	123–125	63.5	6.7	434 (M^+, 100), 93 (65)	337 (3.93)	3346, 3308; 1660	0.87 (12H, d, J=7 Hz, $4CH_3$), 1.74 (2H, m, 2CH, J=7 Hz), 2.93 (4H, d, $2CH_2$, J=7 Hz), 7.04–7.76 (9H arom)	20.5 (4C, $4CH_3$), 27.3 (2C, 2CH), 58.5 (2C, $2CH_2$), 110.0–145.4 (12C arom), 124.5 (q, CF_3, J=273 Hz)
Calcd for $C_{22}H_{29}ClN_4O$		65.9	7.3	M, 400				
(*Z*)-**6b**	49–51	65.6	7.3	400 (M^+, 100), 308 (30)	348 (3.91)	3368, 3313, 1687, 1677	0.86 (12H, d, J=7 Hz, $4CH_3$), 1.73 (2H, m, 2CH, J=7 Hz), 2.92 (4H, d, $2CH_2$, J=7 Hz), 6.84–8.20 (9H arom)	20.6 (4C, $4CH_3$), 27.2 (2C, 2CH), 58.8 (2C, $2CH_2$), 113.6–143.9 (12C arom)
(*Z*)-**6c**	88–90	65.7	7.2	400 (M^+, 100), 308 (25)	342 (4.24)	3374, 3360, 3305; 1678(sh), 1660	0.87 (12 H, d, J=7 Hz, $4CH_3$), 1.71 (2H, m, 2CH, J=7 Hz), 2.84 (4H, d, $2CH_2$, J=7 Hz), 6.82–7.82 (9H arom)	20.6 (4C, $4CH_3$), 27.2 (2C, 2CH), 59.0 (2C, $2CH_2$), 113.0–143.9 (12C arom)
Calcd for $C_{19}H_{22}N_4O$		70.8	6.9	M, 322				
(*Z*)-**7a**	136–138	70.7	6.9	322 (M^+, 90%), 84 (100)	342 (4.34)	3284; 1654	1.58 (m)[a], 1.67 (m)[b], 2.98 (m)[c], 6.81–7.74 (10H, arom)	23.9[d], 25.2[e], 48.5[f], 114.1–144.3 (12C arom)
(*E*)-**7a**	118–120	70.6	6.8	322 (M^+, 100), 84 (20)	358 (4.17)	3332, 3296; 1651	1.59 (s)[a,b], 3.14 (s)[c], 6.61–7.72 (10H arom)	24.0[d], 24.7[e], 47.6[f], 112.6–147.3 (12C arom)
Calcd for $C_{19}H_{21}ClN_4O$		63.9	5.9	M, 356				
(*Z*)-**7b**	194–196	63.9	5.9	356 (M^+, 90%), 84 (100)	337 (3.97)	3297, 3269, 3247; 1652	1.58 (d, J=5 Hz)[a], 1.65 (s)[b], 3.02 (t, J=5 Hz)[c], 6.88–7.77 (9H arom)	23.7[d], 26.1[e], 48.6[f], 115.1–139.2 (12C arom)
(*E*)-**7b**	>150 (transf.)			356 (M^+, 100), 230 (55), 84 (100)	355 (3.81)	3347, 3326; 1656	1.59[a], 1.64[b], 3.14 (t, J=5 Hz)[c], 6.70–7.73 (9H arom)	23.9[d], 24.5[e], 47.8[f], 113.2–142.2 (12C arom)
(*Z*)-**7f**	133–136	63.8	5.9	356 (M^+, 100), 84 (62)	350 (4.13)	3355, 3245; 1677	1.54 (d, J=5 Hz)[a], 1.67 (d, J 5)[b], 3.02 (t, J=5 Hz)[c], 6.84–8.21 (9H arom)	23.9[d], 25.3[e], 48.6[f], 115.3–145.4 (12C arom)
(*Z*)-**7g**	146–149	63.9	6.0	356 (M^+, 100), 84 (100)	344 (4.13)	3354, 3267; 1667	1.54 (s)[a], 1.68 (s)[b], 2.97 (t, J=5 Hz)[c], 6.81–7.92 (9H arom)	23.9[d], 25.3[e], 48.5[f], 114.2–144.1 (12C arom)
Calcd for $C_{19}H_{21}FN_4O$		67.0	6.2	M, 340				
(*Z*)-**7c**	148–150	67.0	6.2	340 (M^+, 91%), 84 (100)	336 (4.14)	3286; 1656	1.56 (t, J=4 Hz)[a], 1.61 (d, J 5)[b], 3.00 (t, J=5 Hz)[c], 6.84–7.75 (9H arom)	23.8[d], 25.9[e], 48.6[f], 115.0–151.3 (11C arom), 151.8 (d, 1C, J=239 Hz, arom *C*F)
(*Z*)-**7d**	135–137	67.1	6.3	340 (M^+, 75%), 84 (100)	337 (3.93)	3284; 1655	1.54 (d, J=4 Hz)[a], 1.69 (s)[b], 3.00 (t, J=5 Hz)[c], 6.56–7.76 (9H arom)	23.9[d], 25.1[e], 48.5[f], 100.4–140.7 (11C arom), 163.3 (d, 1C, J=241 Hz, arom *C*F)
(*E*)-**7d**	105–108	67.1	6.3	340 (M^+, 85%), 84 (100)	360 (3.95)	3339; 1653	1.58 (s)[a,b], 3.18 (s)[c], 6.35–7.70 (9H arom)	24.0[d], 24.6[e], 47.0[f], 98.6–149.8 (11 C arom), 162.9 (d, 1C, J=239 Hz, arom *C*F)
Calcd for $C_{20}H_{21}F_3N_4O$		61.5	5.4	390				
(*Z*)-**7e**	130–134	61.6	5.4	390 (M^+, 100), 84 (90)	342 (4.07)	3282; 1656	1.55 (s)[a], 1.68 (s)[b], 2.97 (d, J=5 Hz)[c], 6.81–8.04 (9H arom)	24.0[d], 25.3[e], 48.6[f], 114.1–143.9 (11C arom), 124.2 (q, CF_3, J=272 Hz)
Calcd for $C_{19}H_{19}F_3N_4O_2$		58.2	4.9	M, 392				
(*Z*)-**8a**	169–171	58.1	5.0	392 (M^+, 100), 91 (30), 86 (35)	342 (4.16)	3382, 3280; 1676(sh), 1658	3.04 (4H, t, $2NCH_2$, J=4.5 Hz), 3.78 (4H, t, J=4.5 Hz, $2OCH_2$), 6.84–8.22 (9H arom)	47.6 (2C, $2NCH_2$), 66.1 (2C, $2OCH_2$), 115.8–145.4 (11C arom), 125.7 (q, CF_3, J=273 Hz)

(*continued*)

Table 6. (*continued*)

	Mp	Anal.		MS	UV (log ε)	IR NH; CO	^{1}H NMR	^{13}C NMR
		C	H					
Calcd for $C_{18}H_{19}ClN_4O_2$		60.2	5.3	M, 358				
(*Z*)-**8b**	158–161	60.2	5.2	358 (M^+, 100), 91 (45), 86 (51)	349 (4.03)	3362, 3289; 1673	3.08 (4H, t, $2NCH_2$, J=4.5 Hz), 3.78 (4H, t, J=4.5 Hz, $2OCH_2$), 6.86–8.21 (9H arom)	47.6 (2C, $2NCH_2$), 66.1 (2C, $2OCH_2$), 114.0–143.8 (12C arom)
(*E*)-**8b**	139–142	60.3	5.1	358 (M^+, 100), 86 (45)	370 (4.13)	3308, 3246; 1660	3.05 (t, 4H, J=4.5 Hz, $2NCH_2$), 3.77 (t, 4H, J=4.5 Hz, $2OCH_2$), 6.76–8.00 (9H arom)	49.4 (2C, $2NCH_2$), 65.9 (2C, $2OCH_2$), 112.6–139.2 (12C arom)
(*Z*)-**8c**	161–163	60.1	5.4	358 (M^+, 100), 91 (35), 86 (52)	342 (4.11)	3360, 3284; 1665	3.04 (t, 4H, J=4.5 Hz, $2NCH_2$), 3.79 (t, 4H, J=4.5 Hz, $2OCH_2$), 6.83–7.95 (9H arom)	47.5 (2C, $2NCH_2$), 66.0 (2C, $2OCH_2$), 114.2–143.8 (12C arom)
(*Z*)-**8d**	213–215	60.2	5.4	358 (M^+, 100), 86 (45)	342 (3.72)	3281, 3263; 1673(sh), 1652	3.02 (t, 4H, J=4.5 Hz, $2NCH_2$), 3.76, 6.82–7.78 (9H arom)	47.6 (2C, $2NCH_2$), 66.1, 115.7–145.5 (12C arom)

Melting point mp/°C, elemental analysis Anal., mass spectrometry data (MS) *m*/*z* %, UV(EtOH) λ_{max}/nm, IR (KBr) ν_{max}/cm^{-1} and NMR (DMSO-d_6) δ/ppm.

[a] 2H, $NCH_2CH_2CH_2$–.
[b] 4H, $2NCH_2CH_2$–.
[c] 4H, $2NCH_2$–.
[d] 1C, $NCH_2CH_2CH_2$–.
[e] 2C, $2NCH_2CH_2$–.
[f] 2C, $2NCH_2$.

Recrystallization from heptane led first to pale yellow crystals of *Z*-isomer (0.4 g, 27% yield) and then to yellow crystals as 1:1 mixture of (*Z*)- and (*E*)-**5e** (0.9 g, 60% yield).

3.3.6. *N*-(2-Chlorophenyl)-2-dimethylamino-2-phenylhydrazonoacetamide (5f). The preparation from **4i** (1.5 g, 5 mmol) and dimethylamine following GP 1 gave from heptane first (*Z*)-**5f** (0.8 g, 51% yield) as yellow crystals and then an *E*/*Z*-mixture of **5f** (0.3 g, 19% yield).

3.3.7. *N*-(3-Chlorophenyl)-2-dimethylamino-2-phenylhydrazonoacetamide (5g). The preparation from **4j** (1.5 g, 5 mmol) and dimethylamine following GP 1 gave from heptane (*Z*)-**5g** (0.4 g, 25% yield) as pale yellow needles.

3.3.8. *N*-(2-Chlorophenyl)-2-[2-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5h). The preparation from **4l** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave the crude product **5h** as 100% of *Z*-isomer. Recrystallization from heptane led first to pale yellow crystals of (*Z*)-**5h** (0.9 g, 51% yield). The second crystallization fraction gave (*E*)-**5h** as yellow, plate-like crystals (0.1 g, 6% yield).

3.3.9. *N*-(2-Chlorophenyl)-2-[3-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5i). The preparation from **4m** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave from heptane (*Z*)-**5i** (0.8 g, 45% yield) as yellow, short needles.

3.3.10. *N*-(2-Chlorophenyl)-2-[4-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5j). The preparation from **4n** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave from heptane (*Z*)-**5j** as yellow crystals (1.0 g, 57% yield).

3.3.11. *N*-(3-Chlorophenyl)-2-[2-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5k). The preparation from **4o** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave from heptane (*Z*)-**5k** as yellowish-white needles (1.0 g, 57% yield).

3.3.12. *N*-(3-Chlorophenyl)-2-[3-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5l). The preparation from **4p** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave a crude product of a mixture of 97% (*Z*)-**5l** and 3% (*E*)-**5l**. From heptane/dioxane, first (*Z*)-**5l** crystallized as white needles (0.7 g, 40% yield), and then (*E*)-**5l** as a white amorphous solid (0.2 g, 11% yield). (2*E*)-**5l** dissolved in polar solvents with a quiet yellow colour and transformed to an 1:1 mixture of *E*/*Z*-isomers within one week at room temperature.

3.3.13. *N*-(4-Chlorophenyl)-2-[4-(chlorophenyl)hydrazono]-2-dimethylaminoacetamide (5m). The preparation from **4q** (1.7 g, 5 mmol) and dimethylamine following GP 1 gave a crude product of a mixture of 88% (*Z*)-**5m** and 12% (*E*)-**5m**. From heptane, first (*Z*)-**5m** crystallized as yellow crystals (0.4 g, 23% yield), then *E*/*Z*-mixtures (0.6 g, 34% yield) and at least (*E*)-**5m** as fine, dark yellow needles (0.1 g, 6% yield).

3.3.14. 2-Diisobutylamino-*N*-phenyl-2-{[3-(trifluoromethyl)phenyl]hydrazono}acetamide (6a). The preparation

from **4b** (1.7 g, 5 mmol), diisobutylamine and triethylamine following GP 1 gave from heptane (*Z*)-**6a** as pale yellow needles (0.9 g, 41% yield).

3.3.15. *N*-(2-Chlorophenyl)-2-diisobutylamino-2-phenylhydrazonoacetamide (6b). The preparation from **4i** (1.5 g, 5 mmol), diisobutylamine and triethylamine following GP 1 gave a crude product, which did not crystallize after pouring into the water. The oily product was separated by extraction with diethyl ether. The solvent was evaporated and the residue was crystallized from heptane to give (*Z*)-**6b** as pale yellow crystals (0.4 g, 24% yield).

3.3.16. *N*-(4-Chlorophenyl)-2-diisobutylamino-2-phenylhydrazonoacetamide (6c). The preparation from **4k** (1.5 g, 5 mmol), diisobutylamine and triethylamine following GP 1 gave from heptane (*Z*)-**6c** as pale yellow needles (0.9 g, 45% yield).

3.3.17. *N*-Phenyl-2-phenylhydrazono-2-piperidin-1-ylacetamide (7a). The preparation from **4a** (1.4 g, 5 mmol) and piperidine following GP 1 gave the crude product **7a** as a mixture of 90% *Z*- and 10% *E*-isomer. From heptane crystallized first (*Z*)-**7a** as white needles (0.9 g, 56% yield). The second crystallization fraction gave (*E*)-**7a** as thin and long yellow needles (50 mg, 3% yield). Recrystallization of **7a** from heptane/chloroform gave yellow crystals as 1:1 mixture of (*Z*)/(*E*)-**7a**, mp 125–132 °C according to Ref. 6.

3.3.18. 2-[2-(Chlorophenyl)hydrazono]-*N*-phenyl-2-piperidin-1-ylacetamide (7b). The preparation from **4c** (1.5 g, 5 mmol) and piperidine following GP 1 gave the crude product **7b** as a mixture of 80% *Z*- and 20% *E*-isomer. From heptane crystallized first (*Z*)-**7b** as white crystals (1.1 g, 61% yield). The second crystallization fraction gave (*E*)-**7b** as thin yellow needles (0.1 mg, 6% yield).

3.3.19. 2-[2-(Fluorophenyl)hydrazono]-*N*-phenyl-2-piperidin-1-ylacetamide (7c). The preparation from **4e** (1.5 g, 5 mmol) and piperidine following GP 1 gave from heptane (*Z*)-**7c** as whitish fine needles (1.4 g, 72% yield).

3.3.20. 2-[3-(Fluorophenyl)hydrazono]-*N*-phenyl-2-piperidin-1-ylacetamide (7d). The preparation from **4f** (1.5 g, 5 mmol) and piperidine following GP 1 gave from heptane first (*Z*)-**7d** (0.9 g, 53% yield) as pale yellow needles. In a second fraction, a mixture of isomers and at least (*E*)-**7d** crystallized from heptane as thin, yellow needles (85 mg, 5% yield).

3.3.21. 2-Phenylhydrazono-2-(piperidin-1-yl)-*N*-[3-(trifluoromethyl)phenyl]acetamide (7e). The preparation from **4h** (1.5 g, 5 mmol) and piperidine following GP 1 gave from heptane (*Z*)-**7e** as pale yellow needles (1.2 g, 62% yield).

3.3.22. *N*-(2-Chlorophenyl)-2-phenylhydrazono-2-piperidin-1-ylacetamide (7f). The preparation from **4i** (1.5 g, 5 mmol) and piperidine following GP 1 gave the crude product **7f** as a mixture of 97% *Z*- and 3% *E*-isomer. Recrystallization from heptane led to (*Z*)-**7f** as yellow crystals (0.8 g, 45% yield).

3.3.23. *N*-(3-Chlorophenyl)-2-phenylhydrazono-2-piperidin-1-ylacetamide (7g). The preparation from **4j** (1.5 g, 5 mmol) and piperidine following GP 1 gave from heptane (*Z*)-**7g** as yellow crystals (1.0 g, 56% yield). Crystal structure analysis of **7g**: Crystal data. $C_{19}H_{21}ClN_4O$, M=356.85, orthorhombic, a=11.860(1), b=15.138(5), c=20.643(3) Å, V=3706.2(13) Å^3, T=293(2) K, space group *Pcab*, Z=8, μ(Mo Kα)=0.220 mm^{-1}, 4658 reflections collected, 2415 unique (R_{int}=0.0272), which were used in all calculations. Final $wR(F^2)$ was 0.1122 (all data).

3.3.24. 2-(Morpholin-4-yl)-2-phenylhydrazono-*N*-[3-(trifluoromethyl)phenyl]acetamide (8a). The preparation from **4h** (1.4 g, 5 mmol) and morpholine following GP 1 gave from heptane (*Z*)-**8a** as white crystals (1.5 g, 76% yield).

3.3.25. *N*-(2-Chlorophenyl)-2-(morpholin-4-yl)-2-phenylhydrazonoacetamide (8b). The preparation from **4i** (1.5 g, 5 mmol) and morpholine following GP 1 gave from heptane first (*Z*)-**8b** as pale yellow needles (1.2 g, 67% yield). In a second fraction (*E*)-**8b** crystallized from heptane as thin, yellow needles (140 mg, 8% yield).

3.3.26. *N*-(3-Chlorophenyl)-2-(morpholin-4-yl)-2-phenylhydrazonoacetamide (8c). The preparation from **4j** (1.5 g, 5 mmol) and morpholine following GP 1 gave from heptane (2*Z*)-**8c** as yellow crystals (1.4 g, 78% yield).

3.3.27. *N*-(4-Chlorophenyl)-2-(morpholin-4-yl)-2-phenylhydrazonoacetamide (8d). The preparation from **4k** (1.5 g, 5 mmol) and morpholine following GP 1 gave the crude product **8d** as a mixture of 86% *Z*- and 14% *E*-isomer. Recrystallization from heptane/acetone led to (*Z*)-**8d** as pale yellow fine crystals (1.1 g, 61% yield).

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Free radical S_H2' reaction mechanism study by comparing free radical S_H2' reaction with free radical addition reaction

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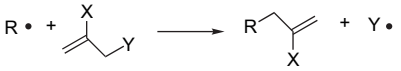
Abstract—It is not clear whether the mechanism of the S_H2' reaction of allyl chloride is concerted or stepwise. The relative rates of the competitive free radical addition to two different double bonds in (2-chloroallyl)-(2-choromethylallyl) ether have been determined. There are two competitive free radical addition reactions, one is free radical S_H2' reaction and the other is free radical addition reaction. The mechanism of the S_H2' reaction is discussed by comparing free radical S_H2' reaction with free radical addition reaction.

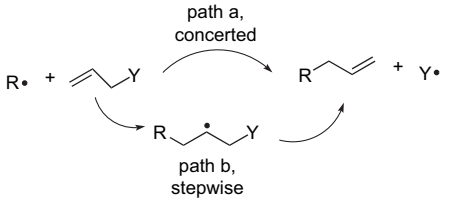
1. Introduction

The addition reactions of alkyl radicals to alkenes have been intensively investigated from both the theoretical and the experimental points of view[1] in the last two decades. The formation of a new carbon–carbon single bond by an S_H2' reaction involving the attack of a carbon radical onto a double bond by displacement of a radical from the allylic position is a useful synthetic process (Eq. 1).

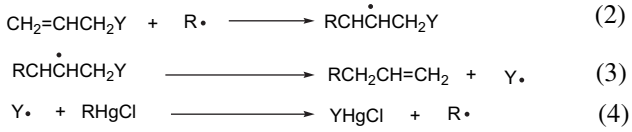


(1)

Barton and Crich indicated[2] that there are two possible mechanisms for the S_H2' process: first, one in which the addition of the radical is concerted with the loss of the leaving radical (Scheme 1, path a); second, a stepwise mechanism in which the adduct radical has a definite existence (Scheme 1, path b). The Migita et al.[3] reported that the reactions of phenyl radical with allylic sulfides and halides yielded allyl benzene as a major product, and the stepwise mechanism was proposed to explain the reactions. Russell et al.[4] indicated that the *t*-butyl radical addition to allyl derivatives proceeded with the stepwise S_H2' reaction mechanism as shown in Scheme 2.



Scheme 1.



Scheme 2.

The alkyl radical adds to the terminal carbon of the double bond to form an intermediate radical, which undergoes fast β-elimination of the leaving group Y• in a chain process, and the radical addition to double bond is a rate determining step (Scheme 2). However, a concerted S_H2' mechanism was suggested by Barton and Crich[2] for the reaction of alkyl radical with allylic derivatives. In our previous work,[5] the mechanism of free radical S_H2' reaction was investigated by the leaving group effect and the secondary α-deuterium kinetic isotope effect. The free radical S_H2' reactions of allyl halides seem to favor the concerted mechanism. Therefore, the controversy that exists in the mechanism of radical S_H2' reaction still remains to be elucidated. The free radical addition reactions, for example: AX+CH_2=CHE→ ACH_2CHEX, have been studied comprehensively. The general mechanism[6] of free radical addition reaction is shown in

Keywords: Free radical S_H2' reaction; *t*-Butyl radical; Radical addition reaction; Concerted mechanism; Stepwise mechanism.
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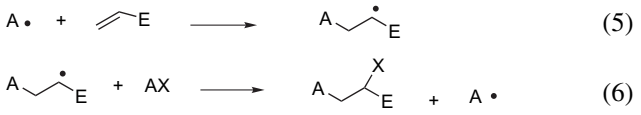
Scheme 3. The mechanism is stepwise and free radical addition to double bond is a rate determining step.

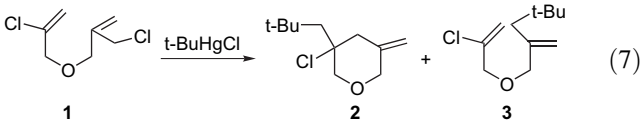


Scheme 3.

In this article, we try to clarify the mechanism of free radical S_H2' reaction by comparing free radical S_H2' reaction with free radical addition reaction.

2. Results and discussion

The reactions of *t*-BuHgCl with (2-chloroallyl)-(2-choromethylallyl) ether (**1**), under photolytic condition, gave the corresponding product (**2**), 3-chloro-3-(2-trimethylpropyl)-5-methylene tetrahydro pyran, the product (**3**), (2-chloroallyl)-(2-trimethylpropyl allyl) ether and a trace amount of unknown (Eq. 7).



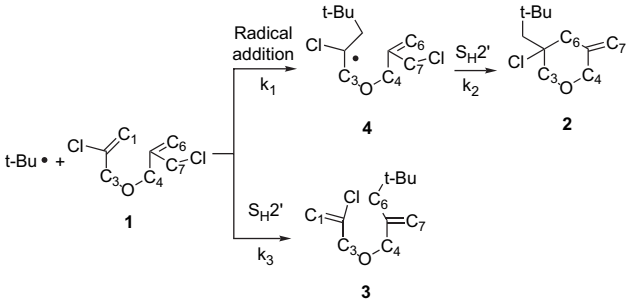
Compound **1** was synthesized by reported method. Compound **1**, *t*-BuHgCl, and internal standard (0.05 mmol of biphenyl) were dissolved in 1 mL of nitrogen-purged dry dimethylsulfoxide and the reaction conditions were shown in Table 1. The solution was added to dry and nitrogen-purged quartz tubes equipped with a rubber septum. The tubes were irradiated at 37±2 °C with a 100 W UV lamp placed about 20 cm from the reaction tubes. Reaction tubes were removed at various times and the yields of the products were determined by gas chromatography. GLC yields were determined by using an internal standard (biphenyl) and were corrected with predetermined response factors. The yields of the products were shown in Table 1. The products were isolated after reaction by flash column chromatography and identified by mass spectroscopy and NMR spectrum.

The possible mechanism of the reaction (Eq. 7) is illustrated as in Scheme 4. The *t*-butyl radical is generated by photolysis of *t*-BuHgCl. The *t*-butyl radical has two possible ways to add to compound **1**, one is the alkyl radical adds to the C_1 carbon of compound **1** to produce the intermediate radical **4** which, then, proceeds the free radical S_H2' reaction to form cyclization product **2**, the other is the alkyl radical adds to the C_6 carbon of compound **1** to progress the S_H2' reaction to generate product **3**. The k_1 and k_3 are the rate constants of *t*-butyl radical addition to the C_1 carbon and C_6 carbon of compound **1**, respectively, and the k_2 is the rate constant of radical **4** addition to C_6 carbon of compound **1**.

Table 1. Reactions of *t*-butyl radical with (2-chloroallyl)-(2-choromethylallyl) ether

Compound **1** (mmol)	*t*-BuHgCl (mmol)	Conditions[a] *hν* (h)	Compound **2**[b] (%)	Compound **3**[b] (%)	k_1/k_3
0.1	0.1	2	19	39	0.49
0.1	0.1	3	21	42	0.50
0.1	0.1	4	23	44	0.52
0.1	0.1	5	21	45	0.47
0.1	0.1	6	21	44	0.48
0.1	0.1	10	21	44	0.48

[a] The mixture in a 5 mm quartz tube was irradiated at 37±2 °C with a 100 W UV lamp ca. 20 cm from the tube. Each reaction was run at least three times. Error is ±4%.
[b] The yield was determined by gas chromatography.

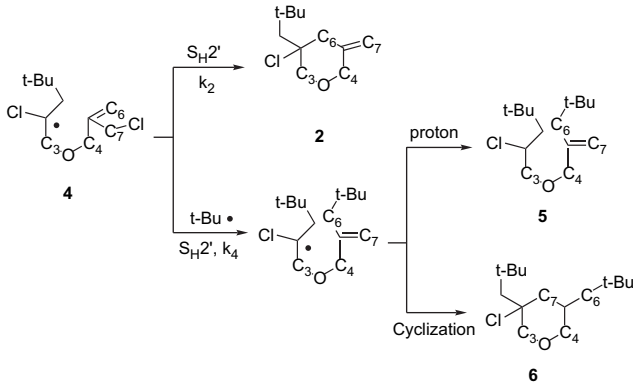


Scheme 4.

The steric effect should be negligible in compound **1** because the positions of these two double bonds attacked by the radical are unsubstituted. Giese[7] has reported that the rate of addition of alkyl radicals to alkenes is controlled mainly by the polar effects of the substituents. Therefore, the substituent effects of the free radical addition reactions must be same for these two double bonds in compound **1**, if the addition reaction rates of these two double bonds would be compared correctly. It should be evident that a number of criteria are important in choosing a model system for evaluating the reaction rates on the radical addition reactions: (1) the steric effect should be negligible, (2) the substituent effect in these two double bonds should be same, (3) the side reaction should be minimized; and the model compound **1** should be readily accessible for these criteria except the substituent effect should be same. Two substituents are on each double bond of compound **1**, one of substituents on each double bond is same and the other is different, therefore, the substituent effects of two double bonds in compound **1** are different. The substituent effects have been studied exclusively on the radical addition reaction and the S_H2' reaction. Wu indicated[8] that the ρ value of free radical S_H2' reaction of *t*-butyl radical addition to 2-substituted allyl chloride is 3.39 in DMSO and the ρ values (3.1–3.8) have been reported by Giese for the addition of cyclohexyl radical to substituted alkene.[9] The ρ values of substituent effects of free radical addition reactions and free radical S_H2' reactions are not exactly same, but they are pretty close. This implies that the substituent effect for both reactions would locate within the same order. We choose the S_H2' reaction of *t*-BuHgCl with compound **1** (Eq. 7) as fulfilling these criteria without excessive experimental difficulty.

The relative rates of free radical addition reaction and free radical S_H2' reaction as given in Table 1, were measured by the relative yields of the two products, compound **2** and compound **3** if the radical addition to C_1C_2 double bond was a rate determining step for the formation of the cyclization product **2**.

From Table 1, it is obvious that k_3 is greater than k_1 or k_2 if either k_1 or k_2 is the rate determining step for the formation of product **2**. If k_2 is the rate determining step for formation of product **2**, then, $k_3>k_2$, it means the rate of *t*-butyl radical addition to C_6 carbon of the intermediate **4**, would be faster than the cyclization rate of the intermediate **4**. The value of k_4 should be close to the value of k_3, therefore, the di-*t*-butyl addition products such as the product **5** or **6**, which are shown in Scheme 5, might be observed in the reaction. However, these products were not found in the photolytic reaction of compound **1** with *t*-BuHgCl. We might guess that k_2 is not the rate determining step for the formation of product **2** and the cyclization rate of the intermediate **4** should be much faster than the addition rate of *t*-butyl radical addition to C_5C_6 double bond, therefore, it seems plausible to assume that k_1 is the rate determining step for the formation of product **2**. It is likely that the relative rates of free radical addition reaction and free radical S_H2' reaction as given in Table 1, were measured by the relative yields of the products **2** and **3**.



Scheme 5.

From Table 1, it is obvious that the rate of free radical addition to C_5C_6 double bond of compound **1** is faster than that to C_1C_2 double bond of compound **1**. It is unlikely that free radical addition rate on C_1C_2 double bond of compound **1** is slower than that on C_5C_6 double bond of compound **1** if it is rational then the assumption of the ρ values of the substituent effect for the radical addition reaction and the radical S_H2' reaction are close. There are two substituents on the C_2 carbon of compound **1**, one is the chloro substituent and the other is the CH_2OR group. However, the C_5 carbon of compound **1** also has two substituents, one is the CH_2Cl group and the other is the CH_2OR' group. The inductive effect of the substituent plays an important role in both the radical addition reaction and the free radical S_H2' reaction.[7,8] The Hammett σ_m constant is an index of the inductive effect of the substituent,[10] then, the Hammett σ_m constant could be used to represent the degree of the inductive effect of the substituent. The Hammett σ_m constants of chloro, CH_2Cl, and CH_2OR are 0.37, 0.11, and 0.06–0.08 (R=Ph, 0.06; R=Me, 0.08), respectively.[11] The σ_m constants of CH_2OR and CH_2OR' should be close because the structure of R and R′ are related. It is likely that the summation of the σ_m constants of two substituents represents the inductive effect of the substituents on the 1,1-dibustituted alkene. It is apparent that the summation of the σ_m constants of the substituents on C_1C_2 double bond is greater than that on C_5C_6 double bond. The inductive effect of the substituents on C_1C_2 double bond would be greater than that on C_5C_6 double bond, thus, we would expect the rate of alkyl radical addition to C_1C_2 double bond should be faster than that to C_5C_6 double bond. It means the yield of product **2** should be larger than that of product **3**. However, this is controversy to the experimental data in Table 1. It is interesting to clarify this controversy. If alkyl radical addition reaction and free radical S_H2' reaction obey the mechanisms, which are stepwise, shown in Scheme 3 and Scheme 2, respectively, the rate of alkyl radical addition to C_1C_2 double bond (k_1) should be faster than that to C_5C_6 double bond (k_3), that means $k_1>k_3$, because of the inductive effect of substituents. It is unlikely that k_1 is greater than k_3, therefore, we might guess that it is not true that the assumption of both of free radical addition reaction and free radical S_H2' reaction might proceed the stepwise mechanisms.

There is no literature to question the mechanism of free radical addition reaction as shown in Scheme 3. Therefore, there is only one possible way left to resolve this controversy, that is, free radical S_H2' reaction might not process the stepwise mechanism. The other possible mechanism for free radical S_H2' reaction is to process the concerted mechanism as shown in Scheme 1 (path a) if free radical S_H2' reaction does not obey the stepwise mechanism.

The controversy described above might be resolved if free radical S_H2' reaction proceed the concerted mechanism. The larger the inductive effect of the substituent is, the faster the radical addition to double bond is. This is not observed for two different double bonds of compound **1**, owing to one of two double bonds (C_5C_6) proceeds free radical S_H2' reaction, which follows the concerted mechanism, thus, the reaction rate not only depends upon the inductive effect of substituents but also depends upon the leaving group effect.[5,12] The activation energy of alkyl radical addition to C_1C_2 double bond of compound **1** might depend upon the energy of breaking π bond of C_1C_2 double bond. However, the activation energy of free radical S_H2' reaction for alkyl radical addition to C_5C_6 double bond of compound **1** might depend upon the energy of breaking π bond of C_5C_6 double bond and forming π bond of C_5C_7 double bond simultaneously. We might guess that the activation energy of free radical S_H2' reaction would diminish, if the S_H2' reaction proceed the concerted mechanism, because the activation energy might compensate from the formation of π bond between the C_5 and C_7 of compound **1** in the transition state. The above discussion might be the reason for the reaction rate of free radical S_H2' reaction is faster than that of free radical addition reaction in compound **1**. Therefore, we might conclude that the S_H2' reaction of allyl chloride would rather proceed the concerted mechanism than the stepwise mechanism.

3. Experimental

3.1. General

Analytical gas chromatography was performed using Perkin–Elmer Autosystem with a DB-5 column (0.25 μM, 60 M) and a flame ionization detector. ^{1}H NMR spectra

were recorded on a 300 MHz VXR FT-NMR spectrometer with tetramethylsilane as the internal standard. GC–MS were recorded on a Quattro GCMS 5022 spectrometer or HP 5890 Series II Gas Chromatograph with HP 5972A MSD. Melting points were determined on a Thomas–Hoover capillary melting point apparatus and were uncorrected.

3.2. Materials

Solvents were purchased from Riedel-de Haen and Mallinckrodt. Dimethylsulfoxide (DMSO) was distilled from calcium hydride and stored over 4 Å molecular sieves under nitrogen; diethyl ether, and tetrahydrofuran were distilled from sodium metal. Other solvents were purchased and used without purification. 3-Chloro-1-methyl-1-propene, 2-chloro-2-propen-1-ol, *t*-butyl chloride, 3-chloro-2-chloromethyl-1-propene, NaH, and biphenyl were purchased from Aldrich Chemical Company. In most cases, the reagents were used without further purification. Organomercurials were synthesized by the standard Grignard procedure.[4]

3.2.1. The preparation of (2-chloroallyl)-(2-choromethylallyl) ether (1). Compound **1** was prepared by dropwise addition of 2-chloro-2-propen-1-ol (8 mL) into NaH (4.8 g, 50%) in dry THF (200 mL) at 0 °C under nitrogen. The solution was refluxed for 2 h after addition was complete. Then, the reaction was cooled to room temperature, 3-chloro-2-chloromethyl-1-propene (11.5 mL) was added to the solution slowly. The reaction was refluxed for 3 h after addition was complete. The saturated NH_4Cl aqueous solution (100 mL) was added to the reaction after the solution was cooled to room temperature. The filtrate was concentrated in vacuum after the solution was filtrated by suction. Ether was added to the concentrated filtrate, then anhydrous $MgSO_4$ was added to remove water. After removal of the ether in vacuo, the product was purified by distillation to give material with bp 52–53 °C/10 mmHg; MS (EI) *m*/*z* (relative intensity) 184 ($M+4^+$, 0.01), 182 ($M+2^+$, 0.04), 180 (M^+, 0.06), 147 (10), 145 (30), 92 (22), 75 (76), 50 (100); ^1H NMR (300 MHz, $CDCl_3$): δ 4.03 (s, 2H), 4.10 (s, 4H), 5.26 (s, 1H), 5.33 (s, 1H), 5.36 (s, 1H), 5.48 (s, 1H).

3.2.2. General procedure for competitive photostimulated reactions of compound 1 with *t*-butylmercury chloride.[8] Compound **1**, *t*-BuHgCl, and internal standard (0.05 mmol of biphenyl) were dissolved in 1 mL of nitrogen-purged dry dimethylsulfoxide and the reaction conditions were shown in Table 1. The solution was added to dry and nitrogen-purged quartz tubes equipped with a rubber septum. The tubes were irradiated at 37±2 °C with a 100 W UV lamp placed about 20 cm from the reaction tubes. Reaction tubes were removed at various times and the yields of the products were determined by gas chromatography. GLC yields were determined by using an internal standard (biphenyl) and were corrected with predetermined response factors. The yields of the products were shown in Table 1. The products were isolated after reaction by flash column chromatography and identified by mass spectroscopy and NMR spectrum. The mass spectroscopy and NMR spectrum of 3-chloro-3-(2-trimethylpropyl)-5-methylene tetrahydro pyran (product **2**) were shown as following: MS (EI) *m*/*z* (relative intensity) 202 (M^+, 0.5), 167 (13), 116 (11), 79 (14), 57 (100); ^1H NMR (300 MHz, $CDCl_3$): δ 1.06 (s, 9H), 1.81 (d, 1H), 1.83 (d, 1H), 2.70 (s, 2H), 3.75 (s, 2H), 4.04 (d, 1H), 4.11 (d, 1H), 4.87 (d, J=0.6 Hz, 1H), 4.96 (d, J=0.6 Hz, 1H); ^{13}C NMR (75 MHz,$CDCl_3$) δ 29.69, 31.62, 32.19, 47.96, 50.90, 71.93, 76.53, 112.56, 139.94. The mass spectroscopy and NMR spectrum of (2-chloroallyl)-(2-trimethylpropyl allyl) ether (product **3**) were shown as following: MS (EI) *m*/*z* (relative intensity) 202 (M^+, 1.5), 167 (6), 110 (10), 57 (100); ^1H NMR (300 MHz, $CDCl_3$): 0.92 (s, 9H), 1.96 (s, 2H), 3.96 (s, 2H), 4.02 (s, 2H), 4.93 (s, 1H), 5.18 (s, 1H), 5.36 (s, 1H), 5.48 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.84, 31.36, 46.25, 72.16, 74.29, 113.16, 115.27, 138.28, 143.27.

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Fluorescent imidazolium receptors for the recognition of pyrophosphate

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Abstract—Anthracene and binaphthyl derivatives bearing two imidazolium rings, which strongly bind anions and are particularly selective for pyrophosphate, are examined using fluorescence, ^{1}H NMR analysis, and density functional calculations.

1. Introduction

Anions play an important role in a wide range of chemical and biological processes, and numerous efforts have been devoted to the development of abiotic receptors for anionic species.[1] Sensors based on anion-induced changes in fluorescence appear to be particularly attractive due to the simplicity and high detection limit of fluorescence.[1f,2] Particularly, pyrophosphate can be a biologically important target since it is the product of ATP hydrolysis under cellular conditions.[3] However, there have been only a few reports regarding pyrophosphate selective receptors using the fluorescent changes as the means of detection.[4]

In contrast to the well-known type of hydrogen bonding for the anion binding such as amide, pyrrole, urea, etc., various types of receptors containing imidazolium moieties,[5] such as the benzene-based tripodal imidazolium receptors,[6] imidazolium cyclophanes,[7] calix[*n*]imidazolium,[8] imidazolium anthracenes,[9] imidazolium calix[4]arene,[10] imidazolium cavitand,[11] and imidazolium polythiophene[12] have been reported. Especially, we have recently reported a fluorescent anthracene derivative bearing two imidazolium moieties on its 1,8-positions (**1**) (Fig. 1), which shows selective binding for $H_2PO_4^-$ over other anions when the anions are monitored individually.[9b] We have further demonstrated that the selectivity of these imidazolium receptors against anions can be controlled by the topology of the binding site (e.g., enhancement of rigidity).[9c] Compared to the host **1**, the more rigidity in host **2** enhances the binding selectivity for $H_2PO_4^-$ over F^-.[9c] In both cases, anthracene being fluorophore has the advantage of being considered as rigid templates in terms of sensing anions by the change in the fluorophore intensity due to photo-induced electron transfer (PET) mechanism.

In an effort to understand the conceptual design of this class of anion sensors, we have further synthesized two new fluorescent chemosensors by the diversification of the frame and investigated more in details for its anion binding properties. Herein, we report two new fluorescent anion receptors (**3** and **4**) bearing two imidazolium groups at the 9,10-positions of anthracene and 2,2′-positions of binaphthyl ring, respectively. The crystal structure of **3** is also reported. The binding properties of these new host systems toward various anions including $HP_2O_7^{3-}$ and $H_2PO_4^-$ were examined using fluorescence. Two known systems (**1** and **2**) were reinvestigated for the binding affinity toward pyrophosphate. We also carried out theoretical investigation in order to understand the binding mode of the anions with these receptors. Host (*S*)-**4** shows a unique selectivity for $HP_2O_7^{3-}$, which is simply induced from two imidazolium groups immobilized on a binaphthyl moiety. Furthermore, the binding property of hosts **3** and **4** toward various anions was compared with that of hosts **1** and **2**. We notice that **2** has the highest binding affinity and selectivity toward $HP_2O_7^{3-}$ via ion-pairing interaction mode against the conventional ionic–hydrogen bonding of anions with the imidazolium based receptors. Finally, we briefly describe the relationship between the receptor structure and anion binding strength.

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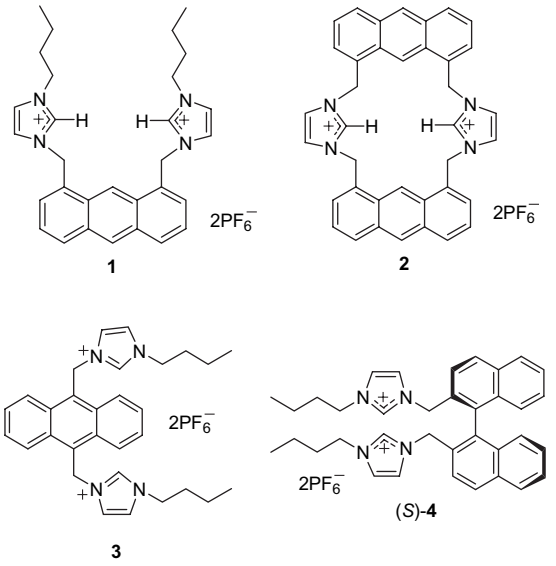
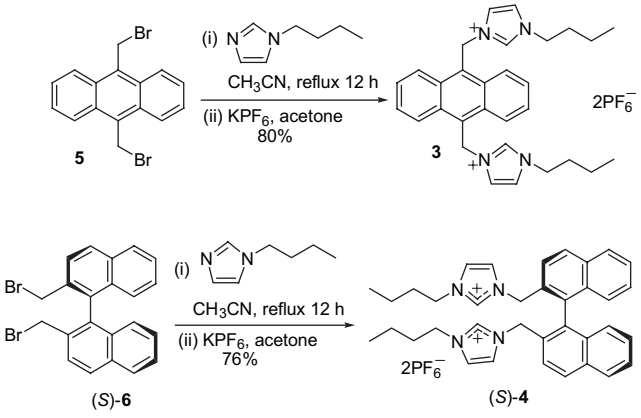


Figure 1. Structures of fluorescent imidazolium receptors.

2. Results and discussion

The synthetic procedures of compounds **3** and **4** are summarized in Scheme 1. Compounds **3** and **4** were synthesized by the reactions of 9,10-bis(bromomethyl)anthracene **5**[4c] and (*S*)-(-)2,2′-bis(bromomethyl)-1,1′-binaphthyl **6**[12] with 1-butylimidazole, respectively, in CH_3CN. The solvent was evaporated to dryness; 10 mL of acetone was added to the residue and stirred for 20 min at room temperature, followed by anion exchange with KPF_6. After another 24 h stirring at room temperature, the reaction mixture was filtered and the filtrate was evaporated. To the oily crude product, about 5 mL of ethyl acetate was added and precipitation occurred. The precipitate was then filtered and washed with CH_2Cl_2 to give analytically pure product.



Scheme 1. Synthesis of hosts **3** and **4**.

The X-ray crystal structural analysis of $\mathbf{3\cdot 2[PF_6]^-}$ revealed a 'trans' conformation of two butyl imidazolium groups on either side of anthracene moiety with C_{2v} inversion symmetry. The positively charged $(C–H)^+$ imidazolium groups point individually toward the counter anions (PF_6^-) (Fig. 2). Selected hydrogen interionic distances are d(H1···F4)=2.623 Å and d(H1···F3)=2.802 Å.

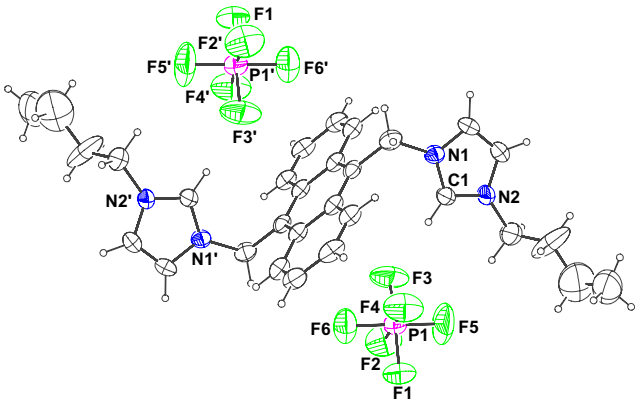


Figure 2. Crystal structure of $\mathbf{3\cdot 2(PF_6^-)}$ (thermal ellipsoids set at 30% probability). Selected interionic distances: H1–F4=2.623 Å, H1–F3=2.802 Å.

The fluorescence emission changes of **3** upon the addition of HSO_4^-, $CH_3CO_2^-$, I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$ are illustrated in Figure 3. Among the anions examined, compound **3** displays strong fluorescent quenching effects with $H_2PO_4^-$ and $HP_2O_7^{3-}$. From the fluorescence titration experiments, the association constants for $HP_2O_7^{3-}$ (Fig. 4), $H_2PO_4^-$, $CH_3CO_2^-$, Br^-, and I^- are observed to be 3.58×10^6, 6.31×10^5, 7.30×10^3, 2.87×10^3, and 1.09×10^3 M^{-1} (errors≤10%), respectively.[14] As shown in Job's plot (Fig. 5), host **3** shows 1/1 binding with $HP_2O_7^{3-}$ in acetonitrile. The change in Gibbs free energy for Br^- as determined by the ^1H NMR titration is 4.1 kcal/mol, which is in good agreement with the fluorescence titration (4.7 kcal/mol). Host **3** shows selective binding with $HP_2O_7^{3-}$ and $H_2PO_4^-$ ions over $CH_3CO_2^-$, F^-, Cl^-, and Br^- ions (Table 1). We observed the ^1H NMR spectral change upon the addition of the anion as tetrabutylammonium salts in acetonitrile-d_3. Upon the addition of 1 equiv of Cl^-, Br^-, I^-, and HSO_4^- to host **3**, downfield shifts ($\Delta\delta\cong$1.38, 1.12, 0.33, and 0.16, respectively) were observed for the C(2) proton of imidazolium moieties, clearly suggesting **3**·anion complexation by $(C–H)^+$–anion ionic hydrogen bonds. However, in acetonitrile-d_3, addition of F^- or $H_2PO_4^-$ to host **3** resulted in a precipitate.

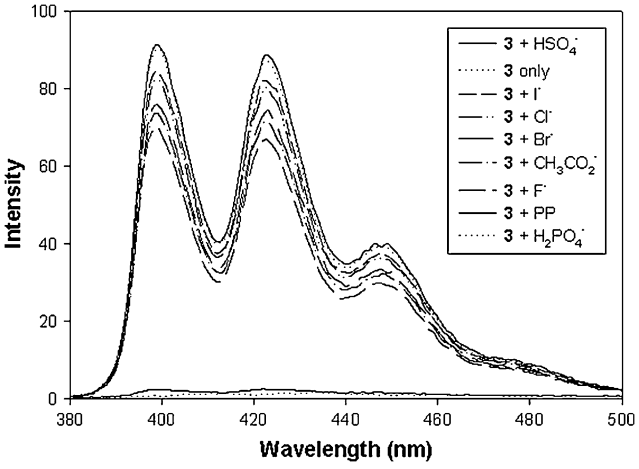


Figure 3. Fluorescent emission changes of **3** (6 μM) upon the addition of tetrabutylammonium salt of HSO_4^-, $CH_3CO_2^-$, I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$ (10 equiv) in acetonitrile (excitation at 365 nm) (excitation and emission slit: 3 nm).

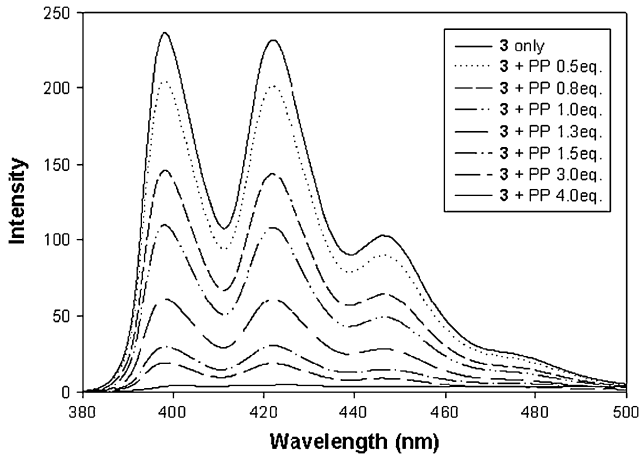


Figure 4. Fluorescent titrations of compound **3** (1 μM) with tris(tetrabutylammonium) hydrogenpyrophosphate in acetonitrile (excitation at 365 nm) (excitation and emission slit: 5 nm).

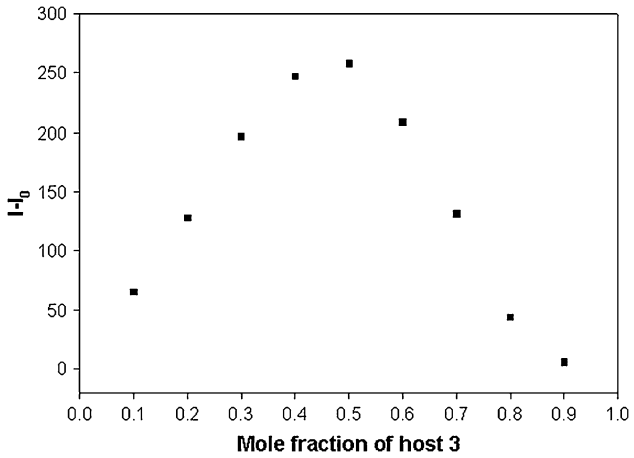


Figure 5. Job's plot of compound **3** (1 μM) with tris(tetrabutylammonium) hydrogenpyrophosphate in acetonitrile using its fluorescent changes (excitation at 365 nm and emission at 422 nm) (excitation and emission slit: 5 nm).

There are quite a few papers regarding fluorescent chemosensors for anions bearing benzylic amine[1f,4g] or urea groups,[1f,2,4a,c] which are based on photo-induced electron transfer (PET) mechanism. However, only a few fluorescent signaling systems bearing imidazolium groups for anions have been reported.[9b,c,11b,15] Our anthracene and binaphthalene based receptors (**1**–**4**) should in principle show also ideal PET behavior upon anion recognition. As shown in Figure 3, $H_2PO_4^-$ and $HP_2O_7^{3-}$ quenched the emission effectively (~95%); on the other hand, no other spectral changes were observed in the emission spectra, i.e., there was no evidence of either exciplex or excimer emission. Furthermore, the changes in the absorption spectra of anthracene moiety were negligible. Since the binding sites of these receptors are separated from the fluorophore via methylene spacer, the observations are consistent with the typical PET behavior.

Figure 6 shows fluorescent emission changes of **4** (6 μM) upon the addition of tetrabutylammonium salt of HSO_4^-, $CH_3CO_2^-$, I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and $HP_2O_7^{3-}$ (10 equiv) in acetonitrile, while Figure 7 shows the fluorescence titration experiments of host **4** with $HP_2O_7^{3-}$. As shown in Table 1, from the fluorescence titration, the association constants for $HP_2O_7^{3-}$, $H_2PO_4^-$, $CH_3CO_2^-$, F^-, Cl^-, Br^-, and I^- are observed to be 6.76×10^6, 4.21×10^5, 1.26×10^5, 4.09×10^5, 2.78×10^3, 1.87×10^3, and 1.14×10^3 M^{-1} (errors≤10%), respectively.[13] The selectivity for $HP_2O_7^{3-}$ is about 12 times greater than $H_2PO_4^-$ and F^-.

Among the series of hosts (**1**–**4**) examined, a dimer host (**2**) displays a largest binding constant with $HP_2O_7^{3-}$ (Fig. 8), which indicates that the preorganized rigid binding pocket may play an important role in the binding with $HP_2O_7^{3-}$.

Table 1. Calculated interaction energies and experimental free energy changes for host–anion complexes in kcal/mol[a]

Host	Anion	K_a (M^{-1})[a]	$-\Delta G_{expt}$	$-\Delta E^{gas}_{calcd}$	$-\Delta E^{MeCN}_{calcd}$	$-\Delta G^{scaled}$
1	$HP_2PO_7^{3-}$	5.43×10^6	9.18	482.11	15.44	10.04
	$H_2PO_4^-$	~1.30×10^6	~8.34	165.50	13.45	8.74
	Cl^-	7900	5.31	—	—	—
	Br^-	4500	4.98	—	—	—
2	$HP_2PO_7^{3-}$	~1.01×10^8	~10.91	484.50	17.60 (11.53)	11.44 (7.49)
	$H_2PO_4^-$	~1.30×10^6	~8.34	169.49	12.76	8.29
	F^-	340,000	7.54	179.71	11.44	7.43
	Cl^-	2000	4.49	—	—	—
	Br^-	780	3.94	—	—	—
3	$HP_2PO_7^{3-}$	3.58×10^6	8.93	469.36	11.06	7.19
	$H_2PO_4^-$	631,000	7.91	164.59	10.57	6.87
	CH_3COO^-	7300	5.27	167.87	9.46	6.15
	Br^-	2870	4.71	—	—	—
4	$HP_2PO_7^{3-}$	6.76×10^6	9.31	471.90	15.81	9.48
	$H_2PO_4^-$	421,000	7.67	155.50	13.04	7.82
	CH_3COO^-	126,000	6.95	163.46	11.39	6.84
	F^-	409,000	7.65	173.49	12.04	7.23
	Cl^-	2780	4.69	—	—	—
	Br^-	1870	4.46	—	—	—

[a] The association constants K_a (M^{-1}) were measured using the fluorescence titration. ΔG_{expt} are the changes in Gibbs' free energy in acetonitrile solution measured by fluorescence titration. Anions used are in the form of tetrabutylammonium salts. ΔE^{gas}_{calcd} is the interaction energy in the gas phase at the B3LYP/6-31(+)G* level of theory. $\Delta E^{soln}_{calcd}=\Delta E^{soln}_{H-anion}-\Delta E^{soln}_{soln-anion}$, where $\Delta E^{soln}_{H-anion}$ is the interaction energy of the H–anion complex (H=**1**–**4**) in acetonitrile solution based on isodensity surface polarized continuum model (IPCM), $\Delta E^{soln}_{soln-anion}$ is the interaction energy of the anion with solvent molecules in the first solvation shell of an anion. The free energy change (ΔG_{scaled}) was approximately obtained by scaling (65%) the internal energy change to fit to the experimental value.

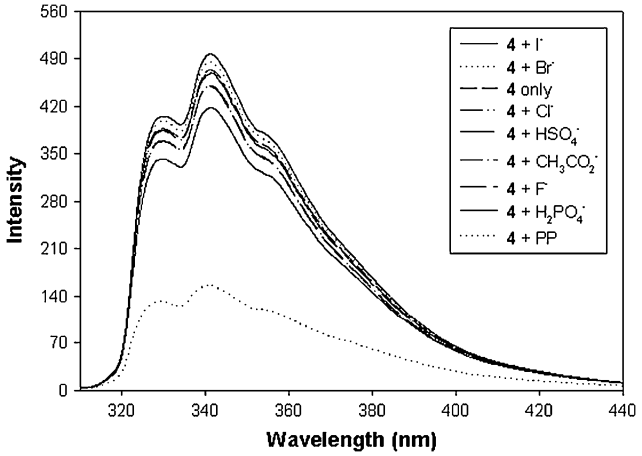


Figure 6. Fluorescent emission changes of **4** (6 μM) upon the addition of tetrabutylammonium salt of HSO_4^-, $CH_3CO_2^-$, I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and hydrogenpyrophosphate (10 equiv) in acetonitrile (excitation at 310 nm) (excitation and emission slit: 3 nm).

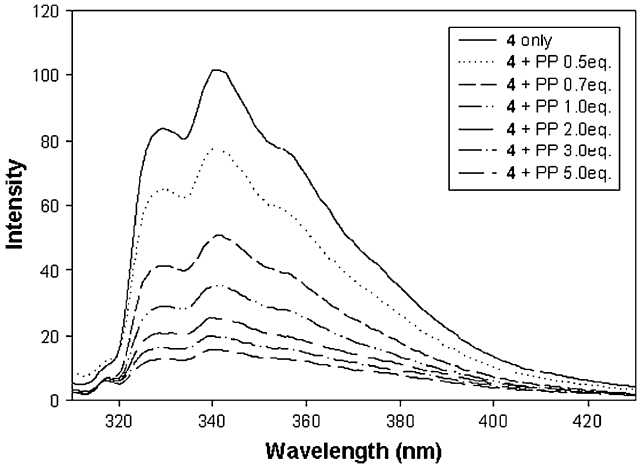


Figure 7. Fluorescent titrations of compound **4** (1 μM) with tris(tetrabutylammonium) hydrogenpyrophosphate in acetonitrile (excitation at 310 nm) (excitation and emission slit: 3 nm).

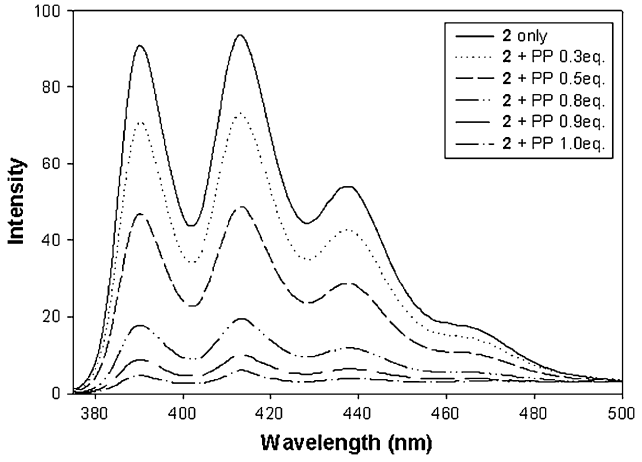


Figure 8. Fluorescent titrations of compound **2** (1 μM) with tris(tetrabutylammonium) hydrogenpyrophosphate in acetonitrile (excitation at 365 nm) (excitation and emission slit: 3 nm).

The binding constants of **1**–**4** with $HP_2O_7^{3-}$ are in the order of **2**>**4**≅**1**>**3**, which is consistent with our assumption.

The competitive binding studies of hosts **2** and **4** with respect to $HP_2O_7^{3-}$ using fluorescent changes clearly show that host **2** binds more tightly with $HP_2O_7^{3-}$ than **4** does. As shown in Figure 9, the fluorescent intensity of host **4** was almost recovered when host **2** was added to the solution of host **4** and $HP_2O_7^{3-}$, and the fluorescent intensity of host **2** was quenched quite significantly.

From ^{1}H NMR it is observed that upon the addition of $HP_2O_7^{3-}$ (0.5 equiv) to the solution of **4** in acetonitrile, both imidazolium C-2 hydrogen peaks (8.53 ppm) moved to 9.66 ppm with severe broadness. And they disappear even at the low concentration of guest (1 equiv) possibly due to the transfer of hydrogen atom from the imidazolium moieties to $HP_2O_7^{3-}$ (Fig. 10). Also, one of the benzyl hydrogens displays large downfield shift (~1 ppm) when $HP_2O_7^{3-}$ was added. On the contrary, imidazolium C-2 hydrogens of host **4** display only downfield shifts (~1 ppm) upon the addition of $H_2PO_4^-$ and one of the benzyl hydrogens displays less downfield shift (<0.5 ppm) compared to that with $HP_2O_7^{3-}$ (Fig. 11). Similar proton transfer was also observed in ^{1}H NMR spectra of host **3** when $HP_2O_7^{3-}$ was added in DMSO-d_6 at room temperature. Similar broadness of the imidazolium C-2 hydrogens as well as a downfield shift (9.09–9.54 ppm) of these protons was observed, while there was only small downfield (~0.3 ppm; 6.56–6.86 ppm) in the benzyl protons.

The thermodynamic origin of the cooperativity of ion-pairing in molecular recognition was investigated with the positively charged anion receptors containing ammonium groups.[16] On the other hand, imidazolium based receptors have strong tendency to form ionic hydrogen bonding with anions, which is explained by the ^{1}H NMR chemical shift of the imidazolium C-2 hydrogen. However, the observation of no chemical shift between some of the receptors studied here upon the addition of $H_2PO_4^-$ and $HP_2O_7^{3-}$ has questioned about the nature of interaction between host and guest. Therefore, the theoretical investigation[17] for the most stable conformer of host–guest complex is essential in order to

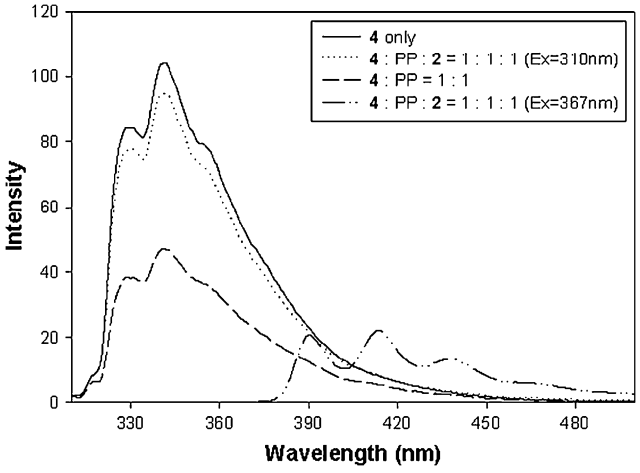


Figure 9. Competitive binding studies of **2** (1 μM) and **4** (1 μM) with $HP_2O_7^{3-}$ (1 equiv) in acetonitrile (excitation at 310 or 367 nm) (excitation and emission slit: 3 nm).

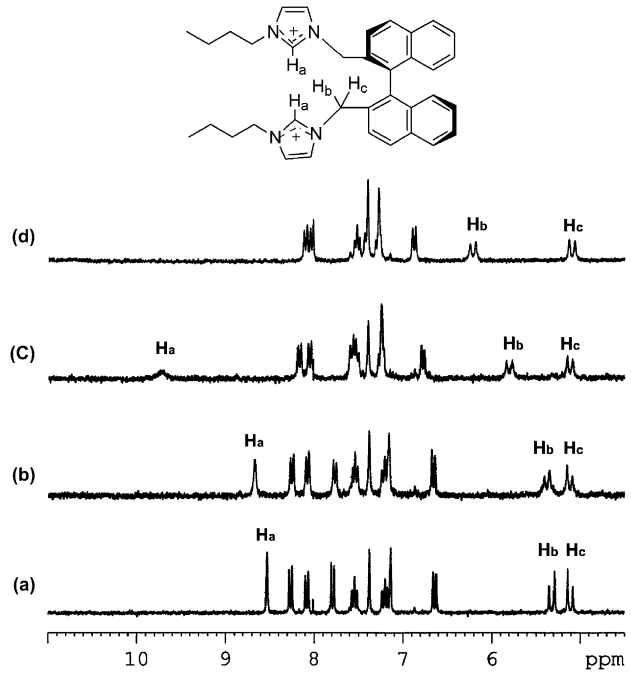


Figure 10. Partial ^{1}H NMR (250 MHz) of **4** (2 mM) in DMSO-d_6. (a) Compound **4** only; (b) **4**+0.2 equiv of tris(tetrabutylammonium) hydrogenpyrophosphate; (c) **4**+0.5 equiv of tris(tetrabutylammonium) hydrogenpyrophosphate; (d) **4**+1 equiv of tris(tetrabutylammonium) hydrogenpyrophosphate.

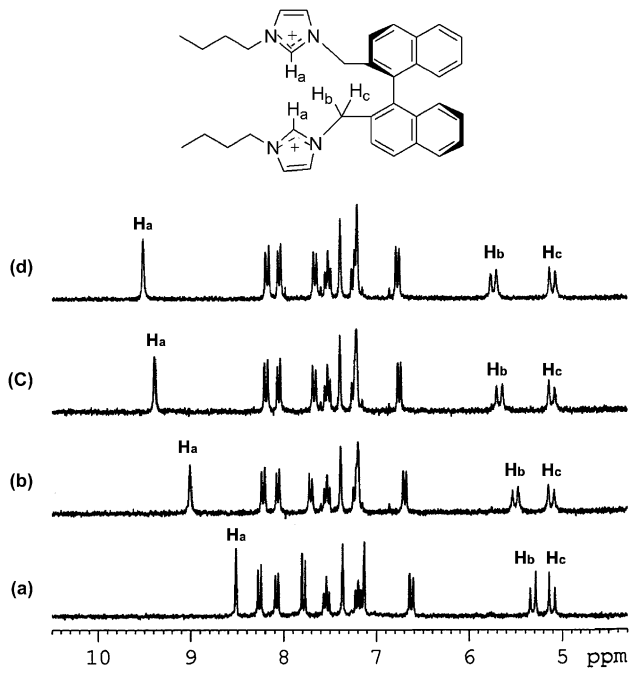


Figure 11. Partial ^{1}H NMR (250 MHz) of **4** (2 mM) in DMSO-d_6. (a) Compound **4** only; (b) **4**+1.5 equiv of tetrabutylammonium dihydrogenphosphate; (c) **4**+3 equiv of tetrabutylammonium dihydrogenphosphate; (d) **4**+5 equiv of tetrabutylammonium dihydrogenphosphate.

understand the nature of binding interaction. At the optimized geometries of **3** and **4** with $HP_2O_7^{3-}$ we note that one of the imidazolium C-2 hydrogen has been completely transferred to the $HP_2O_7^{3-}$ (Fig. 12) as observed in ^{1}H NMR titration. In the optimized geometry of **1** with $HP_2O_7^{3-}$, we do not

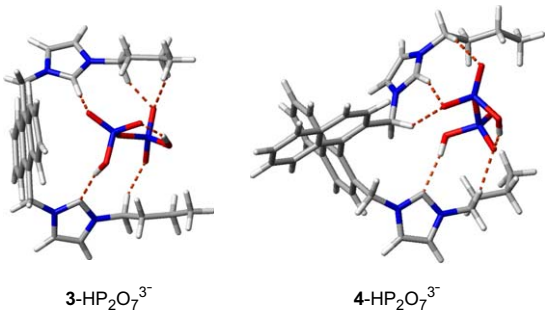


Figure 12. Optimized geometry of (a) **3**·$HP_2O_7^{3-}$ and (b) **4**·$HP_2O_7^{3-}$ complexes. Dotted lines show distances less than 2.5 Å.

see any proton transfer unlike the cases of **3** and **4** with $HP_2O_7^{3-}$. In a while, the optimized geometry of **2** with $HP_2O_7^{3-}$ shows two distinct modes of interactions between host and guest. In one mode one of the imidazolium C-2 hydrogen has been completely transferred to $HP_2O_7^{3-}$. In the other mode the interaction between **2** and $HP_2O_7^{3-}$ surprised us as it forms a complex where the major interaction between host and guest is the ion-pair interaction, thereby the orientation of the oxygen atoms of $HP_2O_7^{3-}$ is not properly angled for the maximal H-bonding with the imidazolium C-2 hydrogen atoms. Both the bonding modes show nearly the same binding energy in the gas phase, which is higher than other anions by at least ~300 kcal/mol. However, in acetonitrile the ion-pair complex conformer is found to be 6 kcal/mol more stable than the complex formed by proton transfer. Similarly, the most stable conformer for **1**–$HP_2O_7^{3-}$ is the ion-pair complex. The ^{1}H NMR titration of **1** and **2** with $HP_2O_7^{3-}$ in DMSO shows that there is no chemical shift of imidazolium C-2 hydrogen at the molar ratio of 0.1–0.3 equiv of $HP_2O_7^{3-}$; the solution starts precipitating upon the addition of ~0.5 equiv of $HP_2O_7^{3-}$. This experimental finding also supports our prediction of ion-pair interaction mode between **1/2** and $HP_2O_7^{3-}$.

Table 1 illustrates the ab initio calculation results for host–anion complexes. In the gas phase, the binding energy of host **3** with $HP_2O_7^{3-}$ is much larger than other anions by at least ~300 kcal/mol. Since ionic hydrogen bond strength is dependent on solvent polarity and interaction of the anion with the solvent molecules, the binding energies are much lowered in polar solvents.[18] Therefore, in acetonitrile, the binding energy gain of host **3** in favor of $HP_2O_7^{3-}$ is 0.3 and 1.0 kcal/mol for $H_2PO_4^-$ and $CH_3CO_2^-$, respectively. The binding energies of **4** with $HP_2O_7^{3-}$ in the gas phase are larger than that of $H_2PO_4^-$, CH_3COO^-, and F^- by 316, 308, and 298 kcal/mol, respectively (Table 1). Therefore, in acetonitrile, the binding energy gain of host **4** is in favor of $HP_2O_7^{3-}$ over $H_2PO_4^-$, $CH_3CO_2^-$, and F^- by 1.7, 2.6, and 2.3 kcal/mol, respectively.

Meanwhile, the binding energies in acetonitrile of host **1** and **2** with $HP_2O_7^{3-}$ in the gas phase were predicted to be at least ~300 kcal/mol more than other anions, whereas in acetonitrile the binding energy **1/2** with $HP_2O_7^{3-}$ is larger than that of $H_2PO_4^-$ by 1.3/3.1 kcal/mol.

The average Mulliken atomic charges (B3LYP/6-31G*) on the oxygen atoms of $HP_2O_7^{3-}$ is −0.79. The same for $H_2PO_4^-$ and $CH_3CO_2^-$ are −0.67 and −0.64, respectively.

Just by considering the columbic interaction between the cationic divalent receptors (**1**–**4**) and non-spherical anions the trivalent anionic species $HP_2O_7^{3-}$ will be more strongly interacting than the monovalent anionic species ($H_2PO_4^-$ and $CH_3CO_2^-$). The binding affinity of $H_2PO_4^-$ is expected to be higher than that of $CH_3CO_2^-$. All the receptors (**1**–**4**) obey the same trends. On the other hand, the open form of the receptors (**1**, **3**, and **4**) has lower binding affinity for $HP_2O_7^{3-}$ than the close form (**2**) despite the fact that all are divalent cationic receptors. The most stable conformers of **1** and **4** have two imidazolium arms in the form of tweezers, meanwhile **3**, in trans form (as in the crystal structure, Fig. 2). Therefore, in order to form the stable complex with anions, it needs to rearrange the binding arms at the cost of the entropy energy. Meanwhile, the energy lost due to entropy will be minimal in the case of **2** as it has rigid/pre-organized form of the binding arms. The combined effect of rigidity and ion-pair interactions leads **2** to have stronger binding affinity toward $HP_2O_7^{3-}$.

From the above experimental and theoretical investigations, we notice that all the dipodal receptors studied have more or at least equal binding affinity toward $HP_2O_7^{3-}$ or $H_2PO_4^-$ against other anions. This suggests that this class of imidazolium dipodal receptors shows strong binding with the V-shaped and tetrahedral shaped anions, which prefers more directed H-bonding interaction. Anthracene was found to be the most appropriate size of the rigid frame in our model system for the maximal interaction between host and $HP_2O_7^{3-}$ (Fig. 13).

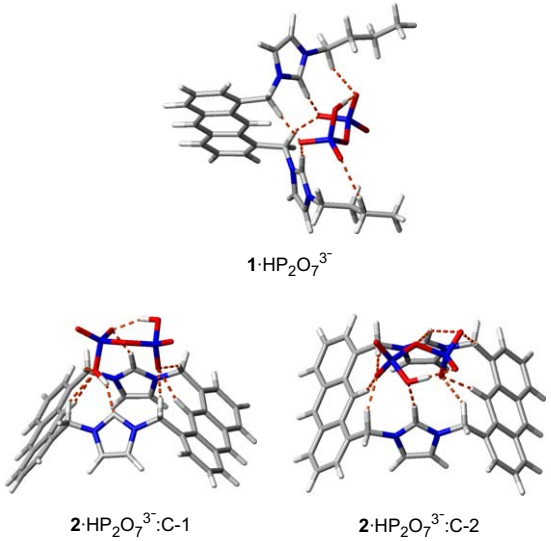


Figure 13. Optimized geometry of $\mathbf{1}\cdot HP_2O_7^{3-}$ and two conformers C-1 and C-2 of $\mathbf{2}\cdot HP_2O_7^{3-}$ complexes. Dotted lines show distances less than 2.5 Å.

3. Conclusion

Anthracene and binaphthyl derivatives bearing two imidazolium moieties were synthesized as fluorescent chemosensors for anions and investigated using fluorescence, ^{1}H NMR analysis, density functional calculations, and X-ray diffractometer analysis. The anthracene and binaphthalene based receptors display particularly selective binding for pyrophosphate and phosphate. Therefore, the selectivity of these imidazolium receptors against anions can be controlled by the topology of the binding site. The conceptual design approach adopted here could be applied to other imidazolium based receptors with diverse topological features.

4. Experimental

4.1. General methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). Thin layer chromatography (TLC) was carried out using Merck 60 F_{254} plates with thickness of 0.25 mm. Preparative TLC was performed using Merck 60 F_{254} plates with the thickness of 1 mm.

Melting points were measured using a Büchi 530 melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker 250 MHz or Varian 500 MHz. Chemical shifts were given in parts per million and coupling constants (J) in hertz. Mass spectra were obtained using a JMS-HX 110A/110A Tandem Mass Spectrometer (JEOL). UV absorption spectra were obtained on UVIKON 933 Double Beam UV/VIS Spectrometer. Fluorescence emission spectra were obtained using RF-5301/PC Spectrofluorophotometer (Shimadzu).

4.1.1. 1,1′-[9,10-Anthracenediylbis(methylene)]bis[3-butyl-1*H*-imidazolium] dihexafluorophosphate (3). *Procedure A*. A solution of 9,10-bis(bromomethyl)anthracene[4a] **10** (100 mg, 0.27 mmol) and 1-butylimidazole (70 mg, 0.56 mmol) in acetonitrile (25 mL) was refluxed for 12 h. After cooling to the room temperature, the solvent was evaporated to dryness under vacuum. To the reaction mixture, 10 mL of acetone was added. After stirring for 20 min at room temperature, 109 mg of KPF_6 (0.54 mmol) was added to the reaction mixture. After another 24 h stirring at room temperature, the reaction mixture was filtered and the filtrate was evaporated. To the oily crude product, about 5 mL of ethyl acetate was added. The addition of ethyl acetate caused the precipitation of the product. The precipitate was then filtered and washed with CH_2Cl_2 to give analytically pure product as a pale yellow solid (160 mg, 80%); mp 248–252 °C, dec; ^{1}H NMR (CD_3CN) δ 8.39 (m, 4H), 8.26 (s, 2H), 7.75 (m, 4H), 7.36 (m, 4H), 6.39 (s, 4H), 3.99 (t, 4H, J=7.4 Hz), 1.71 (quintet, 4H, J=7.3 Hz), 1.20 (sextet, 4H, J=7.3 Hz), 0.86 (t, 6H, J=7.4 Hz); ^{13}C NMR (CD_3CN) δ 135.6, 131.4, 128.4, 126.6, 124.6, 122.9, 122.8, 49.9, 146.1, 31.8, 19.3, 12.9; MS (FAB) m/z=597.2587 $(M-PF_6)^+$, calcd for $[C_{30}H_{36}F_{12}N_4P_2-PF_6]$=597.2582.

4.1.2. (*S*)-(−)-2,2′-Bis[(*n*-butyl)imidazoliummethyl]-1,1′-binapthyl dihexafluorophosphate (4). Application of procedure A to (*S*)-(-)2,2′-bis(bromomethyl)-1,1′-binapthyl **11**[12] (80 mg, 0.18 mmol) and 1-butylimidazole (70 mg, 0.56 mmol) in acetonitrile (25 mL) gave **4** as an analytically pure solid (129 mg, 76%); mp 166–170 °C, dec; ^{1}H NMR (DMSO-d_6, 250 MHz) δ 8.54 (s, 1H), 8.26 (d, 2H, J=8.5 Hz), 8.08 (d, 2H, J=8.5 Hz), 7.79 (d, 2H, J=8.5 Hz), 7.51 (t, 2H, J=7.2 Hz), 7.36 (br s, 2H), 7.19 (t, 2H,

J=7.2 Hz), 7.41 (t, 2H, J=1.8 Hz), 7.15 (br s, 2H), 6.63 (d, 2H, J=8.4 Hz), 5.33 (d, 2H, J=15.0 Hz), 5.11 (d, 2H, J=15.0 Hz), 3.38 (m, 4H), 1.50 (quintet, 4H, J=7.3 Hz), 1.14 (sextet, 4H, J=7.3 Hz), 0.83 (t, 6H, J=7.3 Hz); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 135.7, 133.9, 132.9, 131.8, 130.2, 129.6, 128.2, 127.6, 127.0, 126.9, 124.9, 122.4, 121.9, 51.1, 48.3, 31.0, 18.7, 13.2; HRMS (FAB) m/z= 673.2894 $(M-PF_6)^+$, calcd for $[C_{36}H_{40}F_{12}N_4P_2-PF_6]$= 673.2895.

4.2. Preparation of fluorometric anion titration solutions

Stock solutions (1 mM) of the tetrabutylammonium salts of $HP_2O_7^{3-}$, $H_2PO_4^-$, HSO_4^-, $CH_3CO_2^-$, F^-, Cl^-, Br^-, and I^- in acetonitrile were prepared. Stock solutions of **1–9** (0.1 mM) were also prepared either in acetonitrile or DMSO. Test solutions were prepared by placing 4–40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with acetonitrile. For all measurements, excitation was at 365 nm (for **1**, **2**, **3**), 310 nm (for **4**), 272 nm (for **5**) or 320 nm (for **6–9**); emission was measured at 421 nm (for **1** and **3**), 418 nm (for **2**) or 342 nm (for **4**). Both excitation and emission slit widths were 3 nm or 5 nm.

4.3. Preparation of NMR-titration solutions

The solution of receptors as 1 mM in CD_3CN was titrated by adding known quantities of concentrated solution (4 mM) of anions in the form of their tetrabutylammonium salts. All tetrabutylammonium anions were purchased from Aldrich. All titrations were repeated at least once to get the consistent values.

4.4. X-ray structure determination

The X-ray diffraction data for suitable crystals were collected and mounted on a Bruker-SMART-CCD-2000-APEX-diffractometer with monochromated Mo Kα radiation (λ=0.71069 Å) in the $\omega/2\theta$ scan and measured. The SHELX programs were used for structure solution and refinement.[19]

4.4.1. Compound 3·2(PF$_6$). $C_{30}H_{36}F_{12}N_4P_2$; the data crystal is in a colorless plate form and had approximate dimensions 0.1×0.1×0.05 mm^3, orthorhombic, space group *Pbca*, a=12.731(4) Å, b=10.549(3) Å, c=24.840(8) Å; V= 3336.0(2) Å^3, Z=4, $F(000)$=1528, σ=1.478 Mg/m^3, $2\theta_{max}$= 49.46°, $R1$=0.0735, $wR2$=0.1739, GOF=1.001, residual electron density between 0.403 and −0.196 e Å^{-3}. Crystallographic data for the structure (**3·2(PF$_6$)**) have been deposited to the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-275816. These data can be obtained free of the charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/_conts/retrieving.html.

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Longipedlactones A–I, nine novel triterpene dilactones possessing a unique skeleton from *Kadsura longipedunculata*

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Abstract—Nine novel triterpene dilactones with an unprecedented rearranged pentacyclic skeleton, longipedlactones A–I (**1**–**9**), have been isolated from the leaves and stems of *Kadsura longipedunculata* Finet et Gagnep (Schisandraceae). Their structures were determined on the basis of comprehensive spectroscopic analysis and single-crystal X-ray structure determination. A biogenetic pathway for longipedlactone A (**1**) was also proposed. Compounds **1**–**3**, **6**, and **8** showed significant cytotoxicity against A549, with HT-29 and K562 cell lines having IC_{50} values of 0.84–11.38 μM in vitro.

1. Introduction

The genus *Kadsura* belongs to the family Schisandraceae. Some species of this genus have been reported to contain dibenzocyclooctadienlignans, lanostane, and cycloartane triterpenoids, including anti-HIV, antitumor, anti-HBeAg, and anti-lipid peroxidative activities.[1–8] Nowadays, some novel triterpenoids and lignans with unprecedented new skeletons, such as kadsuphilactone A and taiwankadsurins A–C,[9,10] have been isolated from this genus. Therefore, in the research field of phytochemistry, this genus is of interest for the identification of new natural compounds with interesting biological activities, and the investigation of natural compounds that have potential as natural sources of intermediates for the synthesis of high-added-value compounds.

Kadsura longipedunculata Finet et Gagnep is a climbing plant widely distributed in the southern part of China. It has been used in folk medicine for the treatment of rheumatoid arthritis as well as gastric and duodenal ulcers.[11,12] Previously, we reported the isolation and structure elucidations of two novel triterpenoids, kadlongilactones A and B. These have a unique skeleton and are extracted from the leaves and stems of *K. longipedunculata*.[13] In the continuous search for bioactive metabolites from this plant, nine novel triterpene derivatives, longipedlactones A–I (**1**–**9**), were isolated, which featured an unprecedented rearranged pentacyclic backbone derived from cycloartane. The C and D rings of longipedlactones A–I were rearranged to 5/6 consecutive carbocycle systems with an exocyclic double bond in the D ring, which is different from the previously isolated 6/5 consecutive carbocycles of lancilactones A and B.[3] In this paper, the isolation, structure elucidation, and plausible hypotheses on the biogenetic pathway are described. The biological activity of these novel compounds is also reported.

2. Results and discussion

Longipedlactone A (**1**) was isolated as colorless crystals, which gave a $[M-H]^-$ ion at *m*/*z* 477.2630 in HR-ESIMS consistent with a molecular formula $C_{30}H_{38}O_5$ (calcd 477.2640 for $C_{30}H_{37}O_5$), requiring 12 sites of unsaturation. The UV spectrum of **1** showed absorption maxima at 224, 254 and 280 nm, indicating the presence of conjugated systems. The IR spectrum showed the presence of hydroxyl group (3464 cm^{-1}) and two lactone groups (1655 and 1695 cm^{-1}). The ^1H NMR spectrum (Table 1) exhibited signals for one secondary methyl (δ_H 1.14, d, J=7.3 Hz), four tertiary methyls (δ_H 1.03, 1.48, 1.53, and 1.86), five olefinic proton signals (δ_H 5.70, 5.74, 6.25, 6.66, and 6.72), and

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Table 1. ^{1}H NMR spectroscopic data of compounds **1–5**[a]

Proton	1	2	3	4	5
1	6.66 (d, 12.2)	6.70 (d, 12.4)	6.61 (d, 12.3)	5.89 (dd, 1.5, 12.5)	6.50 (d, 12.4)
2	5.70 (d, 12.2)	5.72 (d, 12.4)	6.04 (d, 12.3)	6.34 (d, 12.5)	5.90 (d, 12.4)
5	3.75 (br d, 9.8)	3.79 (br d, 9.4)	4.10 (br d, 9.3)	2.92 (overlap)	4.02 (br d, 9.4)
6α	2.13 (overlap)	2.06 (overlap)	2.16 (overlap)	2.02–2.10 (m)	2.10 (overlap)
6β	1.15 (overlap)	1.69 (overlap)	1.69 (overlap)	1.24–1.30 (m)	1.03–1.14 (m)
7α	2.00 (overlap)	2.13 (overlap)	2.22–2.25 (m)	1.91 (overlap)	2.19–2.26 (m)
7β	1.73–1.75 (m)	1.70 (overlap)	1.32 (overlap)	1.54–1.57 (m)	1.64–1.69 (m)
8	1.39 (dd, 2.6, 12.4)	1.64 (overlap)	1.66 (overlap)	1.64 (overlap)	1.55 (dd, 1.7, 12.2)
11α	2.16 (overlap)	1.95 (overlap)	2.14 (overlap)	2.53 (dd, 8.0, 13.1)	2.45 (dd, 8.1, 13.3)
11β	1.65 (overlap)	1.78–1.84 (m)	1.86 (overlap)	2.14 (overlap)	2.14 (overlap)
12	2.78 (dd, 8.5, 10.7)	2.57 (dd, 7.0, 13.0)	3.12 (dd, 6.8, 13.3)	3.08 (t, 8.6)	3.10 (dd, 8.1, 10.7)
15α	1.60 (overlap)	0.99 (overlap)	1.44 (overlap)	1.81 (dd, 3.0, 16.4)	1.71 (overlap)
15β	2.05 (overlap)	1.28–1.33 (m)		2.17 (overlap)	2.07 (overlap)
16α	5.74 (d, 2.6)	1.51 (overlap)	2.08 (overlap)	5.85 (overlap)	5.97 (d, 3.0)
16β		1.63 (overlap)	1.84 (overlap)		
17		2.15 (overlap)			
18a	4.96 (br s)	4.94 (d, 2.2)	5.58 (d, 2.3)	5.07 (br s)	5.25 (br s)
18b	4.84 (br s)	4.73 (d, 2.2)	5.27 (d, 2.3)	4.90 (br s)	4.96 (br s)
19	6.25 (s)	6.31 (s)	6.26 (s)	3.42 (s)	6.41 (s)
20	2.89–2.92 (m)	2.01 (overlap)	2.29–2.31 (m)	2.95 (overlap)	3.30–3.35 (m)
21	1.14 (d, 7.3)	0.96 (d, 7.2)	1.27 (d, 6.8)	1.12 (d, 7.0)	1.31 (d, 7.3)
22	4.44 (ddd, 4.3, 6.0, 11.1)	4.63 (ddd, 4.4, 8.3, 13.2)	5.09–5.13 (m)	4.49 (ddd, 5.0, 6.8, 11.6)	4.77 (dd, 4.1, 7.5)
23α	2.27 (overlap)	2.24 (overlap)	2.79–2.84 (m)	2.20 (overlap)	4.70 (br s)
23β	2.36 (overlap)	2.34–2.42 (m)	2.49–2.57 (m)	2.15 (overlap)	
24	6.72 (br d, 5.2)	6.75 (dd, 1.7, 6.6)	6.51 (br d, 6.3)	6.45 (br d, 6.1)	6.75 (d, 1.3)
27	1.86 (s)	1.86 (s)	1.95 (s)	1.86 (s)	1.90 (s)
28	1.03 (s)	0.92 (s)	1.12 (s)	1.21 (s)	1.27 (s)
29	1.48 (s)	1.48 (s)	1.42 (s)	1.36 (s)	1.40 (s)
30	1.53 (s)	1.54 (s)	1.46 (s)	1.62 (s)	1.42 (s)
9-OH	4.56 (s)		6.57 (s)	6.50 (s)	6.48 (s)
17-OH			5.96 (s)		
23-OH					7.42 (d, 5.6)

[a] Data were recorded on a Bruker DRX-500 MHz spectrometer, chemical shift values δ are in ppm, and the coupling constant J is in Hz (in parentheses). Data of compounds **1** and **2** were recorded in CD_3OD, and compounds **3**, **4**, and **5** were recorded in C_5D_5N.

a characteristic exocyclic methylene (δ_H 4.84 and 4.96, each br s). Analysis of ^{13}C NMR, DEPT, and HSQC data revealed that **1** contains two α,β-unsaturated carbonyl carbons, seven quaternary carbons (including four olefinic and one oxygenated carbons), 10 methines (including five olefinic and one oxygenated), six methylenes (including an exocyclic methylene), and five methyls (including one secondary methyl). Apart from five double bonds and two carbonyl groups, the remaining elements of unsaturation in **1** were assumed to be a pentacyclic skeleton. These data were consistent with the HRMS empirical formula and suggested that **1** was probably a pentacyclic triterpene. Since the NMR data of **1** were quite distinctive from those of the known triterpene skeleton, the possible structure of **1** was firstly established by a detailed analysis of 2D-NMR data, and finally confirmed by single-crystal X-ray analysis.

Extensive analysis of ^{1}H–^{1}H COSY, HMBC, and HSQC spectral data led to the establishment of three substructures **1a**–**1c** (Fig. 1), which were deduced as follows. In the HMBC spectrum (Fig. 2), the correlations of CH_3-30 (δ_H 1.53, s) with C-4, C-5, and C-29, and of CH_3-29 (δ_H 1.48, s) with C-4 and C-30, required that CH_3-30 and CH_3-29 be attached to the same oxygenated quaternary carbon (δ_C 82.5, s, C-4). In addition, the proton signal at δ_H 5.70 (d, J=12.2 Hz, H-2) showed HMBC correlations with C-3 and C-10, and the proton signal at δ_H 3.75 (br d, J=9.8 Hz, H-5) showed correlations with C-1, C-4, C-19, and C-29. Other correlations were noted between H-19 (δ_H 6.25, s) and C-8, C-9. These facts, along with two proton spin systems (**a** and **b**) deduced from ^{1}H–^{1}H COSY correlations (Fig. 2), and the lack of any absorption band due to carboxylic group in the IR spectrum, led to the establishment of substructure **1a**. HMBC correlations were observed from CH_3-28 (δ_H 1.03, s) to C-12, C-14, and C-15, from H_2-18 (δ_H 4.96-a, 4.84-b, each br s) to C-12, C-13, and C-17, and from CH_3-21 (δ_H 1.14, d, J=7.3 Hz) to C-17 and C-20. The above evidence, in combination with two proton spin systems (**c** and **d**), determined the existence of substructure **1b**. Furthermore, HMBC correlations from CH_3-27 (δ_H 1.86, s) to C-24, C-25, and C-26, together with the critical MS

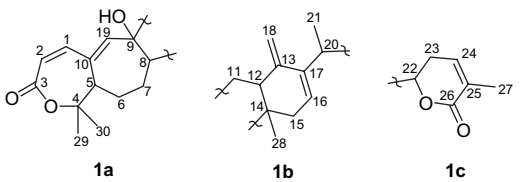


Figure 1. Substructures (**1a**–**1c**) of **1**.

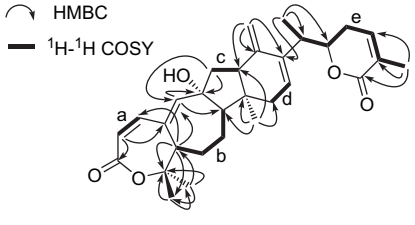


Figure 2. Key ^{1}H–^{1}H COSY and HMBC correlations of **1**.

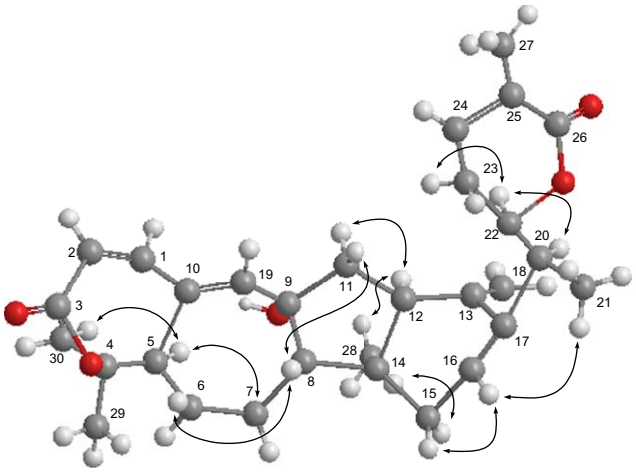


Figure 3. Key ROESY correlations and relative configurations assigned for **1**.

fragment at *m/z* 111 $[C_6H_7O_2]^-$, indicated the presence of a six-membered α-methyl-α,β-unsaturated lactone ring (**1c**).[3] In the HMBC spectrum, the proton signal H-11β (δ_H 1.65, overlap) showed correlations with C-9 and C-19, and CH_3-28 showed correlation with C-8 requiring the connection of **1a** and **1b**. In addition, HMBC correlation from CH_3-21 to C-22, in conjunction with proton spin system (**e**) (Fig. 2), determined the direct combination of **1b** and **1c**. Accordingly, the planar structure of **1** could be established. Its relative stereochemistry was determined by ROESY (Fig. 3) experiment and X-ray crystallographic analysis (Fig. 4). Thus, the structure of **1** was established as shown in Scheme 1.

Longipedlactone B (**2**) was obtained as an amorphous powder. Its molecular formula, $C_{30}H_{40}O_5$, was determined by the $[M-1]^-$ ion peak in the negative HR-ESIMS at *m/z* 479.2794 (calcd 479.2797). The ^1H and ^{13}C NMR spectra of **2** showed close resemblance to that of **1**, the obvious differences were the absence of a double bond between C-16 and C-17 (δ_C 126.7, d and 141.7, s) in **1**, and the presence of a methylene (δ_C 25.9, t) and a methine (δ_C 44.5, d) in **2**, which indicated that a double bond in **1** was reduced. HMBC and ^1H–^1H COSY spectra confirmed the above deduction. On the basis of these observations, the structure of **2** was proposed as shown in Scheme 1 and its relative stereochemistry was determined to be the same as that of **1** by the analysis of ROESY data.

Longipedlactone C (**3**) was obtained as an amorphous powder with the empirical formula $C_{30}H_{40}O_6$, in agreement with the HR-ESIMS (*m/z* 495.2748 $[M-1]^-$, calcd for $C_{30}H_{39}O_6$, 495.2746) and ^{13}C NMR spectral data. The NMR data of **3** were strikingly similar to those of **2**, except for the lack of a methine at δ_C 44.5 (C-17), the appearance of a new oxygenated quaternary carbon (δ_C 75.3, s) and a hydroxyl group (δ_H 5.96, s) in **3**. HMBC (Fig. 5) correlations observed from the proton signal of OH to C-13, C-17, and C-20 indicated this hydroxyl group to be located at C-17. In the ROESY (Fig. 5) spectrum, OH-17 had ROE correlations with H-16β and H-21β, indicating OH-17 to be in β-orientation. Thus, the structure of **3** was determined to be 17β-hydroxyl-longipedlactone B.

HR-ESIMS analysis of longipedlactone D (**4**) demonstrated that it has the molecular formula $C_{30}H_{38}O_6$, differing from **1** by the addition of an oxygen atom. Detailed comparison of ^1H and ^{13}C NMR data of **4** with those of **1** was analogous. The only significant differences include the appearance of a trisubstituted epoxide (δ_C 62.4, s and 67.1, d; δ_H 3.42, s) in **4** and the disappearance of a double bond (δ_C 146.5 and 149.1; δ_H 6.25, s) in **1**. The HMBC (Fig. 5) correlations of H-2 and H-5 with C-10, of H-1 with C-19, and of H-19 with C-9, C-10, and C-11 verified that the epoxide group was positioned between C-10 and C-19. This assignment was in accord with the observed downfield chemical shifts for the C-1 and C-2 signals from δ_C 146.8 and 118.5 in **1** to δ_C 145.1 and 126.1 in **4**, respectively. In the ROESY (Fig. 5) experiment, H-19 showed correlations with H-1, H-8β, and H-11β, indicating an α-orientation of the epoxy ring.

HR-ESIMS of longipedlactone E (**5**) gave a quasi-molecular ion at *m/z* 517.2558 $[M+Na]^+$, corresponding to the molecular formula $C_{30}H_{38}O_6$, indicating 16 mass units more than compound **1**. The signals in its ^1H and ^{13}C NMR

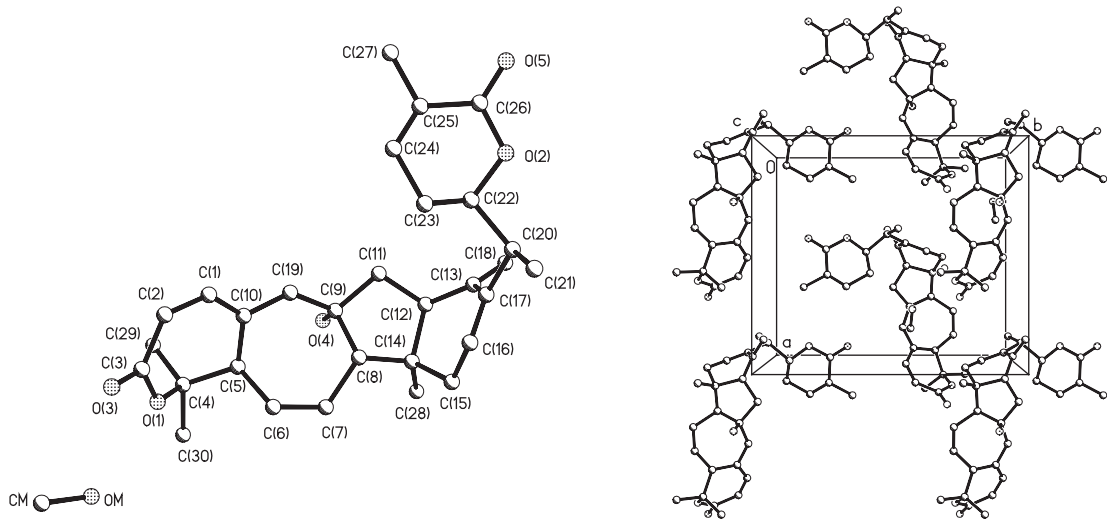
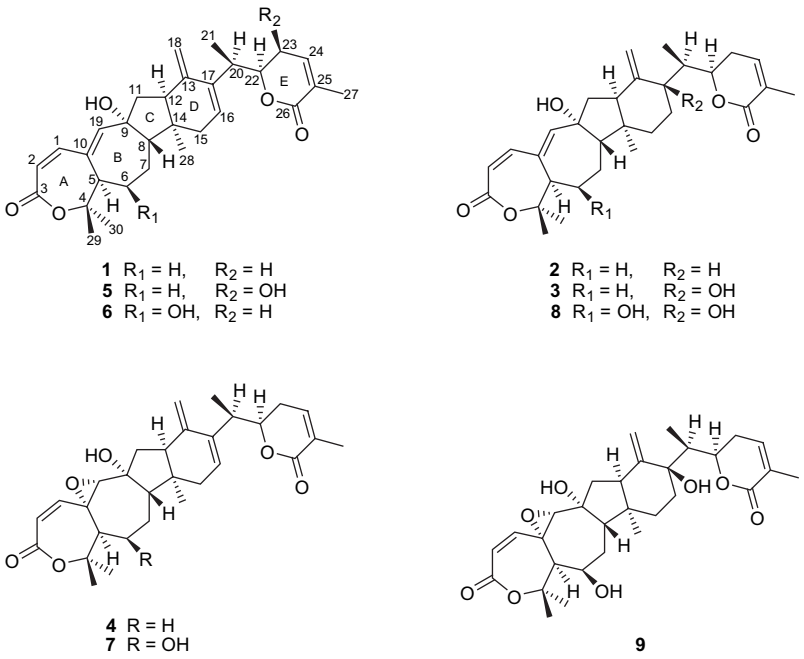


Figure 4. X-ray crystal structure of **1**.



Scheme 1. Structures of longipedlactones A–I (**1**–**9**).

spectra strikingly matched those of **1** (Tables 1 and 3). The only significant differences included the obvious presence of a new hydroxyl group (δ_H 7.42, d, J=5.6 Hz), and the lack of a H_2-23 signal in the ^{1}H NMR spectrum, implying that this new hydroxyl group is present at C-23. This was further confirmed by the HMBC (Fig. 5) correlations of H-22 and H-20 with C-23 (δ_C 63.3, d). The ROESY (Fig. 5) experiment of **5** showed correlations between H-23/H-20α, H-23/H-11β, and H-22α/H-20α. This, along with the smaller value of cis-coupling constants of H-22 in the ^{1}H NMR spectrum, confirmed OH-23 to be in β-orientation.

Longipedlactone F (**6**) was obtained as colorless crystals. Its molecular formula $C_{30}H_{38}O_6$ was determined by the $[M+Na]^+$ ion peak at m/z 517.2576 (calcd for $C_{30}H_{38}O_6Na$,

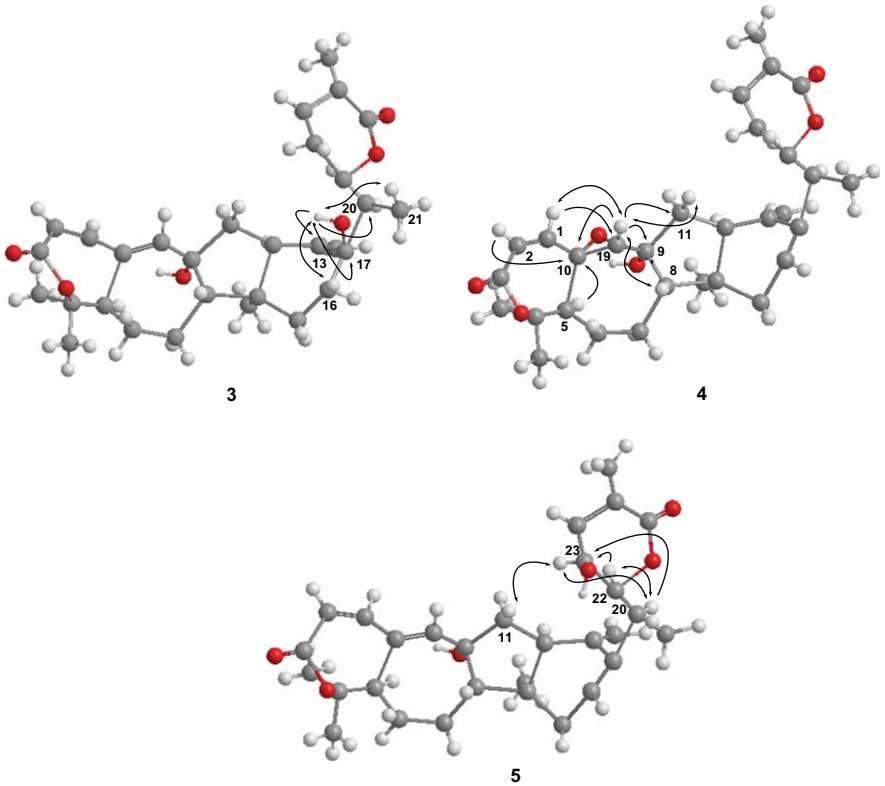


Figure 5. Key HMBC (→) and ROESY (↔) correlations and relative configurations assigned for **3**–**5**.

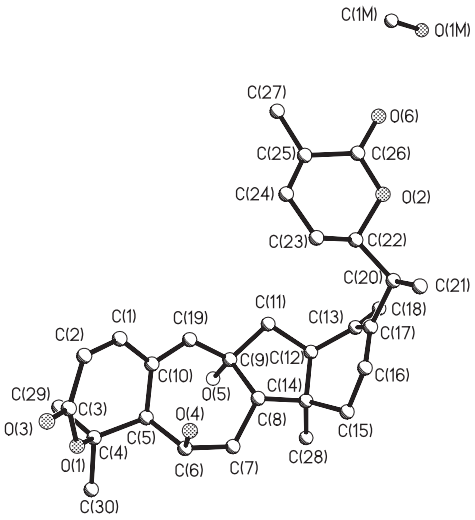


Figure 6. X-ray crystal structure of **6** showing relative configuration.

517.2566) in the HR-ESIMS. The NMR spectra of **6** were quite similar to those of **1**, suggesting that they had the same basic structure with the difference as observed between **2** and **3**. Thus, **6** was considered to have a new hydroxyl group located at C-6 (δ_C 65.4, d), which was confirmed by the HMBC correlations observed from H-19, H-5 and H-8 to C-6. Furthermore, **6** was obtained as colorless crystals after several recrystallizations in methanol solvent. The analysis of the single-crystal X-ray diffraction (Fig. 6) confirmed the relative configuration of **6** as proposed in Scheme 1, which showed a β-orientation for OH-6.

Longipedlactone G (**7**) was obtained as an amorphous powder. The $[M-H]^-$ ion peak at *m/z* 509.2550 (calcd for $C_{30}H_{37}O_7$, 509.2539) in the HR-ESIMS determined its molecular formula to be $C_{30}H_{38}O_7$. Side-by-side comparison of the ^1H and ^{13}C NMR data (Tables 2 and 3) between **7** and **6** indicated that these two compounds were almost identical, except for the presence of a trisubstituted epoxide (δ_C 60.8, s and 68.1, d; δ_H 3.39, s) in **7** and the disappearance of a double bond (δ_C 141.9 and 147.1; δ_H 6.60, s) in **6**. The epoxide group was positioned between C-10 and C-19 on the basis of HMBC correlations, which was same as that observed in **4**. The ROESY spectrum indicated the epoxide group was in an α-orientation similar to that of **4**. Thus, **7** had the structure shown in Scheme 1.

The structures of longipedlactones H (**8**) and I (**9**) were determined to be as shown in Scheme 1 on the basis of spectral data comparisons in an analogous manner to the structure elucidation of **3**, **4**, and **6**. The locations of hydroxyl group and epoxide group were assigned by the observed HMBC and ^1H–^1H COSY (Figs. 7 and 8) correlations. ROESY correlations observed between H-6/H-5α, H-6/H-7α and OH-17/H-16β, OH-17/H-18a were consistent with a β-orientation of OH-6 and OH-17 in **8** and **9**, respectively. Furthermore, ROEs between H-19/H-1, H-19/H-8β, and H-19/H-11β indicated that the epoxy ring of **9** was in an α-orientation like that of **4** and **7**. Therefore, the structures of **8** and **9** were determined to be 6β-hydroxy-longipedlactone C and 9,19α-epoxy-longipedlactone H, and were named as longipedlactones H and I, respectively.

Table 2. ^1H NMR spectroscopic data of compounds **6–9**[a]

Proton	6	7	8	9
1	6.80 (d, 12.2)	5.91 (d, 12.2)	6.84 (d, 12.4)	5.95 (dd, 1.5, 12.5)
2	6.00 (d, 12.2)	6.35 (d, 12.2)	6.05 (d, 12.4)	6.42 (d, 12.5)
5	4.37 (br s)	3.03 (overlap)	4.40 (br s)	3.07 (br s)
6α	4.89 (br s)	4.80 (d, 4.4)	4.89 (br s)	4.85 (br s)
7α	2.43–2.46 (m)	2.07 (overlap)	2.47 (overlap)	2.14–2.20 (m)
7β	2.06 (overlap)	1.86 (overlap)	2.02 (overlap)	1.92–1.96 (m)
8	2.32–2.36 (m)	2.56 (d, 11.3)	2.56 (overlap)	2.75 (overlap)
11α	2.51–2.54 (m)	2.61 (dd, 7.9, 13.5)	2.19 (overlap)	2.24 (dd, 7.0, 12.5)
11β	1.81 (overlap)	2.18 (overlap)	1.93 (overlap)	2.03 (overlap)
12	3.12 (t, 8.8)	3.05 (overlap)	3.13 (dd, 6.0, 12.9)	3.19 (dd, 7.0, 13.6)
15α	1.67 (d, 15.6)	1.87 (overlap)	1.40–1.41 (m)	1.54–1.62 (m)
15β	2.16 (overlap)	2.22 (overlap)		1.46–1.50 (m)
16α	5.61 (d, 4.0)	5.71 (br s)	1.89 (overlap)	2.07–2.10 (m)
16β			1.65–1.68 (m)	1.72–1.75 (m)
18a	5.09 (br s)	5.19 (br s)	5.56 (d, 2.0)	5.58 (d, 2.6)
18b	4.94 (br s)	4.97 (br s)	5.29 (d, 2.0)	5.30 (d, 2.6)
19	6.60 (s)	3.39 (s)	6.50 (overlap)	3.37 (s)
20	3.05 (t, 12.3)	3.08–3.10 (m)	2.21 (overlap)	2.31–2.33 (m)
21	1.07 (d, 7.0)	1.09 (d, 6.9)	1.26 (d, 6.9)	1.23 (d, 7.0)
22	4.47 (ddd, 4.0, 9.1, 10.1)	4.47 (ddd, 4.4, 9.3, 12.2)	4.82–4.84 (m)	4.95 (overlap)
23α	2.01 (overlap)	2.21 (overlap)	2.75–2.79 (m)	2.78 (overlap)
23β	2.11 (overlap)	2.11 (overlap)	2.52 (overlap)	2.46–2.53 (m)
24	6.48 (dd, 1.8, 4.0)	6.51 (br d, 5.9)	6.50 (overlap)	6.48 (br d, 6.7)
27	1.85 (s)	1.87 (s)	2.01 (s)	1.98 (s)
28	1.30 (s)	1.23 (s)	1.15 (s)	1.11 (s)
29	1.50 (s)	1.43 (s)	1.50 (s)	1.44 (s)
30	1.52 (s)	1.74 (s)	1.54 (s)	1.77 (s)
6-OH	6.31 (s)	6.68 (d, 4.4)		
9-OH	6.56 (s)	6.41 (s)	6.57 (s)	6.36 (s)
17-OH			5.86 (s)	5.87 (s)

[a] Data were recorded on a Bruker DRX-500 MHz spectrometer, chemical shift values δ are in ppm, and the coupling constant *J* is in Hz (in parentheses). Data of compounds **6–9** were recorded in C_5D_5N.

Table 3. ^{13}C NMR spectroscopic data of compounds **1–9**[a]

Carbon	1	2	3	4	5	6	7	8	9
1	146.8 (d)	146.6 (d)	144.2 (d)	145.1 (d)	144.2 (d)	146.3 (d)	146.6 (d)	146.3 (d)	146.7 (d)
2	118.5 (d)	118.6 (d)	119.3 (d)	126.1 (d)	119.1 (d)	119.7 (d)	126.7 (d)	120.0 (d)	126.8 (d)
3	169.5 (s)	169.5 (s)	166.6 (s)	165.6 (s)	166.5 (s)	166.9 (s)	166.6 (s)	166.7 (s)	166.6 (s)
4	82.5 (s)	82.4 (s)	80.3 (s)	81.5 (s)	79.8 (s)	80.0 (s)	81.1 (s)	80.0 (s)	81.0 (s)
5	49.5 (d)	49.4 (d)	48.7 (d)	49.7 (d)	48.8 (d)	52.8 (d)	53.3 (d)	53.1 (d)	53.5 (d)
6	29.5 (t)	28.7 (t)	28.1 (t)	26.4 (t)	28.3 (t)	65.4 (d)	65.8 (d)	65.9 (d)	66.1 (d)
7	28.2 (t)	29.4 (t)	28.6 (t)	24.9 (t)	27.5 (t)	36.3 (t)	34.4 (t)	36.9 (t)	34.9 (t)
8	57.4 (d)	55.0 (d)	54.5 (d)	56.3 (d)	56.2 (d)	49.3 (d)	47.4 (d)	46.9 (d)	47.3 (d)
9	80.8 (s)	80.9 (s)	79.7 (s)	77.9 (s)	79.8 (s)	79.5 (s)	77.6 (s)	79.8 (s)	78.3 (s)
10	146.5 (s)	146.9 (s)	145.8 (s)	62.4 (s)	144.6 (s)	141.9 (s)	60.8 (s)	142.1 (s)	61.0 (s)
11	51.7 (t)	48.5 (t)	48.3 (t)	51.0 (t)	51.0 (t)	51.7 (t)	51.1 (t)	48.5 (t)	48.2 (t)
12	54.1 (d)	54.5 (d)	53.7 (d)	53.5 (d)	53.5 (d)	53.4 (d)	52.9 (d)	53.9 (d)	54.8 (d)
13	149.7 (s)	149.2 (s)	153.4 (s)	148.5 (s)	148.6 (s)	148.3 (s)	147.6 (s)	153.5 (s)	153.3 (s)
14	44.9 (s)	45.1 (s)	44.9 (s)	43.4 (s)	44.2 (s)	43.7 (s)	42.3 (s)	44.3 (s)	43.4 (s)
15	38.1 (t)	36.0 (t)	34.2 (t)	37.3 (t)	37.5 (t)	37.2 (t)	36.8 (t)	33.7 (t)	34.6 (t)
16	126.7 (d)	25.9 (t)	35.1 (t)	125.4 (d)	127.0 (d)	126.2 (d)	125.7 (d)	35.1 (t)	35.6 (t)
17	141.7 (s)	44.5 (d)	75.3 (s)	140.2 (s)	140.4 (s)	139.8 (s)	138.7 (s)	75.3 (s)	75.3 (s)
18	108.2 (t)	115.6 (t)	115.6 (t)	108.2 (t)	108.1 (t)	108.2 (t)	109.3 (t)	115.9 (t)	115.5 (t)
19	149.1 (d)	148.5 (d)	147.3 (d)	67.1 (d)	148.0 (d)	147.1 (d)	68.1 (d)	146.5 (d)	66.7 (d)
20	41.1 (d)	42.2 (d)	44.3 (d)	40.1 (d)	38.6 (d)	39.8 (d)	38.9 (d)	45.3 (d)	43.4 (d)
21	15.8 (q)	13.7 (q)	9.5 (q)	16.3 (q)	16.6 (q)	14.0 (q)	14.5 (q)	9.4 (q)	9.5 (q)
22	82.5 (d)	81.2 (d)	79.7 (d)	81.1 (d)	86.2 (d)	80.2 (d)	80.3 (d)	79.6 (d)	79.5 (d)
23	27.5 (t)	24.7 (t)	27.1 (t)	27.1 (t)	63.3 (d)	25.7 (t)	25.8 (t)	27.1 (t)	27.1 (t)
24	141.6 (d)	142.1 (d)	141.4 (d)	139.7 (d)	144.6 (d)	139.9 (d)	140.4 (d)	141.3 (d)	141.3 (d)
25	128.9 (s)	128.7 (s)	127.6 (s)	128.1 (s)	127.4 (s)	128.1 (s)	127.7 (s)	127.8 (s)	127.7 (s)
26	168.2 (s)	168.6 (s)	166.6 (s)	166.0 (s)	164.8 (s)	166.0 (s)	166.1 (s)	166.9 (s)	166.5 (s)
27	16.9 (q)	16.9 (q)	17.1 (q)	17.1 (q)	17.0 (q)	17.1 (q)	17.1 (q)	17.2 (q)	17.1 (q)
28	27.4 (q)	26.3 (q)	25.9 (q)	27.0 (q)	27.5 (q)	27.5 (q)	26.1 (q)	26.3 (q)	25.8 (q)
29	29.3 (q)	29.5 (q)	29.4 (q)	29.2 (q)	29.4 (q)	30.0 (q)	30.0 (q)	30.0 (q)	29.9 (q)
30	26.0 (q)	25.9 (q)	25.9 (q)	25.0 (q)	26.3 (q)	26.7 (q)	26.2 (q)	26.8 (q)	26.0 (q)

[a] Data were recorded on a Bruker DRX-500 MHz spectrometer, chemical shift values δ are in ppm, assignments were confirmed by ^{1}H–^{1}H COSY, HSQC, and HMBC.

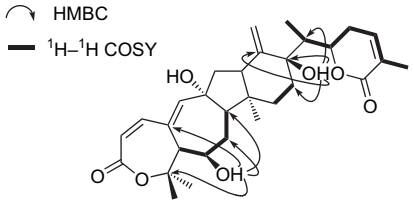


Figure 7. Key ^{1}H–^{1}H COSY and HMBC correlations of **8**.

The cytotoxicity of compounds **1–4** and **6–8** was tested against A549, HT-29 and K562 cell lines in vitro. Compounds **1–3**, **6**, and **8** showed promising cytotoxicity against all three cell lines at the level of IC_{50} values of 0.84–11.38 μM, and no cytotoxicity was observed for compounds **4** and **7** (Table 4). Comparing the structures of these compounds, it was noticeable that the formation of a double bond between C-10 and C-19 conjugated with an α,β-unsaturated lactone in **1–3**, **6**, and **8** made them have a significant IC_{50} values. In contrast, for **4** and **7**, the epoxy ring is displaced by the double bond, which destroys the conjugated system, resulting in no cytotoxicity. From the above observation, it was reasonable to presume that the big conjugated system (α,β,γ,δ-unsaturated lactone) was probably of crucial importance in its antitumor activity. Further investigation on the bioactivity of this series of triterpenoids will be of emphasis in our future research. Due to the small quantity of compounds **5** and **9**, their cytotoxicity was not determined.

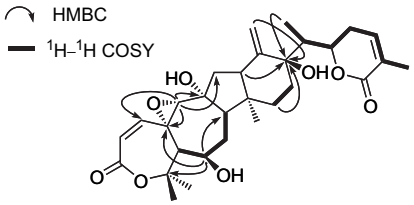
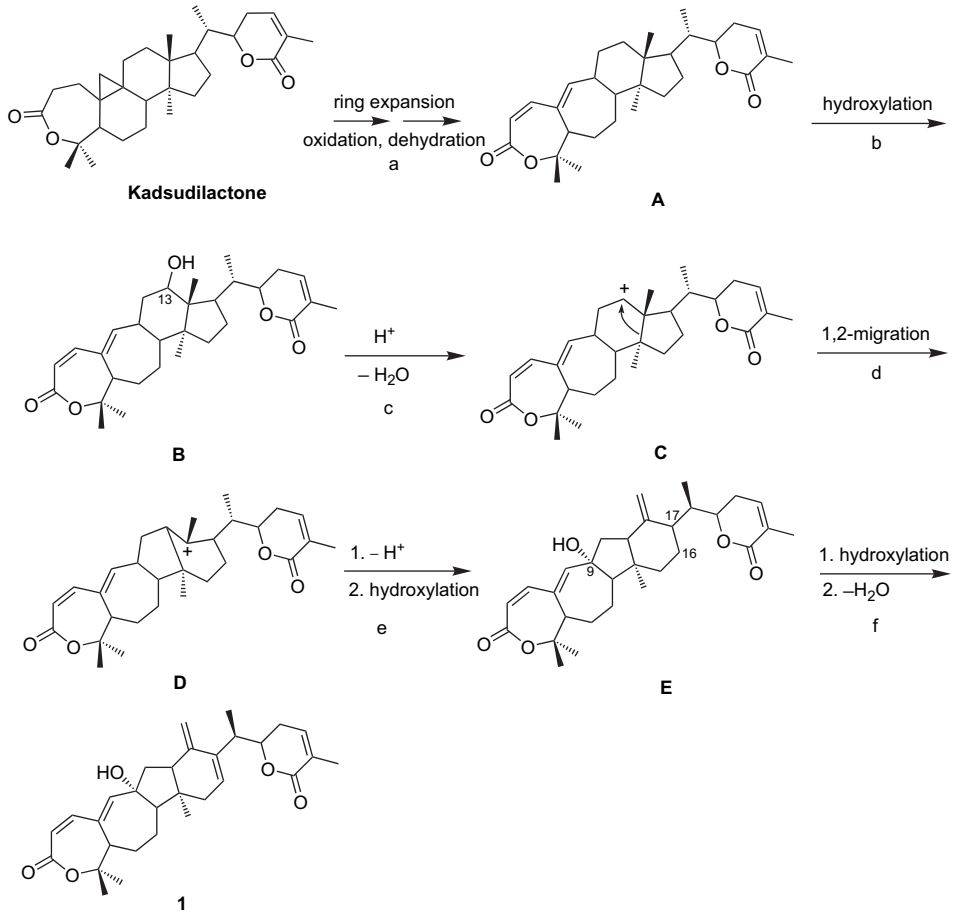


Figure 8. Key ^{1}H–^{1}H COSY and HMBC correlations of **9**.

A plausible biogenetic pathway for longipedlactone A (**1**) was proposed on the basis of kadsudilactone[14] isolated from the same plant, *K. longipedunculata*, Scheme 2. After ring expansion, oxidation and dehydrogenation of kadsudilactone result in intermediate **A**, this is followed by hydroxylation on C-13 to afford intermediate **B**, which then undergoes a Wagner–Meerwein rearrangement and hydroxylation at C-9 (**c–e**) to give **E**.[15] Finally, hydroxylation at C-17 and dehydration at C-16 and C-17 yielded longilactone A (**1**).

Table 4. Cytotoxic activities of compounds **1–4** and **6–8** against tumor cell lines

Compd	IC_{50} (μM)		
	A 549	HT-29	K562
1	1.82	1.64	2.96
2	2.47	1.81	2.72
3	0.24	1.01	1.49
4	>100	>100	>100
6	5.56	2.24	3.55
7	>100	>100	>100
8	11.38	5.63	7.58



Scheme 2. Plausible biogenetic pathway for longipedlactone A (**1**).

3. Experimental

3.1. General

Melting points were measured on an XRC-1 micro melting point apparatus and were uncorrected. Optical rotations were measured on a JASCO DIP-370 digital polarimeter. IR spectra were obtained on a Bio-Rad FtS-135 spectrophotometer with KBr pellets, whereas UV spectral data were obtained using a UV-210A spectrometer. MS were recorded on a VG Auto Spec-3000 spectrometer. 1D- and 2D-NMR spectra were obtained on the Bruker DRX-500 instruments with TMS as an internal standard.

3.2. Plant material

The leaves and stems of *K. longipedunculata* were collected in Erlang mountain region of Sichuan Province, China, in August 2004, and identified by Prof. Xi-Wen Li, Kunming Institute of Botany. A voucher specimen has been deposited in the Herbarium of the Kunming Institute of Botany, Chinese Academy of Sciences.

3.3. Extraction and isolation

The air-dried and powdered stems and leaves (11 kg) of *K. longipedunculata* were extracted with 70% aqueous Me_2CO (4×30 L) at room temperature to yield an extract, which was successively extracted with petroleum ether and EtOAc. The EtOAc extract (300 g) was subjected to column chromatography over silica gel (1.5 kg, 200–300 mesh) eluting with a $CHCl_3/Me_2CO$ gradient system (9:1, 8:2, 7:3, 6:4, 5:5) to give fractions 1–5. Compounds **1** (40 mg), **2** (8 mg), **3** (16 mg), **4** (4 mg), and **7** (12 mg) were obtained from fraction 1, and compounds **5** (1 mg), **6** (11 mg), **8** (84 mg), and **9** (1 mg) were obtained from fraction 2 after repeated silica gel column chromatographic separations ($CHCl_3$/isopropanol), followed by semipreparative HPLC separation (Agilent 1100 HPLC system, U.S.A; Zorbax SB-C-18, Agilent, 9.4 mm×25 cm, U.S.A., MeOH/H_2O).

3.3.1. Longipedlactone A (1). Colorless crystals; mp 166–167 °C; $[\alpha]_D^{23.9}$ −278.9 (*c* 0.62, C_5H_5N); UV (MeOH): λ_{max} (log ε)=352 (1.20), 280 (4.62), 254 (4.25), 224 nm (4.58); IR (KBr): ν_{max}=3464 (br), 2951, 2924, 2882, 2837, 1710, 1695, 1655, 1131 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 3; Negative FABMS: *m*/*z* (%): 569 (98) $[M+Gly-H]^-$, 477 (100) $[M-H]^-$, 325 (17), 111 (8); Negative HR-ESIMS: found: 477.2630, calcd 477.2640 for $C_{30}H_{37}O_5$ $[M-H]^-$.

3.3.2. Longipedlactone B (2). White powder; $[\alpha]_D^{24.4}$ −70.5 (*c* 0.42, C_5H_5N); UV (MeOH): λ_{max} (log ε)=279 (4.58), 248 (3.76), 208 nm (4.44); IR (KBr): ν_{max}=3441 (br), 2933, 2867, 1716, 1694, 1126 cm^{-1}; ^1H and ^{13}C NMR data, see Tables 1 and 3; Negative FABMS: *m*/*z* (%): 571 (91)

[M+Gly−H]$^-$, 479 (100) [M−H]$^-$, 325 (23), 139 (25); Negative HR-ESIMS: found: 479.2794, calcd 479.2797 for $C_{30}H_{39}O_5$ [M−H]$^-$.

3.3.3. Longipedlactone C (3). White powder; $[\alpha]_D^{25.6}$ −233.7 (*c* 0.11, C_5H_5N); UV (MeOH): λ_{max} (log ε)=279 nm (4.81); IR (KBr): ν_{max}=3446 (br), 2941, 2867, 1697, 1673, 1129 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 3; Negative FABMS: *m/z* (%): 587 (8) [M+Gly−H]$^-$, 495 (45) [M−H]$^-$, 478 (5) [M−H_2O]$^-$, 139 (100), 111 (5), 99 (25); Negative HR-ESIMS: found: 495.2748, calcd 495.2746 for $C_{30}H_{39}O_6$ [M−H]$^-$.

3.3.4. Longipedlactone D (4). White powder; $[\alpha]_D^{24.6}$ −138.9 (*c* 0.43, C_5H_5N); UV (MeOH): λ_{max} (log ε)=269 (3.17), 225 (4.59), 199 nm (4.37); IR (KBr): ν_{max}=3436 (br), 2980, 2955, 2920, 2879, 2864, 1710, 1692, 1131 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 3; Negative FABMS: *m/z* (%): 585 (31) [M+Gly−H]$^-$, 494 (100) [M]$^-$, 477 (22); Negative HR-ESIMS: found: 493.2576, calcd 493.2590 for $C_{30}H_{37}O_6$ [M−H]$^-$.

3.3.5. Longipedlactone E (5). White powder; $[\alpha]_D^{23.4}$ −206.2 (*c* 0.58, C_5H_5N); UV (MeOH): λ_{max} (log ε)=378 (1.77), 279 (4.87), 229 (4.79), 201 nm (4.86); IR (KBr): ν_{max}=3398 (br), 2955, 2925, 2854, 1718, 1670, 1643, 1130 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 1 and 3; Negative FABMS: *m/z* (%): 585 (4) [M+Gly−H]$^-$, 493 (37) [M−H]$^-$, 476 (9), 125 (23), 112 (12), 97 (100); Positive HR-ESIMS: found: 517.2558, calcd 517.2566 for $C_{30}H_{38}O_6Na$ [M+Na]$^+$.

3.3.6. Longipedlactone F (6). Colorless crystals; mp 139–141 °C; $[\alpha]_D^{26.5}$ −283.5 (*c* 0.97, C_5H_5N); UV (MeOH): λ_{max} (log ε)=347 (2.69), 278 (4.56), 225 nm (4.49); IR (KBr): ν_{max}=3613, 3525, 3442, 2982, 2948, 2926, 2834, 1717, 1666, 1636, 1614, 1125 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; Negative FABMS: *m/z* (%): 585 (10) [M+Gly−H]$^-$, 493 (100) [M−H]$^-$, 476 (27) [M−H_2O]$^-$, 341 (20), 139 (16); Positive HR-ESIMS: found: 517.2576, calcd 517.2566 for $C_{30}H_{38}O_6Na$ [M+Na]$^+$.

3.3.7. Longipedlactone G (7). White powder; $[\alpha]_D^{25.2}$ −148.9 (*c* 0.62, C_5H_5N); UV (MeOH): λ_{max} (log ε)=271 (2.74), 225 nm (4.58); IR (KBr): ν_{max}=3520 (br), 2972, 2926, 2884, 2839, 1697, 1642, 1133 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; Negative FABMS: *m/z* (%): 601 (3) [M+Gly−H]$^-$, 509 (100) [M−H]$^-$, 493 (23) [M−H_2O−H]$^-$, 339 (19), 325 (28), 297 (18), 167 (21), 138 (27), 123 (52); Negative HR-ESIMS: found: 509.2550, calcd 509.2539 for $C_{30}H_{37}O_7$ [M−H]$^-$.

3.3.8. Longipedlactone H (8). White powder; $[\alpha]_D^{23.3}$ −21.1 (*c* 0.85, C_5H_5N); UV (MeOH): λ_{max} (log ε)=278 (4.50), 202 nm (4.54); IR (KBr): *v*=3444 (br), 2927, 2855, 1697, 1130 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; Negative FABMS: *m/z* (%): 603 (6) [M+Gly−H]$^-$, 511 (68) [M−H]$^-$, 494 (8) [M−H_2O]$^-$, 217 (7), 171 (10), 139 (100), 123 (14), 111 (10); Negative HR-ESIMS: found: 511.2695, calcd 511.2695 for $C_{30}H_{39}O_7$ [M−H]$^-$.

3.3.9. Longipedlactone I (9). White powder; $[\alpha]_D^{23.4}$ −30.5 (*c* 0.40, C_5H_5N); UV (MeOH): λ_{max} (log ε)=355 (2.57), 202 nm (4.66); IR (KBr): *v*=3445 (br), 2926, 2851, 1699, 1639, 1131 cm^{-1}; ^{1}H and ^{13}C NMR data, see Tables 2 and 3; Negative FABMS: *m/z* (%): 620 (29) [M+Gly−H]$^-$, 528 (80) [M]$^-$, 486 (55), 362 (22), 348 (83), 340 (100), 325 (31), 228 (24), 166 (12); Negative HR-ESIMS: found: 527.2622, calcd 527.2644 for $C_{30}H_{39}O_8$ [M−H]$^-$.

3.4. Cytotoxicity bioassays

Cytotoxicity of compounds against suspended tumor cells was determined by trypan blue exclusion method. Cytotoxicity against adherent cells was determined by sulforhodamine B (SRB) assay. Cells were plated in 96-well plate 24 h before treatment and continuously exposed to different concentrations of compounds for 72 h. After compound treatment, cells were counted (suspended cells) or fixed and stained with SRB (adherent cells) as described in Monks et al.[16]

3.5. X-ray crystallographic studies of 1 and 6

3.5.1. Longipedlactone A (1). $C_{30}H_{38}O_5\cdot CH_3OH$, *M*=510.63, orthorhombic system, space group $P2_12_12_1$, *a*=12.420 (3), *b*=14.407 (3), *c*=16.290 (3) Å, *V*=2914.9 (10) Å^3, *Z*=4, crystal dimensions 0.10×0.20×0.80 mm was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω scans, $2\theta_{max}$=50.0°), Mo Kα radiation. The total number of independent reflections measured was 3440, of which 2477 were observed ($|F|^2 \geq 2\sigma|F|^2$). Final indices: R_1=0.0751, wR_2=0.1150, *S*=0.494, $(\Delta/\sigma)_{max}$=0.005, $(\Delta/\rho)_{min}$=−0.463 e/Å^3, $(\Delta/\rho)_{max}$=0.433 e/Å^3.

3.5.2. Longipedlactone F (6). $C_{30}H_{38}O_6\cdot CH_3OH$, *M*=526.65, orthorhombic system, space group $P2_12_12_1$, *a*=12.275 (3), *b*=14.606 (3), *c*=16.360 (3) Å, *V*=2933.2 (10) Å^3, *Z*=4, crystal dimensions 0.50×0.50×0.50 mm was used for measurements on a MAC DIP-2030K diffractometer with a graphite monochromator (ω scans, $2\theta_{max}$=50.0°), Mo Kα radiation. The total number of independent reflections measured was 3609, of which 3606 were observed ($|F|^2 \geq 2\sigma|F|^2$). Final indices: R_1=0.0798, wR_2=0.1247, *S*=1.090, $(\Delta/\sigma)_{max}$=0.000, $(\Delta/\rho)_{min}$=−0.270 e/Å^3, $(\Delta/\rho)_{max}$=0.254 e/Å^3. The crystal structures (**1** and **6**) were solved by the direct method SHELX-86 (Sheldrich, G.M., University of Gottingen, Gottingen, Germany, 1985) and expanded using difference Fourier techniques, refined by the program and method NOMCSDP and the full-matrix least-squares calculations.[17] Crystallographic data for the structures of **1** and **6** have been deposited in the Cambridge Crystallographic Data Centre (deposition number: CCDC 292926 of **1**, and 292927 of **6**). Copies of 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 CB21EZ, UK; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).

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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.2006.03.108.

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Calix[4]quinones. Part 4: The ClO_2 oxidation of calix[4]arene dialkyl ethers

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Abstract—Except for the special case of calix[4]arene diethyl ether **1**, the chlorine dioxide oxidation of dialkyl ethers **2**–**5** yielded only the corresponding calix[4]diquinone dialkyl ethers **8**–**11**. Chlorine dioxide oxidation of calix[4]arene diethyl ether **1** produced two isomeric products **6** and **7**, which were stable enough to be isolated by column chromatography. However, a slow conformational interconversion between isomeric pair **6** and **7** was observed at room temperature, and the equilibrium was reached after 400 h at 18 °C with an amount of 5:3 in favor of *syn*-isomer.

1. Introduction

Electron transport systems are the vital pathways for energy-producing mechanisms in all living cells, and the quinone and dihydroquinone (*p*-hydroxyphenol) pairs are the key moieties in coenzyme Q for the charge transport process. Based on these known principles, it is rational to propose that the calixquinone and *p*-hydroxycalixarene pairs may serve as an enzyme model to probe the charge transport process.

In the literature, two groups of the calix[4]quinones derivatives, e.g., benzoated calix[4]quinones[1] and etherated calix[4]-quinones,[2,3] were reported. The calix[4]quinone benzoates were synthesized by treating the corresponding calix[4]arene benzoates with chlorine dioxide at room temperature,[1] whereas, the oxidation of calix[4]arene ether derivatives occurred under more severe conditions.[3] Although, a milder chlorine dioxide oxidation condition for calix[4]arene ether derivatives was noted by Gutsche and his co-workers,[2] eventually the oxidation reactions were performed on thallium tris-trifluroacetate in trifluroacetic acid.[3] In this paper, we report on the isolation of calix[4]quinone ether derivatives **6**–**11** from the chlorine dioxide oxidation of the corresponding calix[4]arene ethers **1**–**5**, and also describe primarily the kinetic result of a slow conformational interconversion between isomeric pair **6** and **7**.

Keywords: Calix[4]arene; Calix[4]quinone; Chlorine dioxide oxidation; Conformational interconversion.
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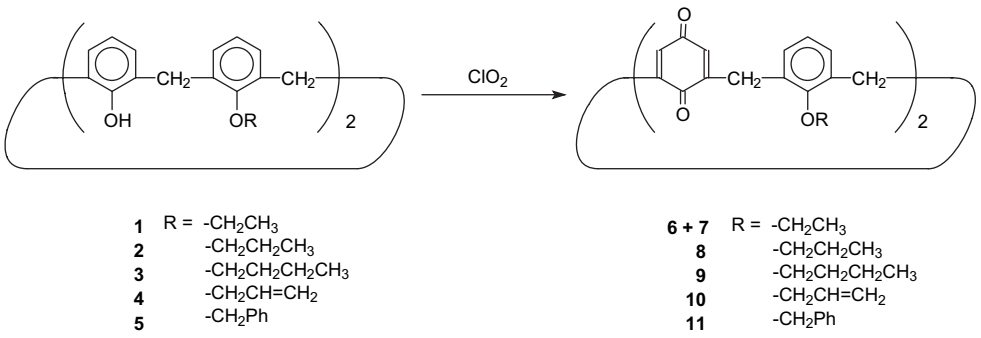
2. Results and discussion

2.1. Calix[4]diquinone dialkyl ethers 6–11

In our earlier work, we have established a standard synthetic procedure for converting the benzoated calix[4]arenes to the corresponding benzoated calix[4]quinones. It would be supportive in calixarenes chemistry if the converting pathway for the calix[4]arene ethers to their corresponding calix[4]-quinones can be established under the same milder reaction conditions.

Due to the conformational flexibility of the calix[4]arene dimethyl ether, five other common calix[4]arene dialkyl ethers (**1**–**5**) were prepared[4] for the study of the chlorine dioxide oxidation as shown in Scheme 1. As in a standard procedure for the oxidation of calix[4]arene benzoated, the calix[4]arene dialkyl ethers **1**–**5** were dissolved in acetonitrile and oxidized with a portion of yellow aqueous chlorine dioxide solution. The reaction mixture was stirred at room temperature, and the reaction was monitored by thin layer chromatography to determine the optimal reaction time for different calix[4]arene dialkyl ethers. Unlike their benzoates counterparts,[1] the oxidization of the calix[4]arene ether derivatives proceeded at various pace, which ranged from 4 h to 96 h. Although the exact solubility of five dialkyl ethers **1**–**5** in acetonitrile was not measured, the solubility, and hence the oxidation rate, seemed to be decreased as the sizes of the substitutent increased.

Large quantities of yellow solids were afforded for all five oxidative reactions after a standard worked up procedure. Except for calix[4]arene diethyl ether, all other oxidation



Scheme 1.

cases produced only one major component. Unfortunately, a simple recrystallization method was not able to isolate the corresponding oxidative products, and therefore, the chromatographic separation was applied for all the oxidation reactions to isolate the corresponding products **6–11**.

In the chlorine dioxide oxidation conditions, only the free phenol moieties were oxidized into quinones and the alkylated phenol moieties were not affected. Therefore, the oxidated products **6–11** retained the structural C_{2v} symmetry, and the products were easy to identify by their ^{1}H NMR spectrum. Of all the ^{1}H NMR spectra of products **6–11**, a singlet for quinone hydrogens appeared, whereas, the signals for the phenol moieties, which composed one singlet for phenolic hydroxy hydrogens, one triplet for *para*-aromatic hydrogens, and one doublet for *meta*-aromatic hydrogens, vanished. The characteristic signals of the different alkoxy groups, which were also not affected by the chlorine dioxide, were the labels for each oxidative product (**6–11**).

2.2. Conformational interconversion of calix[4]diquinone diethyl ether isomeric pair 6 and 7

As mentioned previously, two major components were observed on the chlorine oxidation of calix[4]arene diethyl ether **1**. Using a TLC analysis, two colored fractions with very different R_f values (0.29 and 0.13) were displayed, and the corresponding products **6** and **7** were easily isolated by column chromatography. The first fraction, compound **6**, displayed a clean ^{1}H NMR spectrum (Fig. 1) for the oxidated structure of calix[4]diquinone diethyl ether, and the FABMS confirmed the molecular weight of the diquinone structure. The second colored fraction, which took a longer period to elute, displayed an overlapping ^{1}H NMR signal (Fig. 2) with a contamination of the first colored fraction material. It was puzzling as a small amount of compound **6** always appeared on the ^{1}H NMR spectrum even with a careful selection of the eluted fractions for the product **7**. The molecular weight determination and the ^{1}H NMR spectral analysis

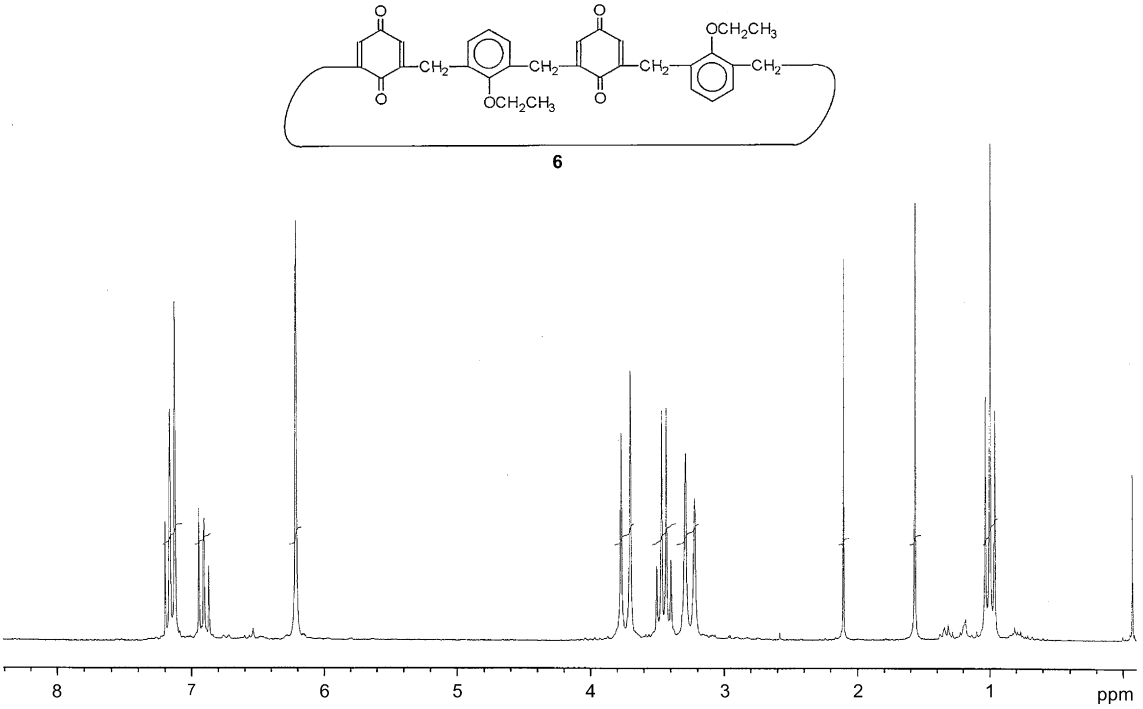


Figure 1. ^{1}H NMR spectrum (200 MHz) of *anti*-25,27-diethoxy-26,28-calix[4]diquinone (**6**).

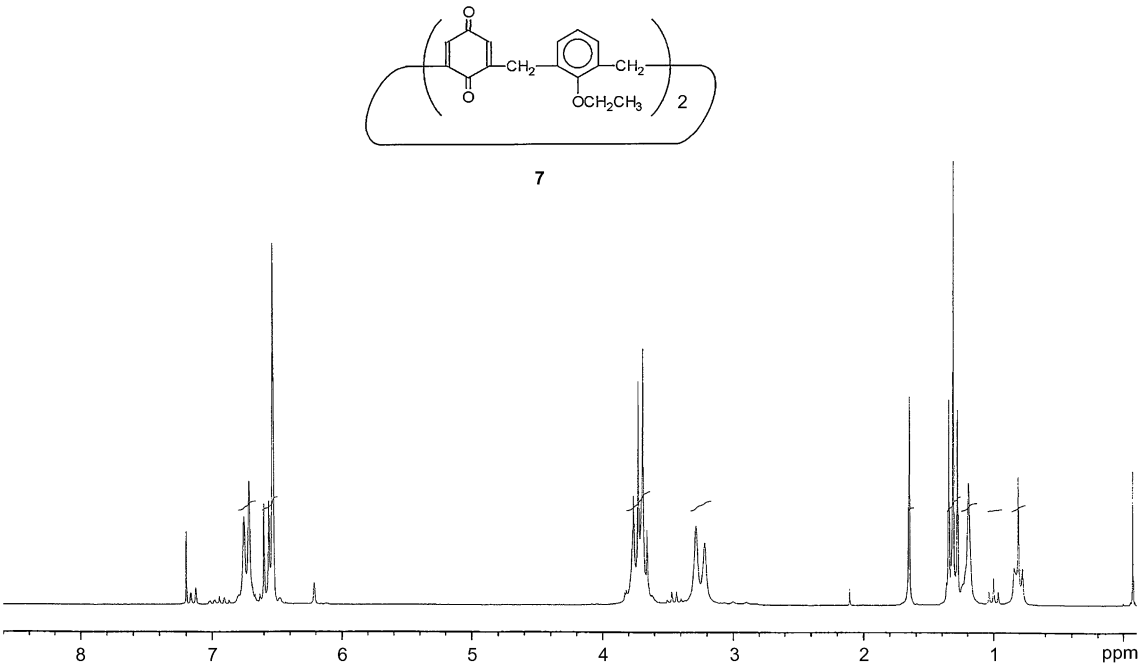


Figure 2. [1]H NMR spectrum (200 MHz) of *syn*-25,27-diethoxy-26,28-calix[4]diquinone (**7**).

indicated that the product **7** also possessed a molecular structure of calix[4]diquinone diethyl ether as the first colored fraction product **6**. The exact structures for each compound were determined by comparing the chemical shift of the quinone hydrogens' singlet. All other *syn*-1,3-dialkylated calix[4]quinones **8–11** displayed a singlet between δ 6.45 and 6.55 for the quinone hydrogens. Based on this observation, a singlet at δ 6.21 was the basis for assigning product **6** as the *anti*-isomer.

The *syn*-1,3-diethylated calix[4]arene (**1**) was not conformational mobile,[5] but an oxidation process with a flexible intermediate was able to explain the formation of the *anti*- and *syn*-isomers (**6** and **7**). However, when products **6** and **7** were sent for a high field NMR spectrum,[6] after a long wait, two identical [1]H NMR spectra were obtained, as shown in Figure 3. It was soon realized that the identical [1]H NMR spectrum resulted from the conformational interconversion between the *anti*- and *syn*-isomers (**6** and **7**) at the ambient temperature, and the earlier flexible intermediate scheme for the formation of the isomeric pairs **6** and **7** was excluded. This 'interconversion' phenomenon was also able to clarify the existence of the 'contamination' during a long elution time for the second colored fraction **7**.

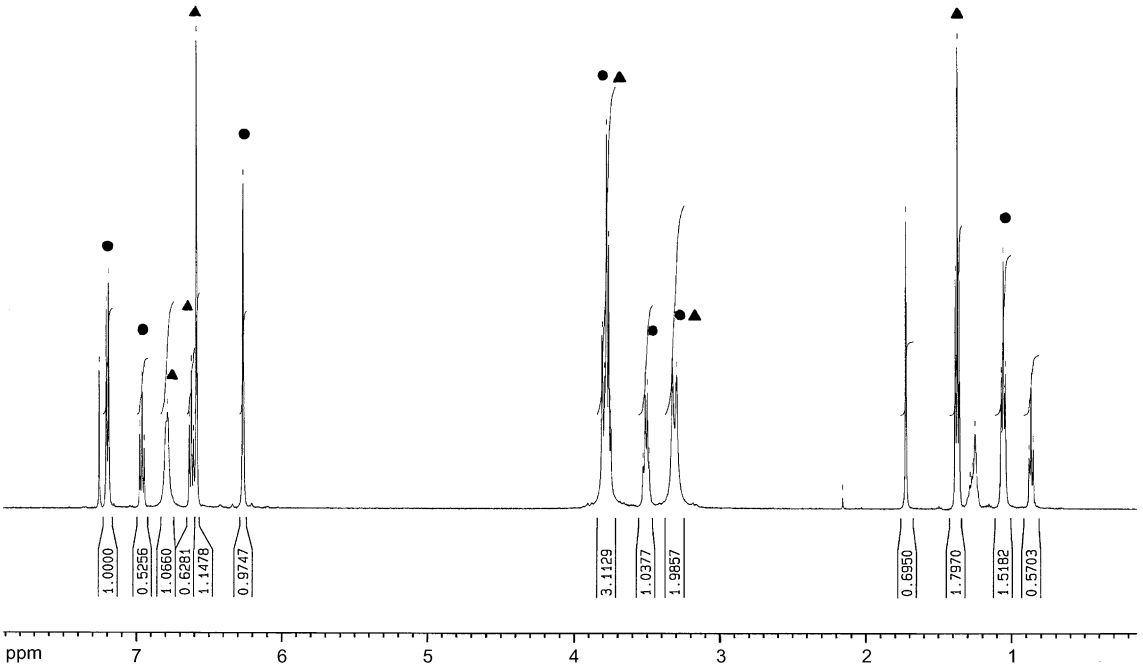


Figure 3. [1]H NMR spectrum (500 MHz) of a mixture of calix[4]diquinones **6** (●) and **7** (▲).

It was known that the conformational interconversion arose from the 'through-the-annulus-rotation' in the calix[4]arene system, and the rotation could be suppressed by introducing an ethoxy or other larger alkoxy moieties in the 'lower rim'.[5] A simple structure analysis indicated that the oxidation on the diethylated calix[4]arene **1** would not only reduce the size of the 'lower rim' substituents but also remove the 'lower rim' hydrogen bond. The result created a suitable space for the ethoxy moieties to slowly rotate through the 'lower rim' annulus, and produced two stable isomers **6** and **7**. Both isomers were stable enough to be isolated from the reaction mixture, but the slow 'through-the-annulus-rotation' of the ethoxy moieties would enable the two isomers to convert to one another. The rate of the interconversion between two isomers **6** and **7** was in the order of days, and a kinetic study to determine an exact rotation rate would be discussed in next section.

2.3. Kinetic study of the interconversion between calix[4]diquinone diethyl ether isomeric pair 6 and 7

As shown in Figure 3, a sharp singlet at δ 6.21 and a triplet at δ 1.01 were the distinct signals from the *anti*-isomer **6**, whereas a triplet at δ 1.31 arose only from the *syn*-isomer **7**. It was obvious that with an appropriate internal standard, such as methylene chloride, the amount of both *anti*-isomer **6** and *syn*-isomer **7** could be determined by comparing the integral ratio of the selected signals with the sharp methylene chloride's singlet at δ 5.30.

Initially, all the kinetic measurements[7] were carried out in an ice bath temperature; however, the conversion rate was too low to display any significant spectral difference on a week's long study. The measuring temperature was then raised to 18 °C (the temperature of the location of the ^{1}H NMR) to promote the interconversion, but it also created an unexpected problem. Since the NMR sample tube was not flame-sealed, the amount of the CH_2Cl_2, which was added in small amount as an internal standard, was depleted during a several weeks' long measurement. As a result, all the kinetic data were not longer valid with CH_2Cl_2 as an internal standard. A closer examination of the ^{1}H NMR spectrum of isomers **6** and **7**, revealed that only the methylene hydrogens, which included eight calix[4]arene's methylene hydrogens and four ethyl's methylene hydrogens, were displayed in a region between δ 3.0 and 4.0. The integral ratio in that range, therefore, provided a suitable standard to estimate the amount of either isomers **6** and **7** for the kinetic measurement.

The samples for the NMR study were isolated by thick layer chromatography and further purified by recrystallization at low temperature. The samples were dissolved in $CDCl_3$ and subjected to ^{1}H NMR measurement twice a day for a period of two weeks. The amount of each isomer was calculated by comparing the integral ratio of three distinct signals with the integral ratio of the 12 methylene hydrogens' signals, and the result is listed in Table 1. The data were subjected to Computer software Origin to produce a plot as shown in Figure 4. The first order exponential decay fit

Table 1. The composition of *anti*- and *syn*-isomers (**6** and **7**) in the interconversion process

Time	*anti*-Isomer **6** with signal at δ 6.3		*anti*-Isomer **6** with signal at δ 1.1		*syn*-Isomer **7** with signal at δ 1.4	
	Number of proton[a]	Composition in %[a]	Number of proton[a]	Composition in %[a]	Number of proton[a]	Composition in %[a]
0[b]	0.59	9.8	0.39	9.8	5.39	89.8
5	0.68	11.4	0.46	11.5	5.27	87.9
21	0.84	14.0	0.57	14.3	5.01	83.5
28	0.95	15.9	0.64	15.9	4.98	83.0
45	1.18	19.6	0.76	19.1	4.79	79.8
53	1.22	20.3	0.85	21.1	4.72	78.7
69	1.38	23.0	0.90	22.4	4.62	77.0
77	1.40	23.3	0.93	23.1	4.46	74.3
90	1.51	25.2	0.98	24.6	4.39	73.2
93	1.49	24.8	1.01	25.3	4.44	74.0
100	1.50	25.0	1.05	26.4	4.38	73.0
117	1.69	28.1	1.09	27.2	4.24	70.6
124	1.69	28.1	1.12	28.1	4.18	69.6
141	1.74	29.1	1.27	31.7	3.92	65.4
148	1.80	30.1	1.16	29.0	4.05	67.5
165	1.86	31.0	1.28	32.1	3.95	65.8
172	1.89	31.5	1.24	31.0	3.93	65.6
190	1.93	32.2	1.32	32.9	3.81	63.4
197	1.94	32.3	1.29	32.2	3.87	64.5
214	1.99	33.1	1.34	33.4	3.78	63.1
220	2.03	33.9	1.32	33.1	3.83	63.9
236	2.07	34.6	1.33	33.3	3.72	62.0
242	2.20	36.7	1.40	34.9	3.78	63.0
259	2.16	35.8	1.37	34.3	3.72	62.1
267	2.18	36.3	1.39	34.8	3.72	61.9
290	2.18	36.3	1.38	34.6	3.63	60.6
307	2.17	36.2	1.42	35.4	3.61	60.2
333	2.13	35.4	1.49	35.1	3.54	59.1
339	2.19	36.4	1.42	35.7	3.46	57.7
361	2.24	37.3	1.40	35.1	3.40	56.7
405	2.33	38.9	1.45	36.2	3.60	60.1

[a] The integral ratio in the region between δ 3.0 and 4.0 was set as 12 protons, for eight calix[4]arene's methylene hydrogens and four ethyl's methylene hydrogens. The selected signal's integrals were then calculated to estimate the amount and the percentage of the *syn*- and/or *anti*-isomers.

[b] The time '0 h' was set as the time for the first NMR measurement.

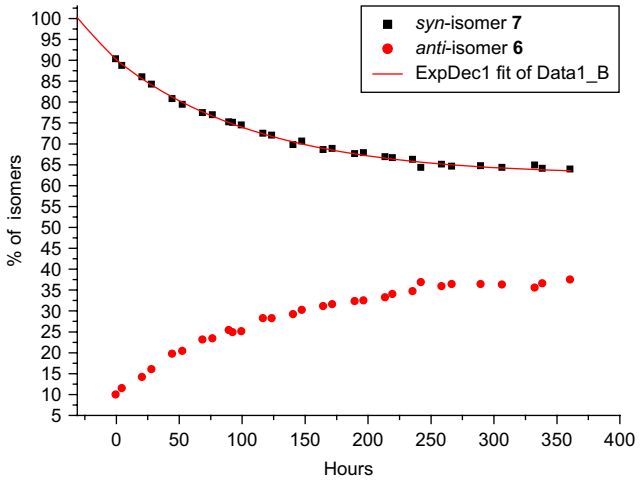


Figure 4. The plot of time versus the composition of *anti*- and *syn*-isomers (**6** and **7**).

indicated that the time elapsed for the purification process; the time between the chromatographic separation and the first NMR measurement was equivalent to 31 h at 18 °C, and the equilibrium was reached after 400 h after the first measurement with the amount of 5:3 in favor of *syn*-isomer **7**. The K_f value was calculated as 9.0×10^{-6} s^{-1} with the aid of Computer software Origin, as shown in Figure 5.

For a practice purpose, the samples were also dissolved in pyridine-d_5 and the spectra were also taken twice a day for a period of two weeks. To our surprise, the conversion rate was faster in the pyridine system. The system took less then 120 h to reach the equilibrium with the amount of 61% *syn*-isomer **7**, and the K_f value was estimated as 2.4×10^{-5} s^{-1}. Although the physical properties between C_5H_5N and $CHCl_3$ were known to be very different, none of them seemed to be able to influence the rate of the interconversion. Therefore, we speculated that the calixarene's cavity might be more suitable for $CHCl_3$ molecule to enter and formed the 'meta-stable' complex, in which the passage for the 'through-the-annulus-rotation' would be blocked and the conversion rate was lengthened. To support this presumption, the system will be further studied with a series of NMR solvents. The results of the different conversion rate may provide an useful information to estimate the calix[4]arene's complexation ability toward the small organic molecules.

3. Experimental[8]

3.1. General procedure

A slurry of 5 mmol of calix[4]arene dialkyl ethers **1**–**5**[4] was dissolved in 150 mL of CH_3CN, and a portion of 100 mL of aqueous ClO_2 solution[9] was then added. The reaction mixture was stirred at room temperature for a specific time, and the organic solvent was removed to leave a yellow and/or orange solid. The solid materials were collected and the purification procedures for the individual product are described separately.

3.1.1. *anti*-25,27-Diethoxy-26,28-calix[4]diquinone (6) and *syn*-25,27-diethoxy-26,28-calix[4]di-quinone (7). The reaction mixture was stirred at room temperature for 6 h, and a yellow solid was collected from a sample of 2.40 g (5.00 mmol) of **1**. Chromatographic separation (eluent: EtOAc/*n*-hexane=1:4) of the first colored fraction (R_f=0.29), which was recrystallized from $CHCl_3$ and CH_3OH, afforded 0.69 g (18.5%) of oxidized product **6** as yellow crystals: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 7.13–7.16 (d, J=7.4 Hz, 4H, Ar*H*), 6.87–6.95 (t, J=7.5 Hz, 2H, Ar*H*), 6.21 (s, 4H, quinone-*H*), 3.70–3.77 (d, J=13.4 Hz, 4H, ArCH_2Ar), 3.40–3.50 (q, J=7.1 Hz, 4H, ArOCH_2CH$_3$), 3.22–3.29 (d, J=13.4 Hz, 4H, ArCH_2Ar), 0.97–1.04 (t, J=7.1 Hz, 6H, ArOCH$_2$CH_3); ^{13}C NMR[10] ($CDCl_3$) δ 188.0, 186.3, 156.3, 147.7, 133.1, 133.0, 131.3, 124.4, 68.6, 32.0, 29.9, 15.4; FABMS *m/z*: 509 (M^++1). Anal.[11] Calcd for $C_{32}H_{28}O_6$: C, 75.59; H, 5.51; for $C_{32}H_{28}O_6\cdot1/4CHCl_3$: C, 71.94; H, 5.25. Found: C, 71.84; H, 5.13.

A second colored fraction (R_f=0.13), which was also recrystallized from $CHCl_3$ and CH_3OH, yielded 0.86 g (42.5%) of yellow crystals of **7**: mp 125–127 °C; ^{1}H NMR ($CDCl_3$)

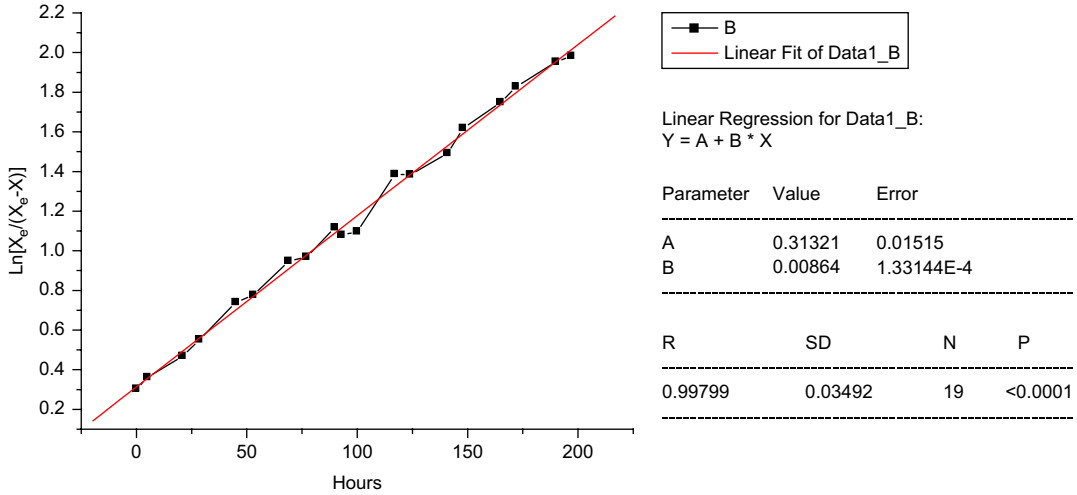


Figure 5. The plot of time versus natural log in the *syn*-**7** to *anti*-**6** interconversion process.

δ 6.72–6.76 (d, J=7.6 Hz, 4H, Ar*H*), 6.54–6.60 (m, 6H, Ar*H* and quinone-*H*), 3.66–3.76 (m, 8H, ArCH_2Ar and ArOCH_2CH$_3$), 3.22–3.29 (d, J=13.2 Hz, 4H, ArCH_2Ar), 1.28–1.35 (t, J=7.0 Hz, 6H, ArOCH$_2$CH_3); ^{13}C NMR (CDCl$_3$) δ 188.6, 186.2, 156.5, 148.1, 132.3, 130.3, 129.8, 123.6, 70.2, 32.1, 16.1; FABMS *m*/*z*: 510 (M^++2). Anal. Calcd for $C_{32}H_{28}O_6$: C, 75.59; H, 5.51; for $C_{32}H_{28}O_6\cdot H_2O$: C, 73.00; H, 5.70. Found: C, 73.03; H, 5.79.

3.1.2. 25,27-Dipropoxy-26,28-calix[4]diquinone (8). The reaction mixture was stirred at room temperature for 36 h, and a yellow solid was collected from a sample of 2.54 g (5.00 mmol) of **2**. Chromatographic separation (eluent: EtOAc/*n*-hexane=1:4) followed by recrystallization from $CHCl_3$ and CH_3OH afforded 1.16 g (43%) of orange color crystals of **8**: mp 178–180 °C; ^{1}H NMR (CDCl$_3$) δ 6.76 (br s, 4H, Ar*H*), 6.57–6.61 (m, 6H, Ar*H* and quinone-*H*), 3.78 (br s, 4H, ArCH_2Ar), 3.60–3.63 (t, J=7.4 Hz, 4H, ArOCH_2CH$_2$CH$_3$), 3.26–3.30 (br d, 4H, ArCH_2Ar), 1.75–1.82 (m, 4H, ArOCH$_2$CH_2CH$_3$), 0.96–0.99 (t, J=7.4 Hz, 6H, ArOCH$_2$CH$_2$CH_3); ^{13}C NMR (CDCl$_3$) δ 188.3, 186.0, 156.4, 148.0, 132.0, 129.9, 129.5, 123.3, 76.3, 31.6, 23.6, 10.6; FABMS *m*/*z*: 537 (M^++1). Anal. Calcd for $C_{34}H_{32}O_6$: C, 76.12; H, 5.97. Found: C, 75.94; H, 5.83.

3.1.3. 25,27-Dibutoxy-26,28-calix[4]diquinone (9). The reaction mixture was stirred at room temperature for 72 h, and an orange solid was collected from a sample of 2.68 g (5.00 mmol) of **3**. Chromatographic separation (eluent: EtOAc/*n*-hexane=1:4) followed by recrystallization from $CHCl_3$ and CH_3OH afforded 1.37 g (48.5%) of orange color crystals of **9**: mp 76–78 °C; ^{1}H NMR (CDCl$_3$) δ 6.76 (br s, 4H, Ar*H*), 6.57–6.61 (m, 6H, Ar*H* and quinone-*H*), 3.79 (br s, 4H, ArCH_2Ar), 3.64–3.67 (t, J=7.0 Hz, 4H, ArOCH_2CH$_2$CH$_2$CH$_3$), 3.29–3.30 (br d, 4H, ArCH_2Ar), 1.72–1.77 (m, 4H, ArOCH$_2$CH_2CH$_2$CH$_3$), 1.38–1.45 (m, 4H, ArOCH$_2$CH$_2$CH_2CH$_3$), 0.92–0.95 (t, J=7.4 Hz, 6H, ArOCH$_2$CH$_2$CH$_2$CH_3); ^{13}C NMR (CDCl$_3$) δ 188.2, 185.9, 156.6, 148.0, 132.0, 129.9, 129.5, 123.3, 74.6, 32.4, 31.7, 19.3, 13.9; FABMS *m*/*z*: 566 (M^++2). Anal. Calcd for $C_{36}H_{36}O_6$: C, 76.60; H, 6.38; for $C_{36}H_{36}O_6\cdot 1/3H_2O$: C, 75.79; H, 6.32. Found: C, 75.72; H, 6.32.

3.1.4. 25,27-Dibenzyloxy-26,28-calix[4]diquinone (10). The reaction mixture was stirred at room temperature for 96 h, and a yellow solid was collected from a sample of 3.02 g (5.00 mmol) of **4**. Chromatographic separation (eluent: EtOAc/*n*-hexane=1:4) followed by recrystallization from $CHCl_3$ and CH_3OH afforded 1.96 g (62%) of yellow crystals of **10**: mp 234–235 °C; ^{1}H NMR (CDCl$_3$) δ 7.33–7.34 (m, 6H, Ar′*H*), 7.26–7.28 (m, 4H, Ar′*H*), 6.77 (br s, 4H, Ar*H*), 6.62–6.65 (t, J=7.5 Hz, 2H, Ar*H*), 6.44 (s, 4H, quinone-*H*), 4.77 (s, 4H, OCH_2Ar′), 3.63 (br d, 4H, ArCH_2Ar), 3.14 (br s, 4H, ArCH_2Ar); ^{13}C NMR (CDCl$_3$) δ 188.1, 185.9, 155.8, 147.8, 136.6, 132.1, 130.2, 129.6, 128.6, 128.5, 128.3, 128.2, 123.6, 76.3, 31.7, 31.5; FABMS *m*/*z*: 634 (M^++2). Anal. Calcd for $C_{42}H_{32}O_6$: C, 79.75; H, 5.06; for $C_{42}H_{32}O_6\cdot 1/2H_2O$: C, 78.63; H, 5.15. Found: C, 78.69; H, 4.81.

The yellow crude product can also be purified by recrystallizing four times from $CHCl_3$ and CH_3OH to afford 1.35 g (42.5%) of the yellow powder of **10**. The physical and the spectral properties of this yellow powder were identical to the product, which was purified from the chromatographic method.

3.1.5. 25,27-Diallyloxy-26,28-calix[4]diquinone (11). The reaction mixture was stirred at room temperature for 4 h, and an orange solid was collected from a sample of 2.52 g (5.00 mmol) of **5**. Chromatographic separation (eluent: EtOAc/*n*-hexane=1:4) followed by recrystallization from $CHCl_3$ and CH_3OH afforded 1.82 g (67.5%) of orange color crystals of **11**: mp 186–188 °C; ^{1}H NMR (CDCl$_3$) δ 6.82–6.83 (br d, 4H, Ar*H*), 6.63–6.66 (t, J=7.6 Hz, 2H, Ar*H*), 6.55 (s, 4H, quinone-*H*), 5.99–6.07 (m, 2H, ArOCH$_2$C*H*=CH$_2$), 5.30–5.34 (dd, J=17.1, 1.3 Hz, 2H, ArOCH$_2$CH=CH_2), 5.23–5.25 (dd, J=10.4, 0.9 Hz, 2H, ArOCH$_2$CH=CH_2), 4.22–4.23 (d, J=5.5 Hz, 4H, ArOCH_2CH=CH$_2$), 3.69 (br s, 4H, ArCH_2Ar), 3.33–3.34 (br d, 4H, ArCH_2Ar); ^{13}C NMR (CDCl$_3$) δ 188.2, 186.1, 156.0, 147.6, 133.4, 132.2, 130.1, 130.0, 123.6, 118.0, 74.6, 32.2; FABMS *m*/*z*: 533 (M^++1). Anal. Calcd for $C_{34}H_{28}O_6$: C, 76.69; H, 5.26. Found: C, 76.62; H, 5.04.

Acknowledgements

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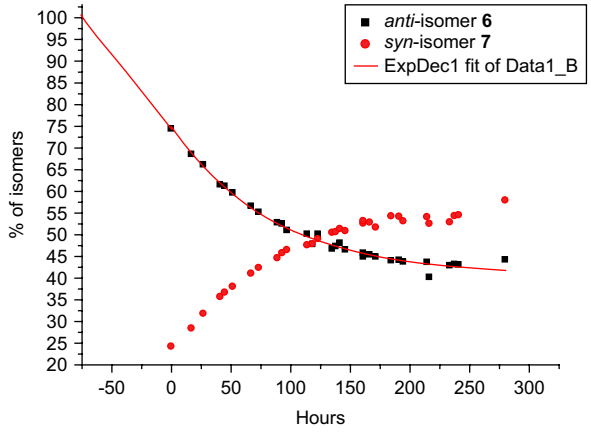
5. Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.
6. We thank Ms. S.-L. Huang of NSC Instrumental Center in Taipei for taking all the high field NMR measurements.
7. All the kinetic studies were preformed on JOEL DMX-200 WB spectrometer. Based on the data from Table 1, the error in the true value of each integral ratio was estimated to be less than 3%. Hence, the inaccuracy of the *K* calcd. value was estimated to be less than 6%.
8. All reagents were obtained from Commercial Chemical Companies and used without further purification. Melting points were taken in capillary tubes on a Mel-Temp apparatus (Laboratory Devices, Cambridge, MA) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra are recorded on Burker DMX-500 SB spectrometer and chemical shifts are reported as δ values in parts per million. FABMS spectra were taken on a JOEL

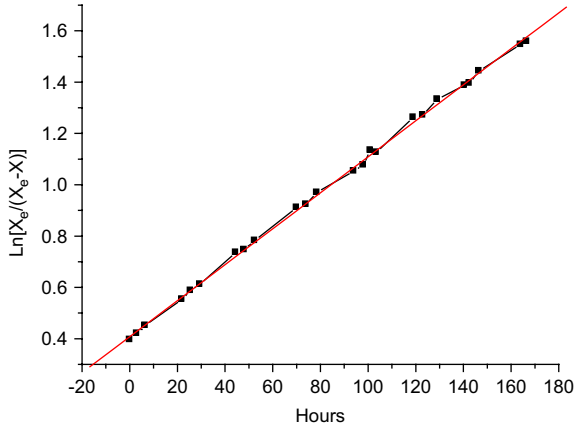
JMS-HX 102 spectrometer and elemental analyses were performed on a Perkin–Elmer 240C analyzer. The kinetic studies were performed on JOEL DMX-200 WB spectrometer. Chromatographic separations were performed with Merck silica gel (230–400 mesh ASTM) on columns of 25 mm diameter filled to height of 150 mm. TLC analyses were carried out on Macherey–Nagel aluminum back silica gel 60 F_{254} plates (absorbent thickness 0.2 mm).

9. Aqueous chlorine dioxide solution was prepared by mixing equal volume of sodium chlorite solution ($NaClO_2 \cdot 2H_2O$, 31.60 g, 0.25 mol in 500 mL of deionized water) and sodium persulfate solution ($Na_2S_2O_8$, 29.70 g, 0.25 mol in 500 mL of deionized water). The solution was then stored in a brown bottle at 0 °C prior to being used.
10. The pure compounds of **6** and **7** will convert into an equilibrium mixture or partial converted mixture during the purification process and/or NMR measurement. Therefore, the ^{13}C NMR spectrum for either compound **6** or **7** consisted spectral signals from the original compound and the converted compound in a minor amount. To properly assign the ^{13}C NMR spectrum for compounds **6** and **7**, the task was achieved by marking all the identical signals from both spectra, and then assigning the lower intensity peaks as the signal arose from the converted compound.
11. All the new compounds, which were submitted for Elemental Analysis (EA), were dried at 120 °C under vacuum for 48 h prior to the analysis. If the analysis value was different from the calculated value, the sample was dried at 140 °C under vacuum for 48 h prior to another analysis. The drying period will be increased further, if the sample still received a different EA value from the theoretical value. The procedure was continued until a constant EA value was attained.

Appendix 1

The results of the kinetic studied for *anti*-**6** to *syn*-**7** conversion in $CHCl_3$.





B
Linear Fit of Data1_B

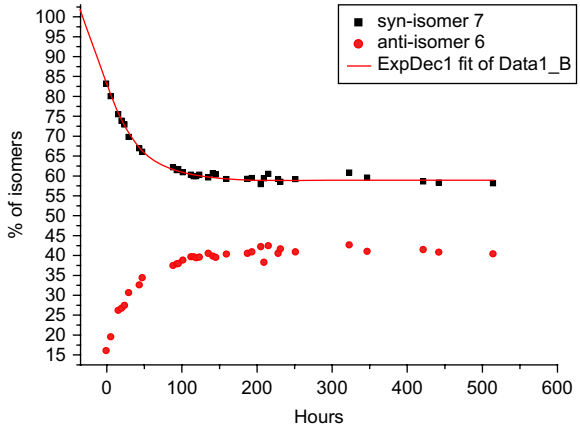
Linear Regression for Data1_B:
Y = A + B * X

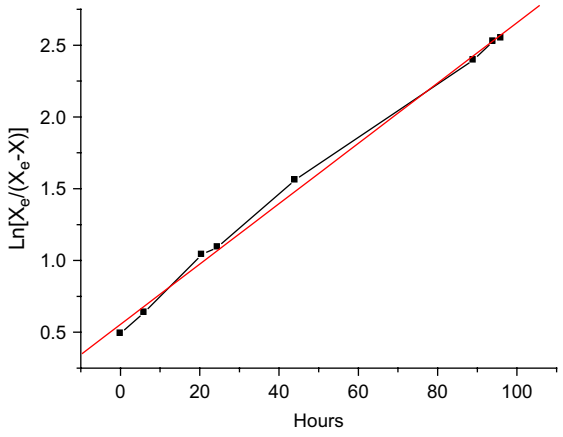
Parameter	Value	Error
A	0.40793	0.00475
B	0.00701	4.88789E-5

R	SD	N	P
0.99947	0.01231	24	<0.0001

Appendix 2

The results of the kinetic studied for *syn*-**7** to *anti*-**6** conversion in C_5H_5N.





B
Linear Fit of Data1_B

Linear Regression for Data1_B:
Y = A + B * X

Parameter	Value	Error
A	0.55468	0.03033
B	0.02102	5.0406E-4

R	SD	N	P
0.99828	0.05401	24	<0.0001

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Selective substitutions in the C10-methyl group in erythromycin derivatives

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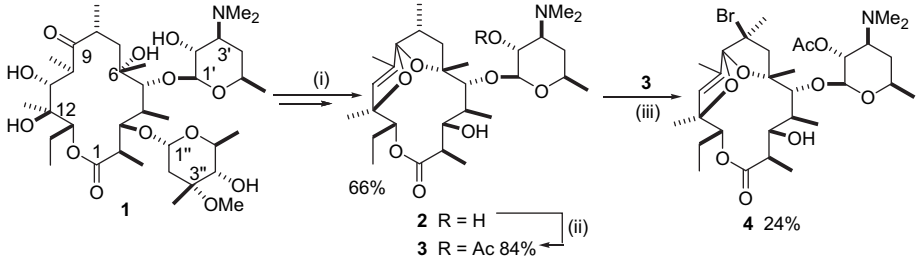
Abstract—A method for chemical modifications of the relatively unreactive C10-methyl group in the erythromycin macrolactone ring has been developed. Erythralosamine was protected as an *N*-oxide in the *N*,*N*-dimethylamino group and reacted with NBS in acetic acid to provide two regioisomeric allylic bromides. The same amine was formed from both isomers on nucleophilic substitution. Both regioisomeric bromides in cross-coupling reactions under Stille conditions provided the same product from substitution in the 10-methyl group via a common π-allylic palladium complex. Under Negishi conditions with trimethylalane, the Pd-catalysed cross-coupling provided the 10-ethyl homologue. X-ray analyses were used to confirm the structure of erythralosamine, and to determine the structures of the allylic bromides from erythralosamine *N*-oxide.

1. Introduction

The erythromycin family of macrolactone antibiotics comprises an important group of antibiotics widely used clinically.[1–3] The parent drug has been subjected to a number of chemical modifications to improve its physicochemical properties and activity profiles. Gradually, all positions in the macrolactone ring and in the ring substituents have been chemically modified with exception of the 10-methyl group. The latter is situated at the non-activated C10-carbon in the macrolide ring. Some modifications in the 10-postion, however, have been effected by genetic engineering techniques, the products being 10-desmethylerythromycin A, 10-ethyl and 10-hydroxy macrolides.[4,5] Very recently quaternisation at C10 has been effected by intramolecular 1,3-dipolar cycloaddition in a C10–C11 unsaturated macrolide, the product being a tricyclic derivative.[6]

A chemical approach for modification of the C10-methyl group, however, was suggested by a structural analysis of the acidic degradation product **2** from erythromycin A (**1**) in Scheme 1.[7] The same product, erythralosamine, is generated in the acidic environment in the stomach during metabolic degradation of erythromycin as a drug. In the literature, the chemistry of erythralosamine has been given little attention presumably because of its low antibacterial activity in comparison with the parent antibiotic.[8]

The numbering system in erythromycin A and erythralosamine is shown in Scheme 1. The basic desosamine sugar in the erythromycin 5-position is retained under moderate acidic degradative conditions whereas loss of water and elimination of the neutral cladinose moiety from the 3-position in erythromycin A lead to the formation of the anhydro spiroketal **2**. The spiroketal structure is remarkably stable



Scheme 1. Reagents and reaction conditions: (i) HCl, aq EtOH, rt, 24 h; (ii) Ac_2O, NEt_3, CH_2Cl_2, rt, 2 h; (iii) Br_2, CCl_4, rt, 2 h.

Keywords: Chemoselective N-oxidation; Allylic bromination; C10-methyl amination; C10-methyl homologation; Pd-catalysed cross-couplings.
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chemically, presumably for skeletal structure reasons. The 10-methyl group in erythralosamine is attached to a carbon–carbon double bond and as such was expected to possess allylic properties.

2. Results and discussion

This report describes some chemoselective transformations of the 10-methyl group in erythralosamine derivatives. Before working with erythralosamine as substrate for chemical transformations, the structure that had been assigned to erythralosamine,[7] was ascertained by an X-ray analysis. The ORTEP plot of a single crystal X-ray analysis of erythralosamine is shown in Figure 1.

Erythralosamine (**2**) was prepared from erythromycin A by HCl induced transformation in aqueous ethanol (Scheme 1). Subsequently, bromination was attempted. With bromine in carbon tetrachloride, a complex reaction mixture resulted. For comparison, erythronolide B is brominated, with molecular bromine, adjacent to the 9-carbonyl group in the 8-position.[9]

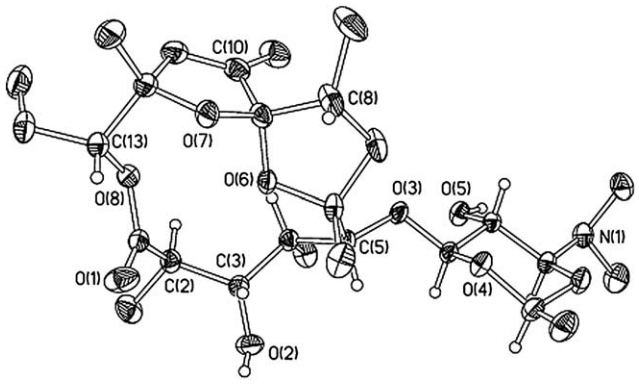
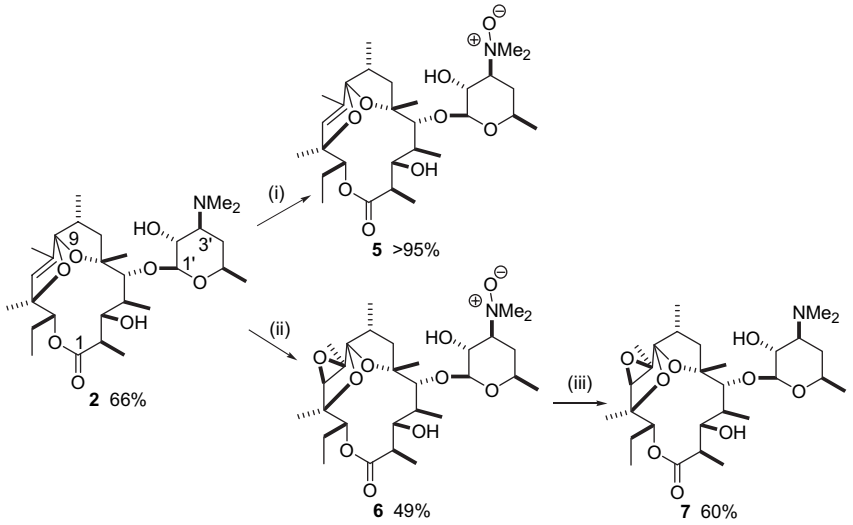


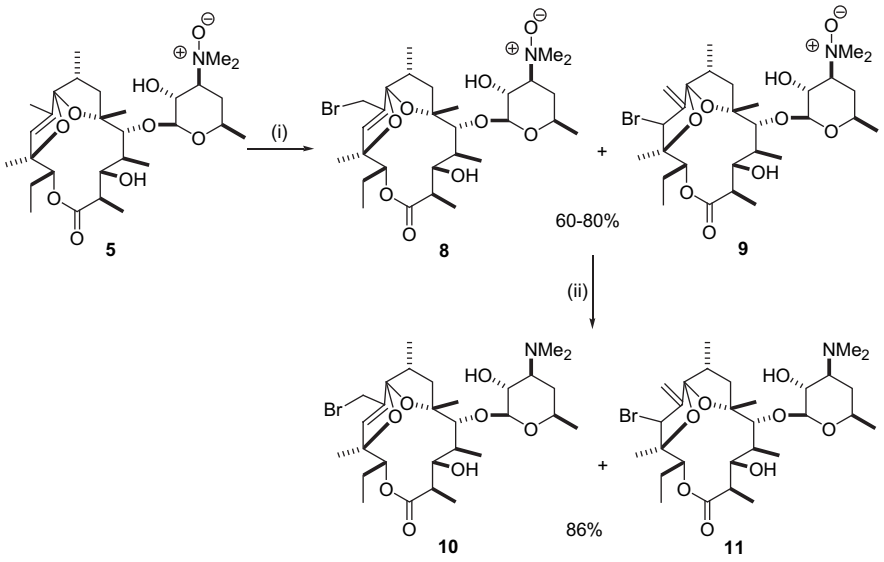
Figure 1. ORTEP plot of compound **2**. Ellipsoids are shown at 50% probability. For clarity only the hydrogen atoms at the oxygen and stereogenic centres are shown.

For erythralosamine attempts were made to reduce any interference from the sugar 2′-hydroxyl group by prior acetylation. Erythralosamine contains two secondary hydroxyl groups, which are located in different chemical environments. The desosamine 2′-hydroxyl group is vicinal to the dimethylamino substituent, which may interact with the acylating agent to promote ester formation. Hence the 2′-hydroxyl group reacted more readily than the 3-hydroxyl group in the macrolide skeleton with acetic anhydride and triethylamine in dichloromethane, the product being the 2′*O*-acetyl derivative **3**.[10] The subsequent reaction with bromine in carbon tetrachloride provided the C8-brominated structure **4** in low yield (24%) (Scheme 1). The NMR spectrum confirmed C8 bromination. The chemical shift for the carbon signal at C8 was moved from 39 to 70 ppm due to the deshielding from the bromine. The chemical shift for the C8-methyl group was also changed from 11 to 27 ppm. Dept 135 experiments showed C8 to be a quaternary carbon. A singlet at 1.74 ppm in the ^{1}H NMR spectrum for the methyl group at C8 indicated the same result. Only one stereoisomer was obtained, most likely the (8*S*)-stereoisomer by analogy to bromination of erythronolide B in the 8-position by NBS in acetic acid.[9] In the reaction between erythralosamine and NBS in acetic acid, NMR analysis of the crude reaction product mixture showed the presence of the 10-bromomethyl derivative as a major component and N-demethylated derivatives as minor components. N-Demethylation reactions were to be expected since demethylation reactions had been reported for erythromycin ketolides when reacted with *N*-iodosuccinimide,[11] and under other reaction conditions between halogens and macrolides.[12] The demethylation reactions presumably proceed via an *N*-bromo-ammonium intermediate with elimination of the iminium ion, which is further hydrolysed.

The demethylation indicates interaction between the amino nitrogen and the bromine electrophile. Attempts were therefore made to reduce or exclude this interaction by initial construction of the *N*-oxide **5** (Scheme 2). A reaction with hydrogen peroxide in methanol at room temperature yielded the *N*-oxide **5** in almost quantitative yield. No epoxide



Scheme 2. Reagents and reaction conditions: (i) H_2O_2, MeOH, rt, 6–8 h; (ii) MCPBA, CH_2Cl_2, reflux, 8 h; (iii) PPh_3, THF, reflux, 17 h.



Scheme 3. Reagents and reaction conditions: (i) NBS, AcOH, rt, 2–3 h; (ii) PPh_3, THF, reflux, 17 h.

formation was observed in the C10–C11-carbon double bond in erythralosamine.

With *m*-chlorobenzoyl peroxide (MCPBA), however, both N-oxidation and C–C epoxidation resulted, the product being the epoxide **6**. The *N*-oxide moiety was chemoselectively deoxygenated on treatment of the product **6** with triphenylphosphine. The resultant epoxide **7** is chemoisomeric with the *N*-oxide **5** (Scheme 2).

When the erythralosamine *N*-oxide (**5**) was reacted with NBS in acetic acid, the major product was the 10-bromomethyl derivative **8**, and the minor product was the isomeric 11-bromo derivative **9** (Scheme 3). No demethylation of the dimethylamino group was observed, nor was bromine introduced into the C8-position. Erythralosamine *N*-oxide (**5**) did not react with bromine in carbon tetrachloride under the conditions used for the bromination of the amine **3** (Scheme 1). The relative amounts of the two bromo isomers **8** and **9** varied from equimolar amounts to 1:10 in favour of the bromomethyl isomer **8**. Chromatographic properties were very similar, but the major product could be isolated in an isomer pure state for analytical purposes. The product is formed under conditions normally associated with an ionic substitution, not an NBS-free radical reaction. The reaction mechanism has not been studied. We postulate that the reaction is initiated by an electrophilic addition to the carbon–carbon double bond whereby the methyl group becomes activated for proton abstraction. The product is the 11-bromo isomer **9**. A subsequent bromine addition and bromide elimination from C11 provides the bromomethyl isomer **8**. The structure of the *N*-oxide bromide **8** has been ascertained by a single crystal X-ray analysis and the ORTEP plot is shown in Figure 2.

For the further transformations, the *N*-oxide protection was removed by phosphine deoxygenation. Heating the pure isomer **8** or the crude mixture of the bromo isomers **8** and **9** under reflux in THF in the presence of triphenylphosphine, provided the amine **10** or the isomeric amine derivatives

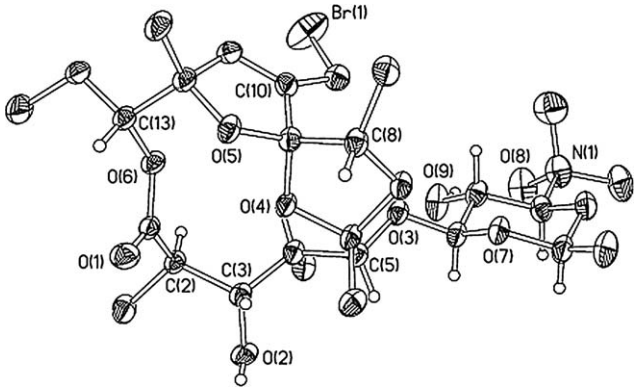


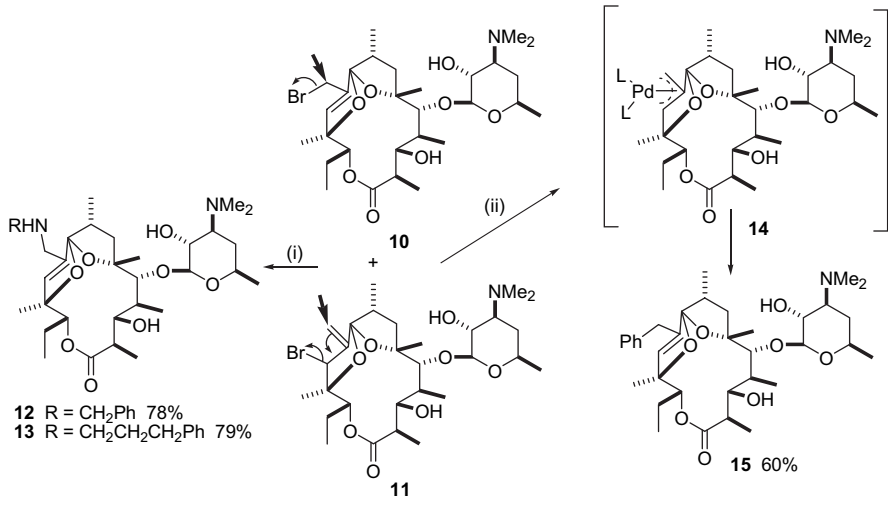
Figure 2. ORTEP plot of bromo compound **8**. For clarity only hydroxyl hydrogen atoms and hydrogen atoms at the stereogenic centres are shown.

10 and **11** without any significant reaction at the allylic bromide positions (Scheme 3).

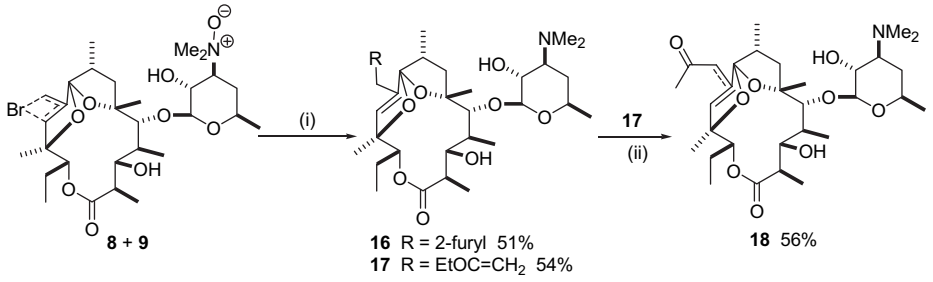
Nucleophiles reacting with the isomeric allylic bromides **10** and **11** can add either at the site of the bromine substituent in isomer **10** in a S_N2 reaction, or add to the terminal double bond in an S_N2' reaction in the isomer **11**. Both pathways will provide the same product as shown for the 10-aminomethyl products **12** and **13** (Scheme 4).

Stille coupling can be effected on the isomeric allylic bromides **10** and **11** by palladium-catalysis using the tris (dibenzylideneacetone)dipalladium chloroform complex $[Pd_2(dba)_3\cdot CHCl_3]$ together with tri(2-furyl)phosphine (TFP) in degassed NMP at 80 °C. The reaction is exemplified in Scheme 4 with phenylation, which yielded a benzyl derivative **15** as the only regioisomeric product.

The *N*-oxides can be used directly in the cross-coupling reaction without prior deoxygenation. For the furyl product **16** in Scheme 5, the substrate was the *N*-oxides **8** and **9**. Excess phosphine was used since 1 M equiv of the phosphine in this reaction was consumed rapidly in deoxygenation of the



Scheme 4. Reagents and reaction conditions: (i) RNH_2, DMF, 80 °C, 20 h; (ii) $PhSnBu_3$, $Pd_2(dba)_3 \cdot CHCl_3$, TFP, NMP, 100 °C, 20 h.

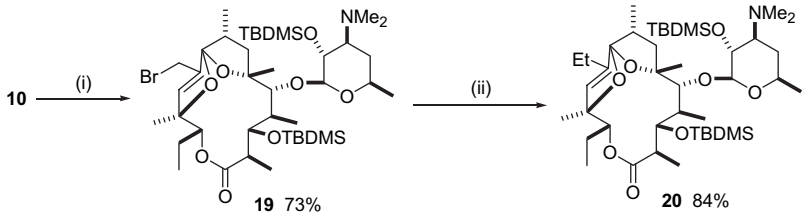


Scheme 5. Reagents and reaction conditions: (i) $RSnBu_3$, $Pd_2(dba)_3 \cdot CHCl_3$, TFP, NMP, 70–80 °C, 22–24 h; (ii) (a) 1 M HCl, rt, 20 h, (b) heat, THF.

N-oxide moiety. The remaining phosphine was ligated to the palladium complex. Tri(2-furyl)phosphine was the preferred ligand in these reactions. The ethoxyvinyl derivative **17** was formed from the *N*-oxide substrate mixture in the same manner. Only one cross-coupled isomer was obtained from the allylic bromide mixtures. Rationalisation is that the same η^3-allylpalladium complex **14** (Scheme 4) is formed from either allylic bromide. The nucleophile would add preferably to the sterically less shielded position, which is at the methylene carbon attached to the 10-position.

Tributyl(α-ethoxyvinyl)tin could be used as a masked ketone as shown in Scheme 5. When the coupled product **17** was treated with 1 M HCl in THF, the methyl ketone **18** was obtained in 56% yield. The product was a double bond isomeric mixture. The endocyclic double bond isomer was the major product, isomer ratio 3:1 (NMR). This was verified by high resolution MS, which showed one molecular ion for the isomeric ketone mixture. The signal for the oxo-carbon in the ^{13}C NMR spectrum was at 207.5 ppm, and in the minor conjugated ketone isomer at 199.5 ppm. A new signal at 40.3 ppm appeared in Dept 135 experiments due to the methylene carbon at C11. The NMR experiments indicated a migration of the double bond into conjugation with the carbonyl group and hence formation of an α,β-unsaturated ketone. The NMR spectrum was only partly resolved due to the mixture of the two products. When the product mixture was heated in THF for 2 h, equimolar amounts of the double bond isomers were present.

Alanes are effective donors of an alkyl group to Pd(II) after the palladium insertion into a carbon–halogen bond. The use of an alane reactant required protection of the 2′- and 3-hydroxyl groups. TBDMS-triflate was used for disilylation. In this case isomer pure allyl bromide **10** was used to provide the disiloxy derivative **19** in a 73% yield (Scheme 6). The transfer of a methyl group from trimethylaluminium was effected by Pd-catalysis in NMP when the 10-ethyl



Scheme 6. Reagents and reaction conditions: (i) TBDMS-triflate, NMe_3, CH_2Cl_2, 0 °C–rt, 17 h; (ii) $AlMe_3$, $Pd_2(dba)_3 \cdot CHCl_3$, TFP, NMP, 100 °C, 24 h.

erythralosamine **20** was isolated in 84% yield. Preliminary experiments with the same catalyst system in THF did not result in any coupling reaction.

3. Conclusion

A method for modification of the chemically stable C10-methyl group in erythromycine macrolide derivatives is described. The C10 methyl group is made allylic by acid catalysed water elimination and acetal formation. The product is erythralosamine. Protection by *N*-oxide formation and bromination with NBS in acetic acid provided allylic bromides. Amines were used to effect heteronucleophilic substitutions. Introduction of carbon substituents were effected under cross-coupling conditions using Stille reaction conditions. Under Negishi conditions with trimethylalane and Pd-catalysis, the 10-ethyl homologue became available.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded in $CDCl_3$ at 500 MHz with Bruker DPX 500 and the ^{13}C NMR spectra were recorded at 75 MHz. Chemical shifts are reported in parts per million using $CHCl_3$ (7.24 ppm) and $CDCl_3$ (77 ppm) as references. Mass spectra were recorded at 70 eV. The spectra are presented as *m*/*z* (% relative intensity). Electrospray spectra were obtained with a Micromass QTOF 2 W spectrometer with electrospray ionisation quadrupole time of flight. IR spectra were recorded on a Nicolet Magna FT-IR 550 spectrometer using ATR (attenuated total reflectance). Elemental analyses were performed by Ilse Beetz Mickroanalytisches laboratorium, Kronach, Germany. Melting points are uncorrected.

All reactions were performed under an inert atmosphere except for the N-oxidations of the macrolides.

THF was distilled from sodium/benzophenone. Dichloromethane and triethylamine were distilled from calcium hydride. NBS was purified by recrystallisation from water. Flash chromatography on silica gel was carried out on Merck kieselgel 60 (230–400).

4.1.1. X-ray crystallographic analysis for compounds 2 and 8. X-ray data were collected on a Siemens SMART CCD diffractometer[13] using graphite monochromated Mo Kα radiation (λ=0.71073 Å). Data collection method: ω-scan, range 0.6°, crystal to detector distance 5 cm. Data reduction and cell determination were carried out with the SAINT and XPREP programs.[13] Absorption corrections were applied by the use of the SADABS program.[14] The structure was determined and refined using the SHELXTL program package.[15] The non-hydrogen atoms were refined with isotropic thermal parameters; hydrogen atoms were located from difference Fourier maps and refined with isotropic thermal parameters.

In the crystals of the bromo compound **8**, a molecule of methanol was located hydrogen bonded to O(2) and O(8) of different molecules. Some additional electron density was located in a cavity at the four-fold axis, probably from disordered solvent molecules, this was accounted for by three dummy carbon atoms in the calculations.

Structural data have been deposited at the Cambridge Crystallographic Data Centre deposition number CCCD 295911 for compound **2**, and CCCD 295912 for compound **8**.

4.1.2. Crystal data for $C_{29}H_{49}NO_8$ (2). M=539.69, monoclinic, $P2(1)$, a=10.540(1) Å, b=10.797(1) Å, c=13.306(1) Å, β=92.40(1)°, V=1512.8(2) Å^3, Z=2, D_x=1.185 Mg m^{-3}, μ=0.085 mm^{-1}, T=105(2) K, measured 27,542 reflections in 2θ range 4.8–72.7°, R_{int}=0.020. Five hundred and thirty-nine parameters refined against 13,651 F^2, R=0.037 for $I_o>2\sigma(I_o)$ and 0.051 for all data.

4.1.3. Crystal data for $C_{29}H_{49}BrNO_8$ (8)+C_xH_4O. M=677.64, tetragonal, $I4$, a=b=21.416(1) Å, c=15.568(1) Å, V=7140.3(9) Å^3, Z=8, D_x=1.261 Mg m^{-3}, μ=1.203 mm^{-1}, T=105(2) K, measured 50,968 reflections in 2θ range 8.3–61.0°, R_{int}=0.030. Six hundred and one parameters refined against 10,751 F^2, R=0.040 for $I_o>2\sigma(I_o)$ and 0.060 for all data. Absolute structure was determined.

4.1.4. Erythralosamine (2).[7] A solution of erythromycin A (6.66 g, 9.10 mmol) in a mixture of EtOH (60 ml) and 10% HCl (200 ml) was stirred at ambient temperature for 24 h. The mixture was diluted with ethyl acetate (3×200 ml), washed with water (3×200 ml), dried ($MgSO_4$) and the solvent was evaporated. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq), initially in ratio 90:4:1, then in ratio 90:8:2. (R_f 0.19). The product was a white crystalline solid; yield 3.22 g (66%). Mp 208 °C [lit.[7a] 207–208 °C]; HRMS: [M] 539.3412. Calcd for $C_{29}H_{49}NO_8$: 539.3458; δ_H (500 MHz; $CDCl_3$): 0.83 (3H, t, J=7.3 Hz, 14-CH_3), 0.93 (3H, d, J=7.0 Hz, 8-CH_3), 1.04 (3H, d, J=7.3 Hz, 4-CH_3), 1.10 (3H, d, J=7.4 Hz, 2-CH_3), 1.10–1.12 (1H, m, 4′-H_a), 1.17 (3H, d, J=6.1 Hz, 5′-CH_3), 1.23 (3H, s, 12-CH_3), 1.29–1.36 (1H, m, 14-H_a), 1.40 (3H, s, 6-CH_3), 1.58 (1H, dd, J=13.0, 6.4 Hz, 7-H_a), 1.59–1.64 (2H, m, 14-H_b/4′-H_b), 1.85 (3H, d, J=1.3 Hz, 10-CH_3), 2.23–2.26 (1H, m, 4-H), 2.26 (6H, s, N(CH_3)$_2$), 2.29–2.34 (1H, pseudo t, J=13 Hz, 7-H_b), 2.44–2.45 (1H, m, 3′-H), 2.44–2.47 (1H, m, 8-H), 2.71–2.74 (1H, m, 2-H), 3.19 (1H, dd, J=10.1, 7.3 Hz, 2′-H), 3.40 (1H, d, J=8.2 Hz, 5-H), 3.44–3.46 (1H, m, 5′-H), 4.16 (1H, d, J=7.3 Hz, 1′-H), 4.25 (1H, m, 3-H), 4.96 (1H, dd, J=11.5, 2.8 Hz, 13-H), 5.29 (1H, d, J=1.4 Hz, 11-H); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.0 (8-CH_3), 12.6 (4-CH_3), 13.7 (2-CH_3), 14.0 (10-CH_3), 21.2 (5′-CH_3), 23.1 (12-CH_3), 24.4 (C-14), 28.9 (C-4′), 29.6 (6-CH_3), 40.1 (C-8), 40.4 (N(CH_3)$_2$), 42.9 (C-7), 44.5 (C-4), 46.8 (C-2), 65.5 (C-3′), 69.4 (C-5′), 70.1 (C-2′), 71.2 (C-3), 78.9 (C-13), 82.1 (C-6), 87.1 (C-5), 88.8 (C-12), 104.5 (C-1′), 120.0 (C-9), 128.5 (C-11), 139.2 (C-10), 178.5 (C-1); IR (ATR plate) (CH_2Cl_2) ν=3461 (m), 2971 (s), 2933 (s), 2860 (s), 1727 (s), 1456 (s), 1381 (m), 1373 (m), 1323 (w), 1277 (w), 1171 (s), 1112 (s), 1098 (s), 1073 (s), 1023 (m), 991 (m), 905 (w). MS (EI): 539 (M^+, 13%), 174 (11), 163 (10), 159 (14), 158 (100), 149 (19), 137 (29), 136 (22), 123 (43), 116 (16), 98 (21), 72 (11).

4.1.5. 2′*O*-Acetylerythralosamine (3). Acetic anhydride (0.88 ml, 9.30 mmol) and triethylamine (1.29 ml,

9.30 mmol) were added to a solution of erythralosamine (**2**) (2.50 g, 4.69 mmol) in CH_2Cl_2 (15 ml) and the reaction mixture was stirred at room temperature for 2 h until TLC monitoring showed full conversion to the product. The reaction mixture was diluted with ethyl acetate, the solution shaken with 5% Na_2CO_3 (aq), with brine, dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography using silica gel, 90:4:1 CH_2Cl_2/MeOH/NH_3 (aq); yield 2.30 g (84%) of a white solid. Mp 153–154 °C; HRMS: [M] 581.3554. Calcd for $C_{31}H_{51}NO_9$: 581.3564; δ_H (500 MHz; $CDCl_3$): 0.82 (3H, t, J=7.1 Hz, 14-CH_3), 0.91–0.93 (6H, m, 8-CH_3/4-CH_3), 1.08 (3H, d, J=7.3 Hz, 2-CH_3), 1.17 (3H, d, J=6.0 Hz, 5′-CH_3), 1.23 (3H, s, 12-CH_3), 1.31–1.35 (2H, m, 4′-H_a/14-H_a), 1.38 (3H, s, 6-CH_3), 1.54 (1H, dd, J=12.0, 5.5 Hz, 7-H_a), 1.57–1.65 (1H, m, 14-H_b), 1.67–1.69 (1H, m, 4′-H_b), 1.76 (3H, d, J=1.0 Hz, 10-CH_3), 2.03 (3H, s, 2′-OCOCH_3), 2.14–2.18 (1H, m, 4-H), 2.25 (6H, s, N(CH_3)$_2$), 2.35–2.40 (1H, pseudo t, J=12.1 Hz, 7-H_b), 2.38–2.42 (1H, m, 8-H), 2.52–2.57 (1H, m, 2-H), 2.68 (1H, dt, J=11.0, 3.0 Hz, 3′-H), 3.34 (1H, d, J=9.5 Hz, 5-H), 3.40–3.47 (1H, m, 5′-H), 4.18 (1H, m, 3-H), 4.23 (1H, d, J=7.5 Hz, 1′-H), 4.78 (1H, dd, J=10.5, 8.0 Hz, 2′-H), 4.97 (1H, dd, J=11.5, 2.8 Hz, 13-H), 5.48 (1H, d, J=1.5 Hz, 11-H); δ_C (75 MHz; $CDCl_3$): 10.2 (14-CH_3), 11.2 (8-CH_3), 11.8 (4-CH_3), 13.7 (2-CH_3), 14.3 (10-CH_3), 21.0 (2′-OCOCH_3), 21.3 (5′-CH_3), 23.3 (12-CH_3), 24.3 (C-14), 30.5 (6-CH_3), 31.0 (C-4′), 39.9 (C-8), 40.7 (N(CH_3)$_2$), 42.7 (C-7), 44.9 (C-4), 46.8 (C-2), 65.1 (C-3′), 69.0 (C-5′), 70.7 (C-2′), 71.0 (C-3), 78.9 (C-13), 81.7 (C-6), 86.7 (C-5), 88.7 (C-12), 102.6 (C-1′), 119.9 (C-9), 128.5 (C-11), 139.3 (C-10), 169.7 (C-2′-OCOCH$_3$), 177.9 (C-1); IR (ATR plate) (CH_2Cl_2) ν=3477 (m), 2971 (s), 2933 (s), 2877 (m), 1747 (s), 1731 (s), 1456 (m), 1372 (s), 1322 (w), 1236 (s), 1171 (s), 1098 (m), 1060 (s), 1022 (m), 991 (m), 906 (w).

4.1.6. 2′*O*-Acetyl-8-bromoerythralosamine (4). Bromine (0.59 ml, 1.20 mmol) was added slowly to a solution of 2′*O*-acylated erythralosamine (**3**) (0.590 g, 1.02 mmol) in carbon tetrachloride (10 ml). Sodium bicarbonate was added after 2 h and dichloromethane was used to extract the product. The organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq) 90:4:1; yield 0.156 g (24%) of a white solid. HRMS: [M+1], 660.2729/662.2711. Calcd for $C_{31}H_{51}BrNO_9$: 660.2741/662.2721; δ_H (500 MHz; $CDCl_3$): 0.81 (3H, t, J=7.3 Hz, 14-CH_3), 0.85 (3H, d, J=7.1 Hz, 4-CH_3), 1.12 (3H, d, J=7.2 Hz, 2-CH_3), 1.18 (3H, d, J=5.9 Hz, 5′-CH_3), 1.26–1.32 (1H, m, 4′-H_a), 1.28 (3H, s, 12-CH_3), 1.35–1.43 (1H, m, 14-H_a), 1.60–1.65 (1H, m, 14-H_b), 1.70–1.72 (1H, m, 4′-H_b), 1.72 (3H, s, 6-CH_3), 1.74 (3H, s, 8-CH_3), 1.78 (3H, s, 10-CH_3), 2.03 (3H, s, 2′-OCOCH_3), 2.12–2.15 (1H, m, 4-H), 2.24–2.27 (7H, m, 7-H_a/N(CH_3)$_2$), 2.42–2.45 (1H, m, 2-H), 2.69 (1H, dt, J=11.8, 4.2 Hz, 3′-H), 3.09 (1H, d, J=16.5 Hz, 7-H_b), 3.32 (1H, d, J=11.0 Hz, 5-H), 3.43–3.47 (1H, m, 5′-H), 4.09–4.11 (1H, m, 3-H), 4.20 (1H, d, J=7.6 Hz, 1′-H), 4.80 (1H, dd, J=10.4, 8.2 Hz, 2′-H), 5.07 (1H, d, J=8.8 Hz, 13-H), 5.67 (1H, d, J=1.5 Hz, 11-H); δ_C (75 MHz; $CDCl_3$): 8.8 (4-CH_3), 10.2 (14-CH_3), 14.4 (2-CH_3), 14.6 (10-CH_3), 21.0 (5′-CH_3), 21.3 (2′-OCOCH$_3$), 23.4 (12-CH_3), 24.4 (C-14), 27.3 (8-CH_3), 31.1 (C-4′), 32.1 (6-CH_3), 40.7 (N(CH_3)$_2$), 43.3 (C-4), 45.7 (C-2), 51.2 (C-7), 62.9 (C-3′), 69.2 (C-5′), 70.7 (C-3), 70.9 (C-2′), 70.9 (C-8), 79.0 (C-13), 80.7 (C-6), 88.2 (C-5), 88.8 (C-12), 103.4 (C-1′), 119.8 (C-9), 132.4 (C-11), 136.6 (C-10), 169.8 (C-2′-OCOCH$_3$), 175.7 (C-1).

4.1.7. Erythralosamine *N*-oxide (5). Hydrogen peroxide (30%, 1 ml) was added to a solution of erythralosamine (**2**) (1.40 g, 2.52 mmol) in methanol (10 ml) and the reaction mixture was stirred at ambient temperature for 7 h. Saturated aqueous sodium bisulfite was added slowly to the reaction mixture to remove excess hydrogen peroxide before extraction with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated. The residual material was the title compound that was sufficiently pure for use in the subsequent reaction. The product was a white crystalline solid, yield 1.4 g (95%), mp 153–155 °C. HRMS: [M+1] 556.3484. Calcd for $C_{29}H_{50}NO_9$: 556.3480; δ_H (500 MHz; $CDCl_3$): 0.82 (3H, t, J=7.2 Hz, 13-CH_3), 0.92 (3H, d, J=7.0 Hz, 8-CH_3), 1.04 (3H, d, J=7.2 Hz, 4-CH_3), 1.10 (3H, d, J=7.4 Hz, 2-CH_3), 1.22 (3H, d, J=6.2 Hz, 5′-CH_3), 1.23 (3H, s, 12-CH_3), 1.32–1.34 (2H, m, 4′-H_a/14-H_a), 1.41 (3H, s, 6-CH_3), 1.55 (1H, dd, J=13.0, 6.4 Hz, 7-H_a), 1.57–1.62 (1H, m, 14-H_b), 1.84 (3H, d, J=1.1 Hz, 10-CH_3), 1.90–1.93 (1H, m, 4′-H_b), 2.25–2.27 (1H, m, 4-H), 2.27–2.33 (1H, pseudo t, J=13 Hz, 7-H_b), 2.44–2.47 (1H, m, 8-H), 2.65–2.68 (1H, m, 2-H), 3.16 (3H, s, NCH_3), 3.17 (3H, s, NCH_3), 3.34–3.38 (1H, m, 3′-H), 3.39 (1H, d, J=8.2 Hz, 5-H), 3.55–3.59 (1H, m, 5′-H), 3.74 (1H, dd, J=9.8, 7.1 Hz, 2′-H), 4.20 (1H, m, 3-H), 4.26 (1H, d, J=7.1 Hz, 1′-H), 4.95 (1H, dd, J=11.5, 2.8 Hz, 13-H), 5.49 (1H, d, J=1.1 Hz, 11-H); δ_C (75 MHz; $CDCl_3$): 10.7 (14-CH_3), 12.2 (4-CH_3), 12.4 (8-CH_3), 14.4 (10-CH_3), 14.5 (2-CH_3), 21.4 (5′-CH_3), 23.6 (12-CH_3), 24.8 (C-14), 30.5 (6-CH_3), 35.3 (C-4′), 40.5 (C-8), 43.4 (C-7), 45.1 (C-4), 47.4 (C-2), 52.8 (N-CH_3), 59.6 (NCH_3), 68.0 (C-5′), 71.4 (C-3), 71.9 (C-2′), 76.9 (C-3′), 79.2 (C-13), 82.4 (C-6), 88.2 (C-5), 89.3 (C-12), 104.8 (C-1′), 120.3 (C-9), 129.0 (C-11), 139.5 (C-10), 178.9 (C-1); IR (film) (CH_2Cl_2) ν=3397 (m), 2973 (s), 2934 (s), 2877 (m), 1717 (s), 1456 (m), 1372 (m), 1171 (s), 1112 (m), 1099 (m), 1076 (s), 1064 (s), 1019(s), 993 (s), 906 (m).

4.1.8. 10,11-Epoxyerythralosamine *N*-oxide (6). A solution of erythralosamine (**2**) (0.573 g, 1.06 mmol) and MCPBA (1.66 g, 7.43 mmol) in dichloromethane (20 ml) was heated under reflux for 4 h, another portion of MCPBA was added (0.55 g, 3.19 mmol) and the heating continued for another 4 h. Sodium hydrogen carbonate was added to the cooled mixture, stirred overnight and extracted with dichloromethane. The organic phase was washed with Na_2SO_3, brine and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using CH_2Cl_2/MeOH 9:1; yield 0.298 g, (49%) of a white crystalline material. HRMS: [M+1] 572.3429. Calcd for $C_{29}H_{49}NO_{10}$: 572.3456; δ_H (500 MHz; $CDCl_3$): 0.86 (3H, t, J=6.9 Hz, 14-CH_3), 1.15 (3H, d, J=7.2 Hz, 8-CH_3), 1.18 (3H, s, 10-CH_3), 1.18–1.22 (9H, m, 4-CH_3/2-CH_3/5′-CH_3), 1.28 (3H, s, 6-CH_3), 1.31–1.36 (1H, m, 4′-H_a), 1.46–1.49 (1H, m, 14-H_a) 1.51 (1H, dd, J=12.4, 6.8 Hz, 7-H_a), 1.61 (3H, s, 12-CH_3), 1.64–1.70 (1H, m, 14-H_b), 1.90–1.93 (1H, m, 4′-H_b), 2.17–2.23 (1H, pseudo t, J=12.7 Hz, 7-H_b), 2.45–2.56 (2H, m, 8-H/4-H), 3.04–3.10 (1H, m,

2-H), 3.13 (3H, s, NCH_3), 3.16 (3H, s, NCH_3), 3.30 (1H, s, 11-H), 3.37–3.41 (1H, m, 3′-H), 3.48 (1H, d, J=6.1 Hz, 5-H), 3.56–3.58 (1H, m, 5′-H), 3.65 (1H, dd, J=9.9, 7.2 Hz, 2′-H), 4.03 (1H, pseudo t, J=5.3 Hz, 3-H), 4.36 (1H, d, J=7.1 Hz, 1′-H), 4.91 (1H, dd, 13-H); δ_C (75 MHz; $CDCl_3$): 10.1 (14-CH_3), 13.8 (8-CH_3), 14.6 (2-CH_3), 15.1 (12-CH_3), 16.8 (4-CH_3), 19.0 (10-CH_3), 20.9 (5′-CH_3), 24.5 (C-14), 25.6 (6-CH_3), 34.8 (C-4′), 39.8 (C-8), 44.1 (C-7/C-4), 46.0 (C-2), 52.2 (N-CH_3), 59.1 (N-CH_3), 63.7 (C-11), 65.4 (C-10), 67.7 (C-5′), 71.3 (C-2′), 73.5 (C-3), 76.1 (C-3′), 78.7 (C-13), 83.3 (C-12), 83.7 (C-6), 85.2 (C-5), 102.3 (C-1′), 113.5 (C-9), 178.5 (C-1).

4.1.9. 10,11-Epoxyerythralosamine (7). A solution of 10,11-epoxyerythralosamine *N*-oxide (**6**) (0.380 g, 0.665 mmol) and triphenylphosphine (0.350 g, 1.33 mmol) in THF (5 ml) was heated at reflux for 17 h. Most of the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine and dried ($MgSO_4$). The solution was evaporated and the residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:8:2; yield 0.216 g (60%) of a white crystalline material, mp 191–192 °C. HRMS: [M+1] 556.3474. Calcd for $C_{29}H_{50}NO_9$: 556.3480; δ_H (500 MHz; $CDCl_3$): 0.89 (3H, t, J=7.3 Hz, 14-CH_3), 1.16–1.21 (15H, m, 8-CH_3/2-CH_3/4-CH_3/10-CH_3/5′-CH_3), 1.22–1.28 (1H, m, 4′-H_a), 1.31 (3H, s, 6-CH_3), 1.49–1.56 (2H, m, 14-H_a/7-H_a), 1.63 (3H, s, 12-CH_3), 1.66–1.73 (2H, m, 14-H_b/4′-H_b), 2.26 (1H, pseudo t, J=13 Hz, 7-H_b), 2.28 (6H, s, $N(CH_3)_2$), 2.40–2.45 (1H, m, 4-H), 2.47–2.55 (2H, m, 8-H/3′-H), 3.10–3.13 (1H, m, 2-H), 3.15 (1H, dd, J=10.1, 7.4 Hz, 2′-H), 3.13 (1H, s, 11-H), 3.44–3.48 (1H, m, 5′-H), 3.49 (1H, d, J=5.8 Hz, 5-H), 4.16–4.18 (1H, m, 3-H), 4.26 (1H, d, J=7.3 Hz, 1′-H), 4.92 (1H, dd, J=10.7, 3.4 Hz, 13-H); δ_C (75 MHz; $CDCl_3$): 10.2 (14-CH_3), 13.6 (8-CH_3), 13.7 (2-CH_3), 15.2 (12-CH_3), 16.7 (4-CH_3), 19.1 (10-CH_3), 21.2 (5′-CH_3), 24.5 (C-14), 25.9 (6-CH_3), 28.8 (C-4′), 39.9 (C-8), 40.3 ($N(CH_3)_2$), 43.7 (C-4), 44.1 (C-7), 45.8 (C-2), 63.7 (C-11), 65.5 (C-10), 65.6 (C-3′), 69.5 (C-5′), 69.7 (C-2′), 73.2 (C-3), 79.1 (C-13), 83.3 (C-12), 83.7 (C-6), 84.9 (C-5), 102.8 (C-1′), 113.6 (C-9), 178.9 (C-1); IR (KBr) (CH_2Cl_2) ν=3460 (m), 2972 (s), 2938 (s), 2878 (m), 1726 (s), 1456 (s), 1380 (m), 1328 (w), 1278 (w), 1168 (s), 1109 (m), 1048 (s), 994 (m), 974 (w).

4.1.10. 10-Bromomethyl-10-desmethylerythralosamine *N*-oxide (8) and isomer (9). A solution of NBS in acetic acid (15 ml) was added to a solution of erythralosamine *N*-oxide (**5**) (1.56 g, 2.50 mmol) in acetic acid (20 ml) and the resultant solution was stirred at room temperature for 3 h when TLC showed the reaction to be complete. Most of the acetic acid was removed under reduced pressure and aqueous potassium hydroxide was added to the reaction mixture until pH 9–11. The product was extracted into chloroform that was washed and dried ($MgSO_4$) before the solvent was distilled off. The product was isolated after flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3, initially in ratio 9:1:0.1, and then 9:2:0.1; yield 0.95 g (60%). The product was a mixture of the bromo regioisomers **8** and **9** with very similar chromatographic properties. The major isomer **8** was obtained in isomerically pure state, after repeated chromatography, as a white crystalline material, mp 149–151 °C (Found: C, 52.85; H, 7.19. Calcd for $C_{29}H_{49}BrNO_9$: C, 54.89; H, 7.62%). HRMS: [M+1] 634.2556. Calcd for $C_{29}H_{50}BrNO_9$: 634.2591; [M+1] 636.2550. Calcd for $C_{29}H_{49}BrNO_9$: 636.2570; δ_H (500 MHz; $CDCl_3$): 0.84 (3H, t, J=7.2 Hz, 14-CH_3), 0.94 (3H, d, J=7.2 Hz, 8-CH_3), 1.09 (3H, d, J=7.5 Hz, 4-CH_3), 1.12 (3H, d, J=7.5 Hz, 2-CH_3), 1.25 (3H, d, J=6.1 Hz, 5′-CH_3), 1.27 (3H, s, 12-CH_3), 1.32–1.36 (2H, m, 4′-H_a/14-H_a), 1.39 (3H, s, 6-CH_3), 1.59 (1H, dd, J=12.6, 6.7 Hz, 7-H_a), 1.61–1.67 (1H, m, 14-H_b), 1.95–1.98 (1H, m, 4′-H_b), 2.19–2.24 (2H, m, 4-H/7-H_b), 2.47–2.50 (1H, m, 8-H), 3.06–3.08 (1H, m, 2-H), 3.18 (3H, s, NCH_3), 3.21 (3H, s, NCH_3), 3.39–3.43 (1H, m, 3′-H), 3.46 (1H, d, J=4.2 Hz, 5-H), 3.57–3.60 (1H, m, 5′-H), 3.72 (1H, dd, J=9.9, 7.2 Hz, 2′-H), 4.00 (1H, dd, J=13.8, 1.6 Hz, 10-CH_a), 4.33 (1 H, d, J=7.1 Hz, 1′-H), 4.37 (1H, dd, J=7.9, 2.9, 3-H), 4.59 (1H, dd, J=13.7, 1.7 Hz, 10-CH_b), 4.92 (1H, dd, J=11.3, 2.9 Hz, 13-H), 6.09 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): 10.2 (14-CH_3), 12.4 (4-CH_3), 12.5 (8-CH_3), 16.5 (2-CH_3), 21.0 (5′-CH_3), 22.4 (12-CH_3), 24.4 (C-14), 27.1 (6-CH_3), 27.3 (10-CH_2), 34.8 (C-4′), 39.9 (C-8), 42.7 (C-7), 42.9 (C-4), 45.4 (C-2), 52.6 (NCH_3), 58.9 (NCH_3), 67.9 (C-5′), 71.0 (C-2′), 71.9 (C-3), 76.4 (C-3′), 70.0 (C-13), 82.1 (C-6), 88.7 (C-5), 89.6 (C-12), 102.9 (C-1′), 119.7 (C-9), 134.0 (C-11), 140.0 (C-10), 179.9 (C-1); IR (film) (CH_2Cl_2) ν=3409 (m), 2973 (s), 2934 (s), 2877 (m), 1721 (s), 1456 (m), 1374 (m), 1169 (s), 1099 (m), 1060 (s), 1027 (m), 995 (m), 907 (w).

4.1.11. 10-Bromomethyl-10-desmethylerythralosamine (10). A solution of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (**8**) (2.60 g, 0.004 mol) and triphenylphosphine (2.20 g, 0.008 mol) in THF (30 ml) was heated under reflux for 17 h when TLC showed the reaction to be complete. Most of the THF was removed by distillation, the residual material extracted into ethyl acetate, the extracts shaken with aqueous sodium bicarbonate, washed with brine, dried ($MgSO_4$), the solution evaporated and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 90:8:2; yield 2.13 g (86%) of a white crystalline material, mp 88–90 °C. HRMS: [M+1] 618.2607. Calcd for $C_{29}H_{49}BrNO_8$: 618.2636; [M+1] 620.2593. Calcd for $C_{29}H_{49}BrNO_8$: 620.2615; δ_H (500 MHz; $CDCl_3$): 0.85 (3H, t, J=7.3 Hz, 13-CH_3), 0.93 (3H, d, J=7.1 Hz, 8-CH_3), 1.09 (3H, d, J=7.5 Hz, 2-CH_3), 1.12 (3H, d, J=7.5 Hz, 4-CH_3), 1.17–1.22 (1H, m, 4′-H_a), 1.19 (3H, d, J=6.1 Hz, 5′-CH_3), 1.28 (3H, s, 12-CH_3), 1.31–1.36 (1H, m, 14-H_a), 1.38 (3H, s, 6-CH_3), 1.59 (1H, dd, J=12.7, 6.6 Hz, 7-H_a), 1.62–1.69 (1H, m, 4′-H_b), 1.62–1.69 (1H, m, 14-H_b), 2.13–2.19 (1H, m, 4-H), 2.21–2.25 (1H, m, 7-H_b), 2.30 (6H, s, $N(CH_3)_2$), 2.45–2.52 (1H, m, 8-H), 2.45–2.52 (1H, m, 3′-H), 3.08 (1H, dq, J=7.4, 2.6 Hz, 2-H), 3.23 (1H, dd, J=10.0, 7.6 Hz, 2′-H), 3.45–3.49 (1H, m, 5′-H), 3.48 (1H, d, J=6.4 Hz, 5-H), 4.00 (1H, d, J=14.0 Hz, 10-CH_a), 4.23 (1H, d, J=7.4 Hz, 1′-H), 4.39–4.41 (1H, m, 3-H), 4.57 (1H, d, J=14.0 Hz, 10-CH_b), 4.92 (1H, dd, J=11.3, 2.7 Hz, 13-H), 6.03 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.2 (4-CH_3), 12.5 (8-CH_3), 16.6 (2-CH_3), 21.3 (5-CH_3), 22.4 (12-CH_3), 24.5 (C-14), 27.1 (10-CH_2), 27.2 (6-CH_3), 28.9 (C-4′), 39.9 (C-8), 40.4 ($N(CH_3)_2$), 42.9 (C-7/C-4), 45.3 (C-2), 65.4 (C-3′), 69.6 (C-5′), 69.7 (C-2′), 71.9 (C-3), 79.2 (C-13), 82.2 (C-6), 86.0 (C-5), 89.6 (C-12), 103.2 (C-1′), 119.7

(C-9), 134.0 (C-11), 140.2 (C-10), 179.7 (C-1); IR (film, CH_2Cl_2) ν=3467 (m), 2973 (s), 2936 (s), 2877 (m), 1720 (s), 1456 (s), 1380 (s), 1315 (w), 1277 (w), 1170 (s), 1099 (s), 1074 (s), 1049 (s), 1027(s), 993 (m), 907 (m).

4.1.12. 10-Bromomethyl-10-desmethylerythralosamine (10) and isomer (11). Deoxygenation of the crude mixture of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (**8**) and isomer (**9**) was effected as above to provide 10-bromomethyl-10-desmethylerythralosamine (**10**) and isomer (**11**) as a mixture reflecting the ratio in the isomeric substrate.

4.1.13. 10-Benzylaminomethyl-10-desmethylerythralosamine (12). A solution of the crude isomeric mixture of 10-bromomethyl-10-desmethylerythralosamine (**10**) and isomer (**11**) (0.502 g, 0.812 mmol), and benzylamine (0.35 ml, 3.25 mmol) in DMF (4 ml) was heated at 60 °C for 16 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq) 90:8:2; yield 0.410 g (78%) of a white solid. HRMS: [M+1] 645.4102. Calcd for $C_{36}H_{57}N_2O_8$: 645.4109; δ_H (500 MHz; $CDCl_3$): 0.85 (3H, t, J=7.3 Hz, 14-CH_3), 0.88 (3H, d, J=7.0 Hz, 8-CH_3), 1.05 (3H, d, J=7.4 Hz, 4-CH_3), 1.08 (3H, d, J=7.4 Hz, 2-CH_3), 1.17 (3H, d, J=6.2 Hz, 5′-CH_3), 1.21–1.23 (1H, m, 4′-H_a), 1.26 (3H, s, 12-CH_3), 1.35–1.42 (1H, m, 14-H_a), 1.39 (3H, s, 6-CH_3), 1.55 (1H, dd, J=12.7, 6.2 Hz, 7-H_a), 1.62–1.68 (2H, m, 4′-H_b/14-H_b), 2.16–2.20 (1H, m, 4-H), 2.22–2.26 (1H, m, 7-H_b), 2.29 (6H, s, $N(CH_3)_2$), 2.45–2.52 (2H, m, 8-H/3′-H), 2.76–2.82 (1H, m, 2-H), 3.27–3.32 (2H, m, 2′-H/10-CH_a), 3.42–3.48 (1H, m, 5′-H), 3.46 (1H, d, J=6.7 Hz, 5-H), 3.63 (1H, d, J=16.3 Hz, 10-CH_b), 3.82 (1H, d, J=13.2 Hz, CH_aPh), 3.92 (1H, d, J=13.2 Hz, CH_bPh), 4.20 (1H, d, J=7.2 Hz, 1′-H), 4.31–4.33 (1H, m, 3-H), 4.96 (1H, dd, J=11.4, 2.7 Hz, 13-H), 5.77 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.3 (8-CH_3), 13.3 (2-CH_3), 14.3 (4-CH_3), 21.2 (5′-CH_3), 23.0 (12-CH_3), 24.4 (C-14), 28.3 (6-CH_3), 29.4 (C-4′), 40.3 (C-8), 40.5 ($N(CH_3)_2$), 43.1 (C-7), 44.2 (C-4), 45.7 (10-CH_2), 46.6 (C-2), 52.7 (CH_2Ph), 65.3 (C-3′), 69.4 (C-5′), 70.1 (C-2′), 71.1 (C-3), 79.1 (C-13), 82.2 (C-6), 85.9 (C-5), 89.3 (C-12), 103.8 (C-1′), 120.0 (C-9), 126.8 (Ar), 128.0 (C-11), 128.1 (Ar), 128.4 (Ar), 140.3 (Ar), 141.9 (C-10), 178.9 (C-1); IR (film) (CH_2Cl_2) ν=3454 (m), 2972 (s), 2934 (s), 2876 (m), 1722 (s), 1455 (s), 1380 (m), 1323 (w), 1278 (w), 1171 (s), 1111 (s), 1097 (s), 1074 (s), 1049 (s), 1025 (s), 993 (m), 905 (m).

4.1.14. 10-(3-Phenylprop-1-ylaminomethyl)-10-desmethylerythralosamine (13). A solution of the crude isomeric mixture of 10-bromomethyl-10-desmethylerythralosamine (**10**) and isomer (**11**) (0.406 g, 0.653 mmol) together with 3-phenylpropylamine (0.37 ml, 2.63 mmol) in DMF was heated to 60 °C for 17 h. Water was added to the cold reaction mixture, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq) 90:8:2; yield (0.439 g, 79%) of a white crystalline solid, mp 139–140 °C (EtOAc/hexane) (Found: C, 67.56; H, 9.12. Calcd for $C_{38}H_{60}N_2O_8$: C, 67.83; H, 8.99%). HRMS [H^+]: M 673.4422. Calcd for $C_{38}H_{61}N_2O_8$: 673.4422; δ_H (500 MHz; $CDCl_3$): 0.84 (3H, t, J=7.3 Hz, 14-CH_3), 0.92 (3H, d, J=7.1 Hz, 8-CH_3), 1.07–1.10 (6H, m, 4-CH_3/2-CH_3), 1.18 (3H, d, J=6.9 Hz, 5′-CH_3), 1.20–1.25 (1H, m, 4′-H_a), 1.26 (3H, s, 12-CH_3), 1.29–1.35 (1H, m, 14-H_a), 1.39 (3H, s, 6-CH_3), 1.56 (1H, dd, J=12.6, 6.5 Hz, 7-H_a), 1.61–1.66 (2H, m, 14-H_b/4′-H_b), 1.82–1.91 (2H, m, Ph$CH_2C\mathit{H}_2CH_2$N), 2.14–2.16 (1H, m, 4-H), 2.21–2.27 (1H, pseudo t, J=13.5 Hz, 7-H_b), 2.28 (6H, s, $N(CH_3)_2$), 2.46–2.52 (2H, m, 8-H/3′-H), 2.64–2.77 (5H, m, 2-H/Ph$C\mathit{H}_2CH_2C\mathit{H}_2$N), 3.22–3.26 (2H, m, 2′-H/10-CH_a), 3.43–3.47 (1H, m, 5′-H), 3.50 (1H, d, J=6.1 Hz, 5-H), 3.59 (1H, d, J=16.3 Hz, 10-CH_b), 4.21 (1H, d, J=7.5 Hz, 1′-H), 4.35 (1H, m, 3-H), 4.94 (1H, dd, J=11.4, 2.7 Hz, 13-H), 5.68 (1H, d, 11-H); δ_C (75 MHz; $CDCl_3$): 10.4 (14-CH_3), 12.4 (8-CH_3), 13.2 (2-CH_3), 14.9 (4-CH_3), 21.2 (5′-CH_3), 22.9 (12-CH_3), 24.4 (C-14), 28.0 (6-CH_3), 29.3 (C-4′), 31.5 (Ph$CH_2C\mathit{H}_2CH_2$N), 33.8 (Ph$C\mathit{H}_2CH_2CH_2$N), 40.4 (C-8), 40.5 ($N(CH_3)_2$), 43.2 (C-7), 44.0 (C-4), 46.3 (10-CH_2), 46.6 (C-2), 48.6 (Ph$CH_2CH_2C\mathit{H}_2$N), 65.3 (C-3′), 69.5 (C-5′), 70.4 (C-2′), 71.3 (C-3), 79.1 (C-13), 82.2 (C-6), 85.6 (C-5), 89.3 (C-12), 103.6 (C-1′), 120.0 (C-9), 125.7 (Ar), 128.3 (Ar/C-11), 142.0 (Ar/C-10), 178.9 (C-1); IR (film) (CH_2Cl_2) ν=3418 (m), 2970 (s), 2933 (s), 2876 (w), 1716 (s), 1456 (m), 1374 (m), 1170 (s), 1111 (s), 1096 (s), 1073 (s), 1049 (s), 1025 (s), 994 (m), 904 (w).

4.1.15. 10-Benzyl-10-desmethylerythralosamine (15). A solution of a crude isomeric mixture of 10-bromomethyl-10-desmethylerythralosamine (**10**) and isomer (**11**) (0.280 g, 0.453 mmol) in NMP (5 ml) was degassed and tris(2-furyl)phosphine (0.025 g, 0.109 mmol) and $Pd_2(dba)_3\cdot CHCl_3$ (0.014 g, 0.014 mmol) were added. The reaction mixture was heated at 50 °C for 10 min before tributyl(phenyl)stannane (0.30 ml, 0.906 mmol) was added. The reaction mixture was then heated at 100 °C for 20 h. The cold reaction mixture was extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvents distilled off at reduced pressure. The residual material was subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq) 90:4:1, and then ratio 9:2:1; yield 0.168 g (60%) of a white crystalline material. HRMS: [M+1] 616.3847. Calcd for $C_{35}H_{54}NO_8$: 616.3843; δ_H (500 MHz; $CDCl_3$): 0.79 (3H, t, J=7.3 Hz, 14-CH_3), 1.06 (3H, d, J=6.9 Hz, 8-CH_3), 1.08–1.11 (1H, m, 4′-H_a), 1.13 (3H, d, J=7.5 Hz, 4-CH_3), 1.15 (3H, d, J=8.2 Hz, 2-CH_3), 1.17 (3H, d, J=6.5 Hz, 5′-CH_3), 1.15–1.18 (1H, m, 14-H_b), 1.19 (3H, s, 12-CH_3), 1.43 (3H, s, 6-CH_3), 1.50–1.55 (1H, m, 14-H_b), 1.56–1.65 (2H, m, 7-H_a/4′-H_b), 2.12 (6H, s, $N(CH_3)_2$), 2.26–2.31 (1H, m, 4-H), 2.40 (1H, pseudo t, J=13.0, 7-H_b), 2.46–2.51 (1H, m, 3′-H), 2.52–2.59 (1H, m, 8-H), 3.01 (1H, dd, J=9.5, 8.0 Hz, 2′-H), 3.14–3.21 (1H, m, 2-H), 3.26 (1H, d, J=17.5 Hz, 10-CH_aPh), 3.41–3.45 (1H, m, 5′-H), 3.50 (1H, d, J=5.0 Hz, 5-H), 4.00 (1H, d, J=17.5 Hz, 10-CH_bPh), 4.21 (1H, d, J=3.66 Hz, 1′-H), 4.36–4.38 (1H, m, 3-H), 4.91 (1H, dd, J=10.9, 1.7 Hz, 13-H), 5.07 (1H, s, 11-H), 7.17–7.22 (1H, m, Ar), 7.26–7.30 (4H, m, Ar); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.3 (8-CH_3), 12.7 (2-CH_3), 15.7 (4-CH_3), 21.2 (5′-CH_3), 22.8 (12-CH_3), 24.3

(C-14), 27.6 (6-CH_3), 29.2 (C-4′), 33.0 (10-CH_2), 40.2 (C-8/$N(CH_3)_2$), 43.1 (C-7), 43.6 (C-4), 45.9 (C-2), 65.3 (C-3′), 69.4 (C-5′), 69.6 (C-2′), 71.9 (C-3), 79.3 (C-13), 82.0 (C-6), 86.4 (C-5), 89.4 (C-12), 103.3 (C-1′), 120.3 (C-9), 126.0 (Ar), 128.3 (Ar), 129.4 (C-11), 129.5 (Ar), 140.1 (Ar), 144.5 (C-10), 179.5 (C-1); IR (film) (CH_2Cl_2) ν=3467 (br), 2972 (s), 2934 (m), 2876 (w), 1719 (s), 1455 (m), 1379 (m), 1321 (w), 1274 (w), 1169 (s), 1111 (m), 1097 (m), 1073 (s), 1050 (s), 1023(s), 992 (m), 906 (w).

4.1.16. 10-(2-Furyl)methyl-10-desmethylerythralosamine (16). A solution of the crude isomeric mixture of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (**8**) and isomer (**9**) (0.196 g, 0.310 mmol) in NMP (3 ml) was degassed and tris(2-furyl)phosphine (0.018 g, 0.077 mmol) and $Pd_2(dba)_3\cdot CHCl_3$ (0.010 g, 0.010 mmol) were added. The reaction mixture was heated at 50 °C for 10 min and more tris(2-furyl)phosphine (0.12 ml, 0.372 mmol) was added. The reaction mixture was heated at 80 °C for 22 h. The product was extracted with ethyl acetate, the organic phase washed with aqueous sodium hydrogen carbonate, brine and dried ($MgSO_4$). The NMP was removed under reduced pressure and the residual material subjected to flash chromatography on silica gel using CH_2Cl_2/MeOH/NH_3 (aq) 90:4:1, yield 0.095 g (51%) of a white solid; δ_H (500 MHz; $CDCl_3$): 0.75 (3H, t, J=7.3 Hz, 14-CH_3), 0.92 (3H, d, J=6.9 Hz, 8-CH_3), 1.02–1.05 (6H, m, 4-CH_3/2-CH_3), 1.12 (3H, d, J=6.1 Hz, 5′-CH_3), 1.18 (3H, s, 12-CH_3), 1.35 (3H, s, 6-CH_3), 2.16 (6H, s, $N(CH_3)_2$), 2.92–3.00 (1H, m, 2-H), 3.07 (1H, dd, J=10.4, 7.4 Hz, 2′-H), 3.32 (1H, dd, J=18.1, 1.3 Hz, 10-CH_a), 3.42 (1H, d, J=5.6 Hz, 5-H), 3.86 (1H, d, J=18.2 Hz, 10-CH_b), 4.14 (1H, d, J=7.4 Hz, 1′-H), 4.28–4.32 (1H, m, 3-H), 4.85 (1H, dd, J=10.9, 2.6 Hz, 13-H), 5.36 (1H, s, 11-H), 6.10–6.11 (1H, m, furan), 6.24–6.25 (1H, m, furan), 7.25–7.26 (1H, m, furan); δ_C (75 MHz; $CDCl_3$): 10.2 (14-CH_3), 12.1, 12.7, 15.1, 21.1, 22.6, 24.2, 26.3, 27.8, 29.0, 40.0 (C-8), 40.2 ($N(CH_3)_2$), 43.0 (C-7), 43.6 (C-4), 45.8 (C-2), 65.0 (C-3′), 69.3 (C-5′), 69.8 (C-2′), 71.3 (C-3), 78.9 (C-13), 81.9 (C-6), 86.1 (C-5), 89.3 (C-12), 103.5 (C-1′), 106.1 (furan), 110.1 (furan), 120.1 (C-9), 129.3 (C-11), 140.5/140.9 (C-10/furan), 153.7 (furan), 179.2 (C-1).

4.1.17. 10-(2-Ethoxyprop-2-en-1-yl)methyl-10-desmethylerythralosamine (17). A solution of a crude isomeric mixture of 10-bromomethyl-10-desmethylerythralosamine *N*-oxide (**8**) and isomer (**9**) (0.100 g, 0.158 mmol) was deoxygenated together with tris(2-furyl)phosphine (0.036 g, 0.158 mmol) in NMP (1 ml) and was heated at 70 °C for 17 h. The catalyst $Pd_2(dba)_3\cdot CHCl_3$ (0.005 g, 0.005 mmol) and tris(2-furyl)phosphine (0.009 g, 0.038 mmol) were added to the reaction mixture together with tributyl(1-ethoxyethenyl)stannane (0.064 ml, 0.189 mmol). The resultant mixture was heated at 70 °C for 24 h. The solvent was removed at reduced pressure, the residue extracted into ethyl acetate, the solution shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$), evaporated and the residual material subjected to flash chromatography on silica gel CH_2Cl_2/MeOH/NH_3 (aq) 90:4:1; yield 0.052 g (54%) of a white material. HRMS: [M+1], 610.3948. Calcd for $C_{33}H_{56}NO_9$: 610.3949; δ_H (500 MHz; $CDCl_3$): 0.83 (3H, t, J=7.3 Hz, 14-CH_3), 0.94 (3H, d, J=7.1 Hz, 8-CH_3), 1.07 (3H, d, J=3.2 Hz, 4-CH_3), 1.09 (3H, d, J=3.0 Hz, 2-CH_3), 1.19 (3H, d, J=6.2 Hz, 5′-CH_3), 1.21–1.22 (1H, m, 4′-H_a), 1.24 (3H, s, 12-CH_3), 1.27 (3H, t, J=7.1 Hz, OCH_2CH_3), 1.28–1.32 (1H, m, 14-H_a), 1.40 (3H, s, 6-CH_3), 1.56 (1H, dd, J=12.6, 6.5 Hz, 7-H_a), 1.60–1.66 (1H, m, 4-H), 1.60–1.66 (1H, m, 14-H_b), 2.26–2.30 (1H, m, 4-H), 2.26–2.30 (1H, m, 7-H_b), 2.30 (6H, s, $N(CH_3)_2$), 2.42–2.55 (1H, m, 8-H), 2.42–2.54 (1H, m, 3′-H), 2.77 (1H, dd, J=17.0, 1.8 Hz, 10-CH_a), 3.01 (1H, dq, J=7.5, 3.5 Hz, 2-H), 3.24 (1H, dd, J=10.1, 7.4 Hz, 2′-H), 3.41 (1H, d, J=17.0 Hz, 10-CH_b), 3.41–3.45 (1H, m, 5′-H), 3.48 (1H, d, J=5.5 Hz, 5-H), 3.70–3.78 (1H, m, OCH_2CH_3), 3.97 (1H, d, J=1.1 Hz, C=CH_a), 4.04 (1H, s, C=CH_b), 4.20 (1H, d, J=6.8 Hz, 1′H), 4.36–4.38 (1H, m, 3-H), 4.91 (1H, dd, J=11.1, 2.9 Hz, 13-H), 5.55 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.3 (8-CH_3), 12.7 (4-CH_3), 14.4 (OCH_2CH_3), 15.4 (2-CH_3), 21.2 (5′-CH_3), 22.8 (12-CH_3), 24.5 (C-14), 27.9 (6-CH_3), 29.8 (C-4′), 33.4 (10-CH_2), 40.3 (C-8), 40.5 ($N(CH_3)_2$), 43.2 (C-7/C-4), 45.9 (C-2), 62.9 (OCH_2CH_3), 64.8 (C-3′), 69.4 (C-5′), 70.1 (C-2′), 71.7 (C-3), 79.1 (C-13), 82.1 (C-6), 83.1 (=CH_2), 85.9 (C-5), 89.3 (C-12), 103.3 (C-1′), 120.4 (C-9), 128.4 (C-11), 140.5 (C-10), 161.1 (EtOCR=CH_2), 179.5 (C-1).

4.1.18. 10-(2-Oxopropyl)-10-desmethylerythralosamine (18). 10-(2-Ethoxyprop-2-en-1-yl)methyl-10-desmethylerythralosamine (**17**) (0.180 g, 0.295 mmol) was dissolved in THF (1.5 ml) and 1 M HCl (0.30 ml) was added. The reaction mixture was stirred for 20 h at room temperature. $NaHCO_3$ was added to the reaction mixture and the mixture extracted with ethyl acetate, washed with brine and dried ($MgSO_4$). The product was isolated as a white solid 0.120 g (56%) after flash chromatography on silica gel using CH_2Cl_2/MeOH 9:1, then ratio 9:2. HRMS: [M+1] 582.3646. Calcd for $C_{31}H_{52}NO_9$: 582.3636; δ_H (500 MHz; $CDCl_3$): 0.84 (3H, t, J=7.2 Hz, 14-CH_3), 0.90 (3H, d, J=7.0 Hz, 8-CH_3), 1.27 (3H, s, 12-CH_3), 1.40 (3H, s, 6-CH_3), 2.27 (6H, s, $N(CH_3)_2$), 3.00 (1H, dd, J=16.8, 1.7 Hz, 10-CH_a), 3.47 (1H, d, J=4.9 Hz, 5-H), 3.91 (1H, d, J=16.8 Hz, 10-CH_b), 4.23 (1H, d, J=7.3 Hz, 1′H), 4.94 (1H, dd, 13-H), 5.60 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): 10.3 (14-CH_3), 12.4 (8-CH_3), 12.5 (4-CH_3), 16.0 (2-CH_3), 21.2 (5′-CH_3), 22.5 (12-CH_3), 24.5 (C-14), 27.3 (6-CH_3), 28.7 (C-4′), 29.3 (10-$CH_2CO\mathit{C}H_3$), 40.3 (C-8/($N(CH_3)_2$)), 42.3/43.3/43.6 (C-7/C-4/10-$\mathit{C}H_2COCH_3$), 45.7 (C-2), 65.7 (C-3′), 69.6/69.7 (C-5′/(C-2′), 71.6 (C-3), 79.3 (C-13), 82.1 (C-6), 86.0 (C-5), 89.7 (C-12), 103.4 (C-1′), 120.3 (C-9), 130.1 (C-11), 136.5 (C-10), 179.4 (C-1), 207.5 (10-$CH_2\mathit{C}OCH_3$).

4.1.19. 10-Bromomethyl-2′*O*,3*O*-bis(*tert*-butyldimethylsilyl)-10-desmethylerythralosamine (19). A solution of 10-bromomethyl-10-desmethylerythralosamine (**10**) (0.250 g, 0.404 mmol) and trimethylamine (0.17 ml, 1.21 mmol) in CH_2Cl_2 (5 ml) was cooled to 0 °C and TBDMS-triflate (0.23 ml, 1.21 mmol) added dropwise to the reaction mixture. Water was added to the cold reaction mixture after 17 h, the mixture extracted with ethyl acetate, the extracts shaken with aqueous sodium hydrogen carbonate, with brine, dried ($MgSO_4$) and the solvent distilled off. The residual material was subjected to flash chromatography on silica gel using hexane/Et_2O 5:1; yield 0.25 g (73%) of a white crystalline solid. HRMS: [M+1], 846.4329. Calcd for $C_{41}H_{77}NO_8Si_2Br$: 846.4365; δ_H (500 MHz; $CDCl_3$):

0.06/0.07/0.19 (4×3H, 4×s, 2×$(CH_3)_3C(CH_3)_2Si$), 0.85 (3H, t, J=7.5 Hz, 14-CH_3), 0.89/0.90 (2×9H, 2×s, 2×$(CH_3)_3C(CH_3)_2$ Si), 0.96 (3H, d, J=7.0 Hz, 8-CH_3), 0.94 (3H, d, J=7.1 Hz, 4-CH_3), 1.06 (3H, d, J=7.5 Hz, 2-CH_3), 1.14 (3H, d, J=6.0 Hz, 5′-CH_3), 1.16–1.21 (1H, m, 4′-H_a), 1.28 (3H, s, 12-CH_3), 1.30–1.41 (1H, m, 14-H_a), 1.47 (3H, s, 6-CH_3), 1.56–1.66 (3H, m, 7-H_a/14-H_b/4′-H_b), 2.07–2.11 (2H, m, 4-H/7-H_b), 2.18 (6H, s, $N(CH_3)_2$), 2.39–2.44 (1H, m, 3′-H), 2.50–2.57 (2H, m, 8-H/2-H), 3.13 (1H, m, 2′-H), 3.36–3.39 (1H, m, 5′-H), 3.42 (1H, d, J=11.2 Hz, 5-H), 4.07 (1H, d, J=7.2 Hz, 1′-H), 4.22 (1H, d, J=5.0 Hz, 3-H), 4.97 (1H, dd, J=11.6, 2.4 Hz, 13-H), 5.99 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): −4.4/−4.3/−4.2/−3.0 ($(CH_3)_3C(CH_3)_2Si$), 10.3 (14-CH_3), 11.9 (4-CH_3), 13.0 (8-CH_3), 16.2 (2-CH_3), 18.5/18.6 ($(CH_3)_3C(CH_3)_2Si$), 21.2 (5′-CH_3), 22.9 (12-CH_3), 24.1 (C-14), 25.7 (10-CH_2), 26.0/26.2 ($(CH_3)_3C(CH_3)_2Si$), 29.3 (C-4′), 30.0 (6-CH_3), 40.7 (C-8), 41.2 ($N(CH_3)_2$), 43.6 (C-7), 48.3 (C-4), 50.6 (C-2), 66.2 (C-3′), 68.9 (C-5′), 70.0 (C-3), 72.1 (C-2′), 78.1 (C-13), 83.9 (C-6), 84.7 (C-5), 88.4 (C-12), 105.0 (C-1′), 119.4 (C-9), 133.8 (C-11), 139.6 (C-10), 178.4 (C-1); IR (film, CH_2Cl_2) ν=2969 (s), 2934 (s), 2882 (w), 2856 (m), 1736 (s), 1473 (w), 1461 (m), 1381 (w), 1373 (w), 1250 (w), 1172 (s), 1124 (m), 1098 (s), 1067 (m), 1048 (s), 1031 (m), 903 (w), 835 (s), 774 (m).

4.1.20. 10-Ethyl-2′*O*,3*O*-bis(*tert*-butyldimethylsilyl)-10-desmethylerythralosamine (20). A solution of 10-bromomethyl-2′*O*,3*O*-bis(*tert*-butyldimethylsilyl)-10-desmethylerythralosamine (**19**) (0.064 g, 0.080 mmol) in NMP (1 ml) was degassed for 1 h before the $Pd_2(dba)_3 \cdot CHCl_3$ complex (0.002 g, 0.002 mmol) and TFP (0.004 g, 0.016 mmol) were added. The mixture was heated to 50 °C to generate the active catalyst and trimethylaluminium 2 M in hexane, (0.2 ml, 0.400 mmol) added carefully through a syringe. The resultant reaction mixture was heated at 100 °C for 24 h. The cold reaction mixture was filtered through a silica plug and the solvent was removed from the product by distillation. The residual material was subjected to flash chromatography on silica gel using hexane/Et_2O 4:1; yield 0.053 g (84%) of a white crystalline material. HRMS: [M+1], 782.5383. Calcd for $C_{42}H_{80}NO_8Si_2$: 782.5417; δ_H (500 MHz; $CDCl_3$): 0.03/0.05/0.007/0.19 (4×3H, 4×s, 2×$(CH_3)_3C(CH_3)_2Si$), 0.84 (3H, t, J=7.4 Hz, 14-CH_3), 0.88/0.90 (2×9H, 2×s, 2×$(CH_3)_3C(CH_3)_2Si$), 0.92 (3H, d, J=7.2 Hz, 8-CH_3), 0.95 (3H, d, J=7.2 Hz, 4-CH_3), 1.06 (3H, d, J=7.5 Hz, 2-CH_3), 1.08 (3H, t, J=7.2 Hz, 10-CH_2CH_3), 1.14 (3H, d, J=6.1 Hz, 5′-CH_3), 1.15–1.19 (1H, m, 4′-H_a), 1.24 (3H, s, 12-CH_3), 1.32–1.35 (1H, m, 14-H_a), 1.47 (3H, s, 6-CH_3), 1.56–1.65 (3H, m, 7-H_a/14-H_b/4′-H_b), 1.91–1.99 (1H, m, 10-CH_a), 2.05–2.15 (3H, m, 4-H/7-H_b/10-CH_b), 2.18 (6H, s, $N(CH_3)_2$), 2.40–2.43 (1H, m, 3′-H), 2.44–2.54 (2H, m, 8-H/2-H), 3.13 (1H, m, 2′-H), 3.36–3.39 (1H, m, 5′-H), 3.42 (1H, d, J=11.3 Hz, 5-H), 4.05 (1H, d, J=7.1 Hz, 1′-H), 4.22 (1H, d, J=4.9 Hz, 3-H), 4.95 (1H, dd, J=11.6, 2.4 Hz, 13-H), 5.45 (1H, s, 11-H); δ_C (75 MHz; $CDCl_3$): −4.4/−3.0 ($(CH_3)_3C(CH_3)_2Si$), 10.4 (14-CH_3), 11.7 (4-CH_3), 11.9 (8-CH_3), 12.5 (10-CH_2CH_3), 16.3 (2-CH_3), 18.5/18.6 ($(CH_3)_3C(CH_3)_2Si$), 20.4 (10-CH_2CH_3), 21.2 (5′-CH_3), 23.4 (12-CH_3), 24.2 (C-14), 26.0/26.3 ($(CH_3)_3C(CH_3)_2Si$), 29.4 (C-4′), 30.3 (6-CH_3), 40.8 (C-8), 41.2 ($N(CH_3)_2$), 43.5 (C-7), 48.1 (C-4), 50.8 (C-2), 66.2 (C-3′), 68.8 (C-5′), 70.1 (C-3), 72.1 (C-2′), 78.3 (C-13), 83.4 (C-6), 84.9 (C-5), 89.1 (C-12), 104.9 (C-1′), 120.3 (C-9), 125.2 (C-11), 145.5 (C-10), 178.5 (C-1); IR (film, CH_2Cl_2) ν=2969 (s), 2934 (s), 2881 (w), 2856 (m), 1736 (s), 1461 (m), 1372 (w), 1250 (m), 1173 (s), 1125 (w), 1098 (s), 1049 (s), 1032 (m), 993 (w).

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Highly specific N-monomethylation of primary aromatic amines

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Abstract—A synthetic methodology for the specific conversion of primary aromatic amines into their *N*-monomethyl derivatives under very mild conditions is presented. Anilines are treated with 4-nitrobenzenesulfonyl (nosyl) chloride to generate the corresponding sulfonamides **2** in high yields. The subsequent N-methylation reaction of the sulfonamides **2** with a solution of diazomethane is rapid and quantitative. Removal of the nosyl protecting group is readily carried out using the reagent system mercaptoacetic acid/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) affording the *N*-monomethylated aromatic amines **4**. The procedure is convenient, efficient, and gives rise to the *N*-monomethyl-anilines exclusively.

1. Introduction

N-Monomethylated aromatic amines are useful synthetic intermediates in preparative organic chemistry especially in the synthesis of pharmaceuticals and dyes.[1] Although various methods have been reported for the N-methylation of aniline derivatives, most of these procedures suffer from some limitations.

The direct base-promoted N-methylation of primary amines performed with traditional alkylating agents cannot be used because of the formation of mixtures of secondary and tertiary amines along with the corresponding ammonium salt that are difficult to separate.[2] The direct N-methylation of anilines using methanol and different catalysts,[3] solid bases,[4] or nonconventional methylating agents such as sulfur and bismuth derivatives,[5] suffers from lack of selectivity for monomethylation. Moreover, reaction products are obtained in very low yield. Many methods have been developed for the straightforward N-methylation of primary aromatic amines employing dimethyl sulfate or dimethyl carbonate over zeolites,[6] or methanol in either gas[7] or supercritical[8] phase. Nevertheless, these processes need very severe reaction conditions such as high temperature and high pressure, and they don't exclude the formation of by-products derived from further methylation even if only in a little yield.

The difficulties associated with direct N-monomethylation have led to the development of indirect N-methylation procedures through partially protected anilines. In fact, the use of blocking groups permits the N-monomethylation of primary aromatic amines without proceeding N-methylation beyond the desired stage. The indirect N-monomethylation is a multi-step process based on the synthesis of suitable aniline derivatives that are subjected to the N-methylation reaction, or alternatively to the reductive N-methylation. Finally the modified amine function is released. The most popular indirect method for the synthesis of *N*-methyl anilines is the one-pot reductive N-methylation[9] of primary aromatic amines. However, reduction of *N*-aryl methyleneamines using various reagents[9] furnishes the corresponding *N*,*N*-dimethylated by-products too. Besides, this methodology is sometimes limited when functional groups sensitive to reductants are present. Treatment of trifluoroacetanilides with methyl iodide over potassium hydroxide allows the N-monomethylation process[10] exploiting the weak binding of hydrogen to the trifluoroacetylamino-group. *N*-Methyl anilines are successively obtained by hydrolysis of the corresponding *N*-methyl trifluoroacetanilides. *N*-Arylaminomethylsuccinimides,[11] 1-(1′-arylaminomethyl)-benzotriazoles,[12] 3-methylbenzothiazol-2-(3*H*)-imines,[13] and iminophosphoranes[14] have also been used to prepare *N*-monomethyl anilines. Reduction of *N*-arylformamide[15] and *N*-arylformimidate[16] derivatives yields *N*-monomethylated anilines also without isolating the reaction intermediates before reduction.

Such a massive experimental effort indicates that a convenient and general procedure for the N-monomethylation of primary aromatic amines has long been of considerable interest.

2. Results and discussion

Using an appropriate *N*-protecting group, which is able to enhance the acidity of the amine proton could be a valid

Keywords: Aromatic amines; Diazomethane; Methylation; Nosyl; Sulfonamides.
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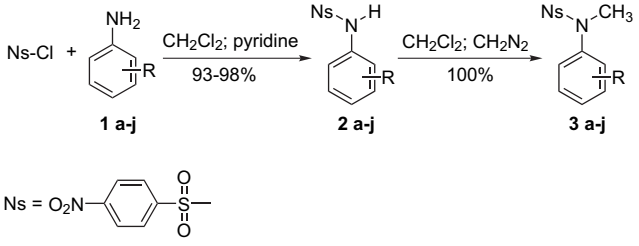
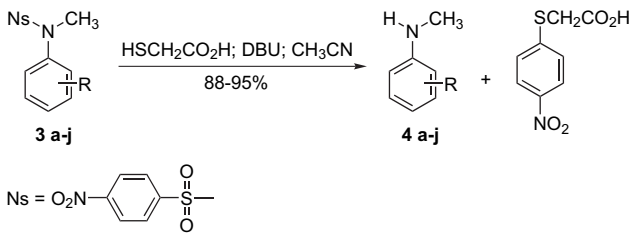
approach to the rapid N-methylation of aromatic primary amines with diazomethane. For this purpose we decided to use the 4-nitrobenzenesulfonyl (nosyl) protecting group to furnish a sulfonamide derivative of exceptional acidity.[17] The pK_a value of the 4-nitrobenzenesulfonamides ranges between 9 and 11;[17b–d] diazomethane could act on the acidic sulfonamide proton to generate the corresponding methyl diazonium ion, that is, the effective methylating agent. Moreover, the nosyl protecting group could preclude competitive over methylation.

In order to study the proceeding of the planned methodology, preliminary reactions were carried out using aniline as a test substrate. Treatment of aniline **1a** with nosyl chloride in dry CH_2Cl_2 and in the presence of pyridine as base (Scheme 1) afforded after work-up the corresponding sulfonamide **2a** as a crystalline solid in 96% overall yield. The subsequent N-methylation reaction, carried out using a solution of diazomethane in dichloromethane, reached completion in only 10 min at room temperature affording the *N*-methylated sulfonamide **3a** as the sole reaction product. The dichloromethane solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea without distillation, thus avoiding the most dangerous operation in other preparations of diazomethane.[18] After the solvent was removed, **3a** was recovered as a solid in 100% yield without need for further purification.



Scheme 1. Synthesis of *N*-methyl-*N*-nosyl sulfonamides **3a**–**j**.

At last, removal of the nosyl protecting group was readily performed in 15 min using the reagent system mercaptoacetic acid/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) in dry acetonitrile (Scheme 2). *N*-Methyl aniline **4a** was recovered in 93% yield after flash chromatography. The thioether formed as coproduct at the end of the deprotection step was easily removed by washing the reaction mixture with an aqueous solution of Na_2CO_3. The chromatographic purification was just served to remove the excess of DBU.



Scheme 2. Removal of the nosyl group.

In order to assess the synthetic validity of the proposed methodology, the same procedure tested for aniline **1a** was then extended to anilines **1b**–**j** bearing different functional groups on the aromatic ring (Table 1).

Table 1. Isolated yield based on substrate **1**

4	R	Yield (%)
a	H	89
b	*o*-CH_3	85
c	*m*-CH_3	87
d	*p*-OCH_3	86
e	*o*-F	81
f	*o*-I	86
g	*p*-NO_2	85
h	*p*-$COCH_3$	88
i	*p*-CO_2CH_3	87
j	*m*-CN	84

In all cases, the *N*-monomethylated anilines **4b**–**j** were obtained as the sole reaction product in overall yields ranging from 81–88% calculated based on the starting anilines **1b**–**j**.

Nosyl protecting group was already employed to prepare various secondary amines under Mitsunobu conditions or under more conventional conditions.[19] The novelty of the proposed methodology is represented by the use of diazomethane as efficient methylating agent. Furthermore, our procedure has an advantage over the ones reported in literature in that the work-up of the *N*-methylation reaction is very simple and rapid. In fact, the N-methylated nosyl anilines were recovered quantitatively by evaporation of the solvent.

3. Conclusion

In contrast to several other methods currently used for the N-monomethylation of anilines the novel adopted methodology presents some inalienable advantages. The application of this methodology permits the specific and high yielding N-monomethylation of primary aromatic amines. The synthetic procedure is accomplished under very mild conditions and all reaction steps are carried out at room temperature. The proposed strategy appears quite general and compatible with a wide range of functional groups.

4. Experimental

4.1. General

All reagents were purchased from Sigma–Aldrich Co. All solvents were purified and dried by standard procedures and distilled prior to use. NMR characterization of all compounds was performed on a Bruker Avance 300 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz, respectively, using $CDCl_3$ or DMSO-d_6 as solvent and tetramethylsilane as an internal standard. ^{19}F NMR spectra were recorded at 470 MHz on a Bruker Avance 500 spectrometer using $CDCl_3$ or DMSO-d_6 as solvent and trichlorofluoromethane as an internal standard. Chemical shift values (δ) are expressed in parts per million. Melting points (mp) were determined on a Kofler hot-stage apparatus and are uncorrected. GC–MS analyzes were carried out using a 30 m HP-35MS capillary column with a 0.25 mm internal diameter and a 0.25 mm film thickness. The mass detector was operated in an electron impact ionization mode (EIMS) at an electron energy of 70 eV. Elemental analyzes

were performed on a Perkin–Elmer Elemental Analyzer. IR spectra were obtained with a Perkin–Elmer FT paragon 1000 PC spectrometer. Reaction mixtures were monitored by TLC using silica gel 60-F_{254} precoated glass plates, purchased from Merck. Short column flash chromatography (SCFC) was performed on Kieselgel 60 H without gypsum. All reactions were carried out under an inert atmosphere (N_2). The dichloromethane solution of diazomethane was prepared from *N*-methyl-*N*-nitrosourea. The concentration of the diazomethane solution (0.66 M) was obtained by a back-titration performed with a standard benzoic acid solution.[20] Dichloromethane solutions of diazomethane are stable for long period if stored on KOH pellets at −20 °C.

4.2. Synthesis of *N*-nosyl anilines 2a–j

4.2.1. General procedure. A solution of nosyl chloride (1.0 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise over 15 min to a magnetically stirred solution of the appropriate aromatic amine **1a–j** (1.1 mmol) and pyridine (1.1 mmol) in dry CH_2Cl_2 (15 mL). The resulting mixture was stirred at room temperature for 2–3 h, monitoring the conversion of **1a–j** by TLC analysis (chloroform/methanol 95:5 v/v, or diethyl ether/light petroleum 60:40 v/v). A 1 M HCl solution was added, then the acidified aqueous phase (pH≅2) was separated and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, then dried over Na_2SO_4, and evaporated to dryness to afford *N*-nosyl anilines **2a–j** as solids (93–98% overall yields).

4.2.1.1. *N*-Nosyl-aniline[21] (2a). Yield 96%, pale yellow solid, mp 174–176 °C. GC–MS (EI): *m/z* 278 [$M^{\bullet+}$, 24%]; 167 (3); 122 (3); 92 (100); 76 (5); 65 (28). ^{1}H NMR (DMSO-d_6): δ 7.02–7.12 (m, 3H, Ar–H); 7.20–7.28 (m, 2H, Ar–H); 7.95–8.02 (m, 2H, Ar–H); 8.33–8.40 (m, 2H, Ar–H); 10.61 (br s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 121.11; 125.11; 125.24; 128.73; 129.81; 137.34; 145.31; 150.28. Anal. Calcd for $C_{12}H_{10}N_2O_4S$: C, 51.79; H, 3.62; N, 10.07; S, 11.52. Found: C, 51.67; H, 3.60; N, 10.11; S, 11.49. IR (KBr): ν_{max} 3308, 3076, 1602, 1525, 1349, 1168 cm^{-1}.

4.2.1.2. *N*-Nosyl-*o*-toluidine (2b). Yield 94%, pink solid, mp 157–159 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 11%]; 106 (100); 79 (10); 77 (17). ^{1}H NMR ($CDCl_3$): δ 2.02 (s, 3H, CH_3); 6.74 (br s, 1H, N–H); 7.11–7.21 (m, 3H, Ar–H); 7.25–7.30 (m, 1H, Ar–H); 7.88–7.95 (m, 2H, Ar–H); 8.25–8.32 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 17.69; 124.28; 125.09; 127.25; 127.33; 128.45; 131.20; 132.19; 133.20; 145.28; 150.19. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.51; H, 4.16; N, 9.55; S, 10.92. IR (KBr): ν_{max} 3313, 3074, 1598, 1524, 1347, 1169 cm^{-1}.

4.2.1.3. *N*-Nosyl-*m*-toluidine (2c). Yield 95%, orange solid, mp 138–139 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 27%]; 106 (100); 79 (29); 77 (25). ^{1}H NMR ($CDCl_3$): δ 2.28 (s, 3H, CH_3); 6.86–7.01 (m, 3H, Ar–H, N–H); 7.12–7.19 (m, 2H, Ar–H); 7.93–8.00 (m, 2H, Ar–H); 8.24–8.31 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.36; 119.06; 122.81; 124.31; 127.22; 128.56; 129.44; 135.25; 139.85; 144.59; 150.20. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.34; H, 4.16; N, 9.53; S, 10.94. IR (KBr): ν_{max} 3327, 3068, 1597, 1524, 1345, 1168 cm^{-1}.

4.2.1.4. *N*-Nosyl-*p*-anisidine (2d). Yield 93%, pale violet solid, mp 187–189 °C. GC–MS (EI): *m/z* 308 [$M^{\bullet+}$, 8%]; 122 (100); 108 (3); 95 (9). ^{1}H NMR (DMSO-d_6): δ 3.64 (s, 3H, OCH_3); 6.76–6.82 (m, 2H, Ar–H); 6.93–6.99 (m, 2H, Ar–H); 7.86–7.92 (m, 2H, Ar–H); 8.32–8.38 (m, 2H, Ar–H); 10.27 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 55.60; 114.91; 124.56; 125.01; 128.76; 129.59; 145.30; 150.16; 157.43. Anal. Calcd for $C_{13}H_{12}N_2O_5S$: C, 50.64; H, 3.92; N, 9.09; S, 10.40. Found: C, 50.78; H, 3.90; N, 9.08; S, 10.36. IR (KBr): ν_{max} 3286, 3101, 1609, 1524, 1345, 1253, 1183 cm^{-1}.

4.2.1.5. *N*-Nosyl-*o*-fluoroaniline[22] (2e). Yield 93%, yellow solid, mp 164–166 °C. GC–MS (EI): *m/z* 296 [$M^{\bullet+}$, 23%]; 122 (4); 110 (100); 83 (41); 76 (6). ^{1}H NMR ($CDCl_3$): δ 6.92–7.03 (m, 2H, Ar–H, N–H); 7.12–7.21 (m, 2H, Ar–H); 7.58–7.64 (m, 1H, Ar–H); 7.92–7.98 (m, 2H, Ar–H); 8.26–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 115.67; 115.93; 124.33; 124.69; 125.10; 125.15; 127.57; 127.67; 128.50; 144.43. ^{19}F NMR ($CDCl_3$): δ −46.87. Anal. Calcd for $C_{12}H_9FN_2O_4S$: C, 48.65; H, 3.06; F, 6.41; N, 9.46; S, 10.82. Found: C, 48.77; H, 3.05; F, 6.38; N, 9.42; S, 10.79. IR (KBr): ν_{max} 3271, 3119, 1607, 1522, 1340, 1259, 1162 cm^{-1}.

4.2.1.6. *N*-Nosyl-*o*-iodoaniline (2f). Yield 94%, yellow solid, mp 141–143 °C. GC–MS (EI): *m/z* 404 [$M^{\bullet+}$, 28%]; 219 (15); 218 (100); 91 (76); 76 (7); 64 (17). ^{1}H NMR ($CDCl_3$): δ 6.89–6.97 (m, 2H, Ar–H, N–H); 7.35–7.42 (m, 1H, Ar–H); 7.65–7.72 (m, 2H, Ar–H); 7.87–7.93 (m, 2H, Ar–H); 8.25–8.31 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 93.61; 124.29; 128.20; 128.80; 129.87; 131.02; 136.35; 139.41; 144.46; 150.40. Anal. Calcd for $C_{12}H_9IN_2O_4S$: C, 35.66; H, 2.24; I, 31.40; N, 6.93; S, 7.93. Found: C, 35.75; H, 2.24; I, 31.43; N, 6.91; S, 7.90. IR (KBr): ν_{max} 3296, 3099, 3063, 1606, 1531, 1469, 1349, 1176, 1089 cm^{-1}.

4.2.1.7. *N*-Nosyl-*p*-nitroaniline[21a] (2g). Yield 93%, yellow solid, mp 177–179 °C. GC–MS (EI): *m/z* 323 [$M^{\bullet+}$, 70%]; 186 (69); 122 (100); 107 (7); 92 (19); 91 (21); 76 (28); 75 (23); 64 (27); 63 (21). ^{1}H NMR ($CDCl_3$): δ 7.24–7.30 (m, 3H, Ar–H, N–H); 8.04–8.10 (m, 2H, Ar–H); 8.15–8.21 (m, 2H, Ar–H); 8.33–8.38 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 119.40; 124.73; 125.62; 128.54; 134.91; 137.93; 146.82; 153.88. Anal. Calcd for $C_{12}H_9N_3O_6S$: C, 44.58; H, 2.81; N, 13.00; S, 9.92. Found: C, 44.69; H, 2.80; N, 12.98; S, 9.88. IR (KBr): ν_{max} 3245, 3105, 2947, 1599, 1529, 1514, 1475, 1346, 1293, 1160, 1087 cm^{-1}.

4.2.1.8. *N*-Nosyl-*p*-aminoacetophenone (2h). Yield 98%, pale pink solid, mp 192–194 °C. GC–MS (EI): *m/z* 320 [$M^{\bullet+}$, 31%]; 305 (100); 134 (5); 122 (6); 119 (35); 106 (23); 92 (13); 91 (12); 79 (11); 77 (12); 64 (13). ^{1}H NMR (DMSO-d_6): δ 2.45 (s, 3H, CH_3); 7.20–7.26 (m, 2H, Ar–H); 7.81–7.87 (m, 2H, Ar–H); 8.03–8.10 (m, 2H, Ar–H); 8.34–8.42 (m, 2H, Ar–H); 11.20 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 26.90; 118.97; 125.32; 128.77; 130.39; 132.95; 141.88; 144.96; 150.48; 196.98. Anal. Calcd for $C_{14}H_{12}N_2O_5S$: C, 52.49; H, 3.78; N, 8.75; S, 10.01.

Found: C, 52.57; H, 3.75; N, 8.71; S, 10.00. IR (KBr): ν_{max} 3163, 3080, 2927, 2861, 1675, 1602, 1537, 1354, 1278, 1157, 1091 cm^{-1}.

4.2.1.9. Methyl *N*-nosyl-*p*-aminobenzoate (2i). Yield 93%, pale pink solid, mp 201–203 °C. GC–MS (EI): *m/z* 336 [$M^{\bullet+}$, 54%]; 305 (31); 150 (100); 122 (95); 119 (16); 92 (19); 91 (11); 76 (21); 64 (20). ^1H NMR (DMSO-d_6): δ 3.73 (s, 3H, OCH_3); 7.20–7.27 (m, 2H, Ar–H); 7.81–7.86 (m, 2H, Ar–H); 8.02–8.08 (m, 2H, Ar–H); 8.34–8.41 (m, 2H, Ar–H); 11.14 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 52.45; 119.26; 125.92; 125.55; 128.76; 131.22; 142.01; 144.93; 150.49; 166.01. Anal. Calcd for $C_{14}H_{12}N_2O_6S$: C, 50.00; H, 3.60; N, 8.33; S, 9.53. Found: C, 50.15; H, 3.57; N, 8.30; S, 9.49. IR (KBr): ν_{max} 3199, 3108, 3027, 2952, 2873, 1702, 1609, 1539, 1512, 1350, 1318, 1298, 1165, 1091 cm^{-1}.

4.2.1.10. *N*-Nosyl-*m*-aminobenzonitrile (2j). Yield 94%, pale orange solid, mp 202–204 °C. GC–MS (EI): *m/z* 303 [$M^{\bullet+}$, 100%]; 273 (7); 186 (74); 156 (26); 122 (68); 117 (73); 92 (24); 90 (39); 76 (29); 75 (25). ^1H NMR (DMSO-d_6): δ 7.38–7.57 (m, 4H, Ar–H); 8.01–8.06 (m, 2H, Ar–H); 8.34–8.40 (m, 2H, Ar–H); 11.12 (s, 1H, N–H). ^{13}C NMR (DMSO-d_6): δ 112.72; 118.61; 123.32; 125.25; 125.33; 128.70; 128.78; 131.42; 138.42; 144.70; 150.51. Anal. Calcd for $C_{13}H_9N_3O_4S$: C, 51.48; H, 2.99; N, 13.85; S, 10.57. Found: 51.61; H, 2.99; N, 13.80; S, 10.55. IR (KBr): ν_{max} 3169, 3081, 2964, 2245, 1606, 1587, 1535, 1415, 1351, 1178, 1089 cm^{-1}.

4.3. Preparation of diazomethane from *N*-methyl-*N*-nitrosourea

Dichloromethane (100 mL) was added to a 40% aqueous potassium hydroxide solution (30 mL). The mixture was cooled to 4 °C, and *N*-methyl-*N*-nitrosourea (10.0 g, 97.0 mmol) was added with shaking, and the reaction temperature was maintained below 5 °C. After 20 min, the organic phase was separated and stored over pellets of pure potassium hydroxide at −20 °C.

4.4. Methylation of *N*-nosyl anilines 2a–j

4.4.1. General procedure. A 0.66 M solution of diazomethane in CH_2Cl_2 (3.0 mmol) was added dropwise over 5 min to a solution of the appropriate *N*-nosyl aniline **2a–j** (1.0 mmol) in CH_2Cl_2 (15 mL). The reaction mixture was stirred at room temperature for 10 min. After this time, TLC analysis (chloroform/methanol 99:1 v/v, or diethyl ether/light petroleum 60:40 v/v) showed complete conversion of the precursor. Evaporation of the solvent under reduced pressure gave *N*-methyl-*N*-nosyl anilines **3a–j** as solids (100% overall yields).

4.4.1.1. *N*-Methyl-*N*-nosyl-aniline[23] (3a). Brown solid, mp 130–132 °C. GC–MS (EI): *m/z* 292 [$M^{\bullet+}$, 12%]; 228 (3); 122 (2); 106 (100); 79 (15); 77 (39). ^1H NMR ($CDCl_3$): δ 3.23 (s, 3H, CH_3); 7.05–7.11 (m, 2H, Ar–H); 7.32–7.36 (m, 3H, Ar–H); 7.70–7.75 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.40; 124.04; 126.60; 128.02; 129.00; 129.28; 140.58; 142.24; 150.13. Anal. Calcd for $C_{13}H_{12}N_2O_4S$: C, 53.42; H, 4.14; N, 9.58; S, 10.97. Found: C, 53.33; H, 4.16; N, 9.53; S, 10.93. IR (KBr): ν_{max} 3078, 2977, 1607, 1526, 1350, 1128 cm^{-1}.

4.4.1.2. *N*-Methyl-*N*-nosyl-*o*-toluidine[23] (3b). Yellow solid, mp 126–128 °C. GC–MS (EI): *m/z* 306 [$M^{\bullet+}$, 9%]; 120 (100); 91 (26); 77 (5); 65 (7). ^1H NMR ($CDCl_3$): δ 2.39 (s, 3H, CH_3); 3.22 (s, 3H, N–CH_3); 6.52–6.57 (m, 1H, Ar–H); 7.05–7.12 (m, 1H, Ar–H); 7.23–7.34 (m, 2H, Ar–H); 7.87–7.93 (m, 2H, Ar–H); 8.34–8.39 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 18.32; 39.15; 124.17; 126.71; 126.76; 128.89; 129.11; 131.86; 138.89; 139.39; 143.92; 144.20. Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 55.05; H, 4.58; N, 9.10; S, 10.42. IR (KBr): ν_{max} 3068, 2975, 1601, 1523, 1348, 1164 cm^{-1}.

4.4.1.3. *N*-Methyl-*N*-nosyl-*m*-toluidine[23] (3c). Yellow solid, mp 114–116 °C. GC–MS (EI): *m/z* 306 [$M^{\bullet+}$, 8%]; 242 (5); 201 (4); 120 (100); 92 (12); 91 (38); 77 (12); 65 (11). ^1H NMR ($CDCl_3$): δ 2.33 (s, 3H, CH_3); 3.22 (s, 3H, N–CH_3); 6.78–6.83 (m, 1H, Ar–H); 6.94–6.99 (m, 1H, Ar–H); 7.09–7.22 (m, 2H, Ar–H); 7.72–7.77 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.34; 38.48; 123.19; 123.98; 127.63; 128.82; 128.97; 129.03; 139.37; 140.50; 142.41; 150.10. Anal. Calcd for $C_{14}H_{14}N_2O_4S$: C, 54.89; H, 4.61; N, 9.14; S, 10.47. Found: C, 54.76; H, 4.59; N, 9.11; S, 10.49. IR (KBr): ν_{max} 3065, 2976, 1599, 1525, 1349, 1158 cm^{-1}.

4.4.1.4. *N*-Methyl-*N*-nosyl-*p*-anisidine (3d). Brown solid, mp 147–149 °C. GC–MS (EI): *m/z* 322 [$M^{\bullet+}$, 10%]; 136 (100); 122 (6); 121 (12); 108 (5); 92 (6); 77 (4). ^1H NMR ($CDCl_3$): δ 3.20 (s, 3H, N–CH_3); 3.81 (s, 3H, OCH_3); 6.78–6.85 (m, 2H, Ar–H); 6.94–6.99 (m, 2H, Ar–H); 7.71–7.77 (m, 2H, Ar–H); 8.27–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.72; 55.49; 114.38; 124.01; 128.06; 129.05; 133.08; 142.46; 154.46; 159.10. Anal. Calcd for $C_{14}H_{14}N_2O_5S$: C, 52.18; H, 4.38; N, 8.69; S, 9.95. Found: C, 52.01; H, 4.36; N, 8.66; S, 9.99. IR (KBr): ν_{max} 3122, 2977, 1606, 1527, 1350, 1252, 1185 cm^{-1}.

4.4.1.5. *N*-Methyl-*N*-nosyl-*o*-fluoroaniline (3e). Yellow solid, mp 115–117 °C. GC–MS (EI): *m/z* 310 [$M^{\bullet+}$, 10%]; 124 (100); 122 (9); 95 (8); 77 (43). ^1H NMR (DMSO-d_6): δ 3.19 (s, 3H, N–CH_3); 7.17–7.32 (m, 3H, Ar–H); 7.38–7.45 (m, 1H, Ar–H); 7.88–7.94 (m, 2H, Ar–H); 8.39–8.45 (m, 2H, Ar–H). ^{13}C NMR (DMSO-d_6): δ 38.74; 117.22; 125.16; 125.55; 129.43; 130.84; 131.10; 143.00; 150.55; 157.45; 160.77. ^{19}F NMR (DMSO-d_6): δ −40.03. Anal. Calcd for $C_{13}H_{11}FN_2O_4S$: C, 50.32; H, 3.57; F, 6.12; N, 9.03; S, 10.33. Found: C, 50.51; H, 3.54; F, 6.10; N, 9.07; S, 10.29. IR (KBr): ν_{max} 3108, 2942, 1606, 1526, 1492, 1355, 1179, 1105 cm^{-1}.

4.4.1.6. *N*-Methyl-*N*-nosyl-*o*-iodoaniline (3f). Yellow solid, mp 166–168 °C. GC–MS (EI): *m/z* 418 [$M^{\bullet+}$, 24%]; 291 (66); 233 (54); 232 (100); 202 (16); 120 (25); 105 (49); 104 (70); 90 (15); 64 (53). ^1H NMR ($CDCl_3$): δ 3.25 (s, 3H, N–CH_3); 7.04–7.12 (m, 2H, Ar–H); 7.31–7.38 (m, 1H, Ar–H); 7.88–7.93 (m, 1H, Ar–H); 7.96–8.02 (m, 2H, Ar–H); 8.35–8.41 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 39.03; 100.61; 124.32; 129.21; 129.46; 129.73; 130.51; 140.67; 142.71; 144.73; 150.20. Anal. Calcd for

$C_{13}H_{11}IN_2O_4S$: C, 37.34; H, 2.65; I, 30.34; N, 6.70; S, 7.67. Found: C, 37.48; H, 2.67; I, 30.20; N, 6.66; S, 7.71. IR (KBr): ν_{max} 3101, 2951, 1607, 1530, 1472, 1355, 1177, 1081 cm^{-1}.

4.4.1.7. *N*-Methyl-*N*-nosyl-*p*-nitroaniline (3g). Yellow solid, mp 169–181 °C. GC–MS (EI): *m/z* 337 [$M^{\bullet+}$, 22%]; 186 (9); 151 (43); 122 (24); 105 (100); 92 (8); 90 (10); 76 (17); 63 (9). ^1H NMR ($CDCl_3$): δ 3.30 (s, 3H, N–CH_3); 7.33–7.38 (m, 2H, Ar–H); 7.74–7.77 (m, 2H, Ar–H); 8.20–8.26 (m, 2H, Ar–H); 8.32–8.37 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 37.90; 124.43; 124.66; 126.07; 128.82; 134.24; 137.73; 146.26; 153.26. Anal. Calcd for $C_{13}H_{11}N_3O_6S$: C, 46.29; H, 3.29; N, 12.46; S, 9.51. Found: C, 46.12; H, 3.27; N, 12.40; S, 9.47. IR (KBr): ν_{max} 3098, 2964, 1602, 1532, 1512, 1498, 1477, 1347, 1318, 1291, 1162, 1085 cm^{-1}.

4.4.1.8. *N*-Methyl-*N*-nosyl-*p*-aminoacetophenone (3h). Pale yellow solid, mp 172–175 °C. GC–MS (EI): *m/z* 334 [$M^{\bullet+}$, 26%]; 319 (25); 148 (100); 133 (13); 132 (20); 122 (3); 106 (18); 105 (27); 91 (8); 77 (11); 76 (7). ^1H NMR ($CDCl_3$): δ 2.59 (s, 3H, $COCH_3$); 3.24 (s, 3H, N–CH_3); 7.21–7.26 (m, 2H, Ar–H); 7.69–7.74 (m, 2H, Ar–H); 7.91–7.96 (m, 2H, Ar–H); 8.28–8.33 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 26.70; 37.96; 124.25; 125.88; 128.88; 129.36; 135.86; 141.82; 144.70; 150.29; 196.94. Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.71; H, 4.25; N, 8.35; S, 9.55. IR (KBr): ν_{max} 3109, 3076, 2978, 1675, 1602, 1538, 1357, 1270, 1174 cm^{-1}.

4.4.1.9. Methyl *N*-methyl-*N*-nosyl-*p*-aminobenzoate (3i). Yellow solid, mp 185–187 °C. GC–MS (EI): *m/z* 350 [$M^{\bullet+}$, 11%]; 319 (3); 164 (100); 132 (18); 120 (5); 105 (13); 104 (15); 92 (6); 91 (5); 77 (13); 76 (7). ^1H NMR ($CDCl_3$): δ 3.24 (s, 3H, N–CH_3); 3.92 (s, 3H, OCH_3); 7.15–7.22 (m, 2H, Ar–H); 7.67–7.83 (m, 2H, Ar–H); 7.96–8.04 (m, 2H, Ar–H); 8.27–8.34 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 37.99; 52.41; 124.20; 125.75; 128.88; 129.24; 130.60; 141.80; 144.6; 150.27; 166.10. Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00; S, 9.15. Found: C, 51.60; H, 4.01; N, 7.97; S, 9.19. IR (KBr): ν_{max} 3107, 3064, 2970, 1701, 1609, 1540, 1351, 1315, 1296, 1168, 1087 cm^{-1}.

4.4.1.10. *N*-Methyl-*N*-nosyl-*m*-aminobenzonitrile (3j). Yellow solid, mp 149–151 °C. GC–MS (EI): *m/z* 317 [$M^{\bullet+}$, 33%]; 253 (24); 212 (10); 186 (8); 131 (100); 122 (13); 104 (14); 102 (22); 77 (10); 76 (13). ^1H NMR ($CDCl_3$): δ 3.24 (s, 3H, N–CH_3); 7.38–7.52 (m, 3H, Ar–H); 7.59–7.64 (m, 1H, Ar–H); 7.71–7.77 (m, 2H, Ar–H); 8.32–8.37 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 38.01; 113.55; 117.60; 124.40; 128.91; 129.63; 130.30; 130.78; 131.28; 141.59; 141.65; 150.44. Anal. Calcd for $C_{14}H_{11}N_3O_4S$: C, 52.99; H, 3.49; N, 13.24; S, 10.10. Found: 53.16; H, 3.48; N, 13.19; S, 10.07. IR (KBr): ν_{max} 3110, 3072, 2943, 2233, 1605, 1532, 1356, 1190, 1165, 1067 cm^{-1}.

4.5. Deprotection of *N*-nosyl-*N*-methyl anilines 3a–j

4.5.1. General procedure. A solution of the appropriate *N*-methyl-*N*-nosyl aniline **3a–j** (1.0 mmol) in dry CH_3CN (10 mL) was added to a solution of mercaptoacetic acid (2.0 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (4.0 mmol) in dry CH_3CN (10 mL). The resulting mixture was stirred at room temperature for 10–15 min, monitoring the conversion of **3a–j** by TLC analysis (chloroform/methanol 99:1 v/v, or diethyl ether/light petroleum 60:40 v/v). The solvent was evaporated under reduced pressure and the residue was dissolved in 9% aqueous Na_2CO_3 (10 mL) and CH_2Cl_2 (15 mL). The organic layer was separated, washed with 9% aqueous Na_2CO_3 (5 mL), dried over Na_2SO_4, and then evaporated under vacuum to give a crude reaction product. The subsequent chromatographic purification (diethyl ether/light petroleum 50:50 v/v) afforded *N*-methyl anilines **4a–j** (88–95% overall yields).

4.5.1.1. *N*-Methyl-aniline[24] (4a). Yield 93%, brown oil. GC–MS (EI): *m/z* 107 [$M^{\bullet+}$, 81%]; 106 (100); 79 (15); 77 (24); 65 (7). ^1H NMR ($CDCl_3$): δ 2.83 (s, 3H, N–CH_3); 6.59–6.67 (m, 2H, Ar–H); 6.71–6.78 (m, 1H, Ar–H); 7.18–7.25 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.32; 112.27; 117.05; 129.07; 149.22. Anal. Calcd for C_7H_9N: C, 78.46; H, 8.47; N, 13.07. Found: C, 78.17; H, 8.45; N, 13.02. IR (liquid film): ν_{max} 3422, 3058, 2932, 2821, 1601, 1511, 1320, 1172 cm^{-1}.

4.5.1.2. *N*-Methyl-*o*-toluidine[25] (4b). Yield 91%, brown oil. GC–MS (EI): *m/z* 121 [$M^{\bullet+}$, 100%]; 120 (62); 106 (72); 91 (26); 77 (13); 65 (12). ^1H NMR ($CDCl_3$): δ 2.21 (s, 3H, CH_3); 2.95 (s, 3H, N–CH_3); 3.50 (br s, 1H, N–H); 6.64–6.76 (m, 2H, Ar–H); 7.07–7.13 (m, 1H, Ar–H); 7.19–7.26 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 17.46; 30.83; 109.16; 116.69; 121.92; 127.24; 129.95; 147.30. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.55; H, 9.11; N, 11.51. IR (liquid film): ν_{max} 3429, 3056, 2934, 2818, 1608, 1592, 1515, 1470, 1318, 1267, 1168 cm^{-1}.

4.5.1.3. *N*-Methyl-*m*-toluidine[26] (4c). Yield 92%, brown oil. GC–MS (EI): *m/z* 121 [$M^{\bullet+}$, 85%]; 120 (100); 201 (4); 120 (100); 106 (6); 92 (6); 91 (22); 77 (10); 65 (9). ^1H NMR ($CDCl_3$): δ 2.34 (s, 3H, CH_3); 2.86 (s, 3H, N–CH_3); 3.41 (br s, 1H, N–H); 6.44–6.51 (m, 2H, Ar–H); 6.57–6.62 (m, 1H, Ar–H); 7.10–7.17 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 21.59; 30.73; 109.58; 113.12; 118.15; 129.02; 138.94; 149.34. Anal. Calcd for $C_8H_{11}N$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.50; H, 9.19; N, 11.50. IR (liquid film): ν_{max} 3426, 3054, 2930, 2821, 1610, 1598, 1517, 1462, 1325, 1170 cm^{-1}.

4.5.1.4. *N*-Methyl-*p*-anisidine[27] (4d). Yield 93%, brown oil. GC–MS (EI): *m/z* 137 [$M^{\bullet+}$, 65%]; 122 (100); 94 (13); 77 (5); 65 (9). ^1H NMR ($CDCl_3$): δ 2.81 (s, 3H, N–CH_3); 3.32 (br s, 1H, N–H); 3.77 (s, 3H, OCH_3); 6.58–6.65 (m, 2H, Ar–H); 6.80–6.86 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 31.57; 55.75; 113.61; 114.79; 143.57; 152.02. Anal. Calcd for $C_8H_{11}NO$: C, 70.04; H, 8.08; N, 10.21. Found: C, 70.29; H, 8.11; N, 10.16. IR (liquid film): ν_{max} 3428, 3046, 2936, 2830, 1616, 1604, 1508, 1467, 1323, 1240, 1162 cm^{-1}.

4.5.1.5. *N*-Methyl-*o*-fluoroaniline[28] (4e). Yield 88%, brown oil. GC–MS (EI): *m/z* 125 [$M^{\bullet+}$, 84%]; 124 (100); 96 (8); 95 (9); 83 (11); 77 (36). ^1H NMR ($CDCl_3$): δ 2.89 (s, 3H, N–CH_3); 6.59–6.75 (m, 2H, Ar–H); 6.93–7.08 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.26; 111.49; 114.06; 114.29; 116.32; 116.43; 124.62. ^{19}F NMR ($CDCl_3$):

δ −14.68. Anal. Calcd for C_7H_8FN: C, 67.19; H, 6.44; F, 15.18; N, 11.19. Found: C, 67.01; H, 6.41; F, 15.23; N, 11.16. IR (liquid film): ν_{max} 3410, 3061, 2935, 1610, 1596, 1509, 1458, 1321 cm^{-1}.

4.5.1.6. *N*-Methyl-*o*-iodoaniline[29] (4f). Yield 92%, dark oil. GC–MS (EI): *m/z* 233 [$M^{\bullet+}$, 98%]; 232 (100); 203 (3); 127 (10); 106 (25); 105 (37); 104 (43); 91 (17); 79 (29); 77 (82); 64 (14); 63 (19). ^1H NMR ($CDCl_3$): δ 2.92 (d, 3H, N–CH_3, J=4.8 Hz); 4.25 (br s, 1H, N–H); 6.46–6.62 (m, 2H, Ar–H); 7.25–7.32 (m, 1H, Ar–H); 7.68–7.73 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 29.97; 85.14; 109.98; 118.45; 129.47; 138.83; 148.11. Anal. Calcd for C_7H_8IN: C, 36.08; H, 3.46; I, 54.45; N, 6.01. Found: C, 36.21; H, 3.48; I, 54.67; N, 6.05. IR (liquid film): ν_{max} 3419, 3052, 2931, 1612, 1600, 1515, 1455, 1319 cm^{-1}.

4.5.1.7. *N*-Methyl-*p*-nitroaniline[30] (4g). Yield 92%, yellow solid, mp 149–151 °C. GC–MS (EI): *m/z* 152 [$M^{\bullet+}$, 100%]; 122 (53); 106 (33); 94 (17); 79 (46); 78 (30); 77 (84); 65 (49). ^1H NMR ($CDCl_3$): δ 2.94 (d, 3H, N–CH_3, J=4.9 Hz); 4.70 (br s, 1H, N–H); 6.50–6.56 (m, 2H, Ar–H); 8.07–8.13 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.14; 110.69; 126.42; 137.90; 154.22. Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.18; H, 5.27; N, 18.34. IR (KBr): ν_{max} 3358, 1603, 1550, 1498, 1324, 1302 cm^{-1}.

4.5.1.8. *N*-Methyl-*p*-aminoacetophenone[31] (4h). Yield 90%, pale yellow solid, mp 106–108 °C. GC–MS (EI): *m/z* 149 [$M^{\bullet+}$, 56%]; 134 (100); 106 (15); 105 (27); 79 (10); 77 (14). ^1H NMR ($CDCl_3$): δ 2.51 (s, 3H, $COCH_3$); 2.89 (d, 3H, N–CH_3, J=5.0 Hz); 4.40 (br s, 1H, N–H); 6.55–6.61 (m, 2H, Ar–H); 7.82–7.89 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 26.04; 30.07; 110.98; 126.39; 130.76; 153.09; 196.50. Anal. Calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39. Found: C, 72.22; H, 7.39; N, 9.44. IR (KBr): ν_{max} 3389, 3064, 1662, 1628, 1594, 1528, 1439, 1310, 1283 cm^{-1}.

4.5.1.9. Methyl *N*-methyl-*p*-aminobenzoate[32] (4i). Yield 95%, pale yellow solid, mp 86–88 °C. GC–MS (EI): *m/z* 165 [$M^{\bullet+}$, 99%]; 134 (100); 120 (5); 106 (23); 91 (4); 77 (13); 79 (16); 77 (22); 65 (9). ^1H NMR ($CDCl_3$): δ 2.88 (s, 3H, N–CH_3); 3.83 (s, 3H, OCH_3); 4.27 (br s, 1H, N–H); 6.52–6.59 (m, 2H, Ar–H); 7.84–7.91 (m, 2H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.11; 51.52; 111.04; 118.03; 131.48; 152.90; 167.41. Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.29; H, 6.74; N, 8.42. IR (KBr): ν_{max} 3394, 3073, 2948, 1692, 1608, 1583, 1517, 1445, 1264, 1244, 1174 cm^{-1}.

4.5.1.10. *N*-Methyl-*m*-aminobenzonitrile[33] (4j). Yield 90%, brown oil. GC–MS (EI): *m/z* 132 [$M^{\bullet+}$, 99%]; 131 (100); 104 (23); 102 (17); 90 (9); 77 (15); 76 (11); 75 (12). ^1H NMR ($CDCl_3$): δ 2.82 (s, 3H, N–CH_3); 3.73 (br s, 1H, N–H); 6.77–6.73 (m, 2H, Ar–H); 6.94–6.99 (m, 1H, Ar–H); 7.20–7.27 (m, 1H, Ar–H). ^{13}C NMR ($CDCl_3$): δ 30.34; 112.85; 114.42; 116.95; 119.61; 120.58; 129.83; 149.35. Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.95; H, 6.07; N, 21.12. IR (liquid film): ν_{max} 3401, 3062, 2933, 2158, 1602, 1516, 1319, 1169 cm^{-1}.

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An efficient method for the synthesis of lignans

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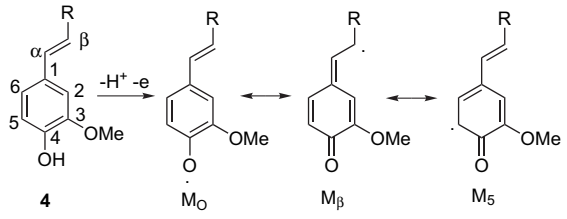
Abstract—An efficient approach for the synthesis of several types of lignans (dibenzylbutanediols, dibenzylbutanes, substituted tetrahydrofurans, aryldihydronaphthalenes, arylnaphthalenes, and aryltetralins) was developed. The regioselective oxidative coupling of ethyl ferulate was used as the key step.

1. Introduction

Lignans, one class of the oldest known natural products, have attracted much interest over the years on account of their broad range of biological activities. The structural diversity of lignans has attracted much attention and many elegant syntheses have been reported.[1–7] One classical route toward lignan structure utilizes the direct oxidative coupling reaction of structurally simple precursors.[6] Though this method is very attractive as it could offer quick access to the skeletons of a wide range of lignans, its application is limited because of the lack of selectivity on the coupling sites. Herein we report an efficient modified strategy hinged on the oxidative coupling reaction for the synthesis of secoisolariciresinol (**1**), dihydroguaiaretic acid (**2**), and divanillyltetrahydrofuran (**3**). Previous attempts to synthesize these compounds using coupling reactions are not successful due to the complexity of coupling pattern and the low yield of the desired product.[8–11] It is expected that other lignan compounds, e.g., arylnaphthalene and aryltetralin derivatives, may also be prepared by this strategy.

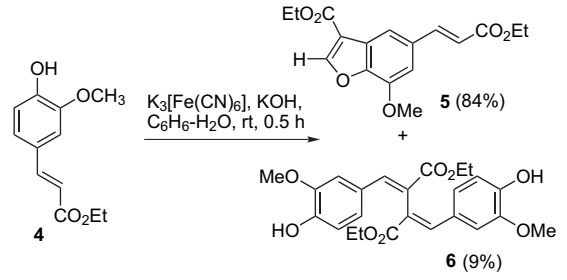
2. Results and discussion

It is known that during the course of oxidative coupling of phenols, phenoxyl radicals are generated as intermediates. In the case of **4** (R=CH_3, CH_2OH), the formed radical has five mesomeric forms, three of which, designated as M_O, M_5, and M_β, are relevant to the coupling reactions (Scheme 1).



Scheme 1.

As a result, six coupling modes for the mesomers are possible (β–β, β–5, β–O, 5–5, 5–O, and O–O), leading to complex products. The major product was reported to be β–5 linked compound.[9] This is verified by our own experiment. Oxidation of ethyl ferulate (**4**: R=CO_2Et) with alkaline potassium ferricyanide in benzene–water two phase system gave rise to β–5 linked **5** as the main product. The desired β–β coupling product **6**[12,13] was only obtained in very low yield (Scheme 2).



Scheme 2.

The chance of β–β coupling could be increased if the β–5 coupling is blocked by another substituent at the 5 position of the phenyl ring.[14] Accordingly, a strategy was developed based on substrate modification. A *tert*-butyl group was introduced to the 5 position of the phenyl ring before oxidation

Keywords: Lignan; Synthesis; Regioselective oxidative coupling.
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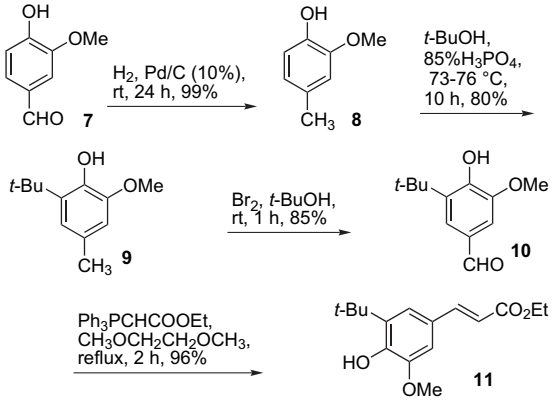
to obstruct the side β–5 coupling. The *tert*-butyl group could be removed afterwards using the method reported by Tashiro et al.[15] It was hoped that this maneuver could improve the yield of desired oxidative coupling product greatly, thus providing a simple concise route for the synthesis of **1**, **2**, and **3**.

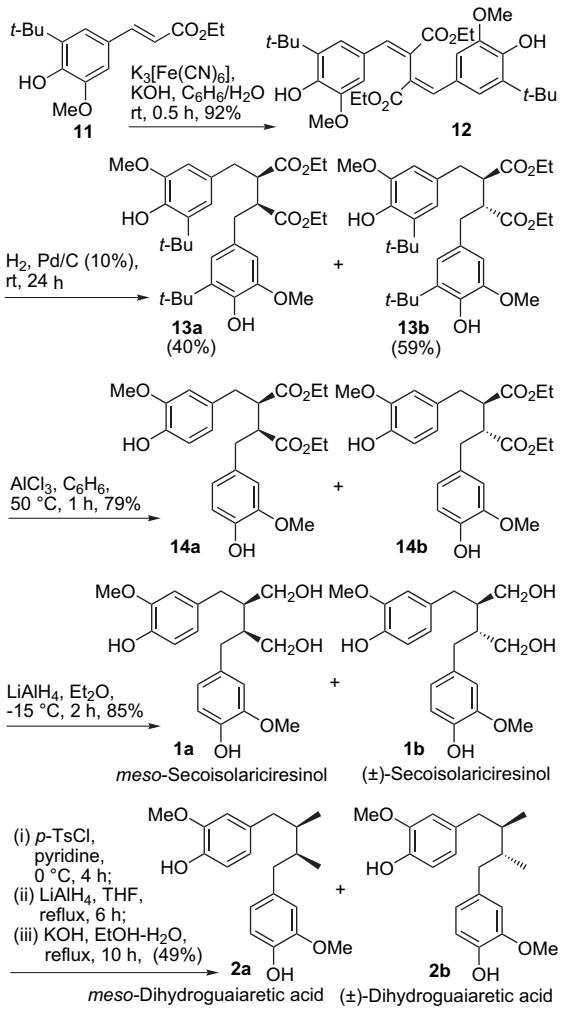
Our syntheses started from the commercially available **7**. Hydrogenation of **7** afforded **8**, which was transformed to **9** by subsequent reaction with *t*-BuOH in H_3PO_4.[16,17] The later step was not complete, but the substrate **8** can be recovered and recycled. Oxidation of **9**, followed by the Wittig reaction, readily gave the desired compound **11**, which served as our key precursor (Scheme 3).[18,19]



Scheme 3.

The stage was now set for the crucial coupling step. As expected, on treatment with alkaline potassium ferricyanide in benzene–water two phase system, **11** was transformed to β–β coupling product **12**[12,13] in excellent yield. Hydrogenation of **12** gave **13** as a mixture of two diastereomers, *erythro*-**13a** and *threo*-**13b**, which could be separated by flash chromatography and each obtained in pure form. The ratio of these two compounds was 2:3 as determined by integration of corresponding signals in the ^{1}H NMR spectra. The relative configurations of **13a** and **13b** were identified by comparing the spectroscopic data of the terminal product **1a** and **1b** with literature data. The *tert*-butyl group was then removed at this stage. Using the method reported by Tashiro et al., the *tert*-butyl groups were transferred from **13a** (**13b**) to solvent benzene via $AlCl_3$ catalyzed Friedel–Crafts reaction.[15] Reduction of **14a** (**14b**) using $LiAlH_4$ afforded **1a** (**1b**). The Compound **2a** (**2b**) was obtained from **1a** (**1b**) by tosylation of the hydroxy groups, reduction with $LiAlH_4$ in THF, and final deprotection of phenol hydroxyl groups with KOH in EtOH–H_2O (Scheme 4).[20,21]

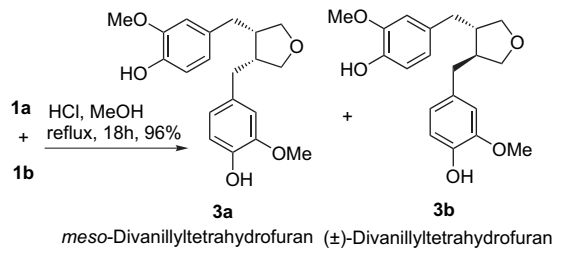
It should be noted that 2,3-dibenzylidenesuccinates, may be in principle readily produced via a double Stobbe condensation, starting from a succinate ester and the appropriate aromatic aldehyde.[12] However, the use of Stobbe condensation reaction for the synthesis of 2,3-dibenzylidenesuccinates containing unprotected phenol hydroxyl group (e.g., compounds **6** and **12**) has not been reported so far to the best of our knowledge. Probably the presence of active phenol hydroxyl group in the starting aromatic aldehyde would hamper the effective condensation. The protection of hydroxyl



Scheme 4.

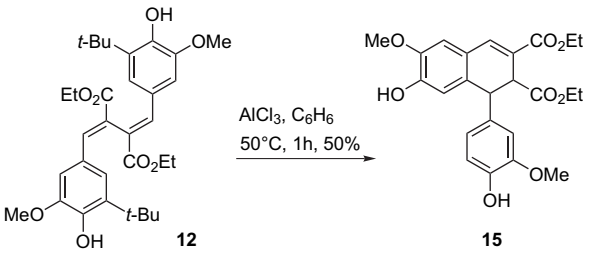
group might overcome this obstacle, but the introduction of a protective group and its removal afterwards would detract from the overall yield and most likely would lead to the generation of byproducts, thus reducing the efficiency of this approach for the preparation of those compounds.

The synthesis of divanillyltetrahydrofuran (**3a** or **3b**) was also achieved by refluxing a methanolic solution of secoisolariciresinol (**1a** or **1b**) under acidic conditions (Scheme 5).



Scheme 5.

Treatment of **12** with $AlCl_3$ in benzene directly afforded aryldihydronaphthalene **15** (Scheme 6). The unreacted starting material **12** can be recovered and recycled.



Scheme 6.

Compound **15** could be converted to a wide variety of arylnaphthalenes and aryltetralins, thus our method reported here might be used for the preparation of these types of natural products.[22,23]

The synthetic secoisolariciresinol (**1**),[24–27] dihydroguaiaretic acid (**2**),[28–31] divanillyltetrahydrofuran (**3**),[32] and aryldihydronaphthalene **15**[33] have identical ^{1}H and ^{13}C NMR spectra to those of the corresponding natural products reported in the literatures.

3. Conclusions

In summary, concise and highly efficient syntheses of dibenzylbutanediol **1**, dibenzylbutane **2**, substituted tetrahydrofuran **3**, and aryldihydronaphthalene **15** have been achieved by employing phenol oxidative coupling reaction as the key step. Modification of the substrate (5–H→5–*t*-butyl) forced the oxidative coupling to undergo an otherwise unfavorable coupling pathway, which dramatically improved the yield of the desired dimer. The *tert*-butyl group can be readily removed via Friedel–Crafts reactions after the coupling. Compared with other methods[34,35] used to synthesize these natural products, secoisolariciresinol (**1**), dihydroguaiaretic acid (**2**), and divanillyltetrahydrofuran (**3**), the strategy described in this paper is convenient and efficient. Furthermore, this route can be applied in the preparation of other lignans, e.g., arylnaphthalenes and aryltetralins via structural modifications. Further investigations will be directed toward stereoselective synthesis of lignan molecules through this methodology.

4. Experimental

4.1. General procedures

All reagents and chemicals were of reagent grade and used as received from commercial suppliers. Melting points were measured on a Kofler apparatus and were uncorrected. IR spectra were obtained in liquid films or KBr disks on an FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded with 300 MHz spectrometer. The chemical shifts are referenced in parts per million relative to TMS. Low-resolution mass spectra were recorded in the ES^{+} mode. The high-resolution mass spectra (HRMS) were recorded in the FAB mode. The preparative HPLC separations were performed using a Nova-pak®Silica 6 μm 7.8×300 mm column. The flow rate was 2.5 mL/min utilizing an *n*-hexane/ethyl acetate mobile phase. Flash column chromatography was generally performed on silica gel (200–300 mesh) and TLC inspections on silica gel GF_{254} plates with petroleum ether/ethyl acetate.

4.1.1. Oxidative coupling of ethyl (*E*)-3-(4-hydroxy-3-methoxyphenyl)-propenoate (4). The compound **4** (500 mg, 2.25 mmol) in benzene (22.5 mL) was vigorously stirred with an aqueous solution (4.5 mL) containing potassium ferricyanide (1.80 g) and potassium hydroxide (700 mg) for 0.5 h under nitrogen. The organic layer was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (5:1, v/v) to afford **5** (301 mg, 84%) and **6** (45 mg, 9%); **5**, colorless crystals, mp 111 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (3H, t, J=7.2 Hz), 1.44 (3H, t, J=7.2 Hz), 4.05 (3H, s), 4.29 (2H, q, J=7.2 Hz), 4.42 (2H, q, J=7.2 Hz), 6.46 (1H, d, J=15.9 Hz), 7.04 (1H, s), 7.79 (1H, d, J=15.9 Hz), 7.82 (1H, s), 8.26 (1H, s). MS *m/z*: 318 (M^{+}), 273, 246, 227. HRMS: $C_{17}H_{18}O_6$+Na calcd 341.0996, found 341.0992; **6**, yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.11 (6H, t, J=6.9 Hz), 3.74 (6H, s), 4.15 (4H, q, J=6.9 Hz), 6.06 (2H, s), 6.84 (2H, d, J=8.1 Hz), 7.06 (2H, dd, J=1.8, 8.1 Hz), 7.13 (2H, d, J=1.8 Hz), 7.86 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.0, 55.6, 61.0, 111.3, 114.5, 124.6, 125.1, 127.3, 142.2, 146.3, 147.3, 167.3. MS *m/z*: 442 (M^{+}), 296, 260, 151, 137.

4.1.2. Synthesis of 2-methoxy-4-methyl-phenol (8). A mixture of compound **7** (200 mg, 1.31 mmol) and 10% Pd/C (5:1, substrate/catalyst) in acetic acid was stirred at 55 °C under hydrogen atmosphere for 24 h, Pd/C was filtered and the solvent was evaporated in vacuo to give **8** (180 mg, 99%) as a colorless oil. ^{1}H NMR data were consistent with literature values.[36] ^{1}H NMR ($CDCl_3$) δ 2.21 (3H, s), 3.74 (3H, s), 5.84 (1H, s), 6.61 (1H, d, J=8.7 Hz), 6.62 (1H, s), 6.80 (1H, d, J=8.7 Hz). MS *m/z*: 138 (M^{+}), 123, 95, 67.

4.1.3. Synthesis of 2-*tert*-butyl-6-methoxy-4-methyl-phenol (9). To a well-stirred emulsion of compound **8** (860 mg, 6.23 mmol) and 85% phosphoric acid (3.20 g, 1.90 mL), *t*-BuOH (1.11 equiv, 0.65 mL) was added at 73–76 °C. The mixture was stirred at the same temperature for 10 h, then the reaction was quenched with water, extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (20:1, v/v) to afford **9** (967 mg, 80%) as a yellowish oil, the unreacted starting material **8** can also be recovered and recycled. ^{1}H and ^{13}C NMR data were consistent with literature values.[37] ^{1}H NMR ($CDCl_3$) δ 1.53 (9H, s), 2.40 (3H, s), 3.94 (3H, s), 5.96 (1H, s), 6.69 (1H, d, J=1.8 Hz), 6.81 (1H, d, J=1.8 Hz). ^{13}C NMR ($CDCl_3$) δ 21.7, 29.7, 34.8, 56.3, 109.6, 119.6, 128.1, 135.4, 142.2, 146.7. MS *m/z*: 194 (M^{+}), 179, 151, 119, 91.

4.1.4. Synthesis of 3-*tert*-butyl-4-hydroxy-5-methoxy-benzaldehyde (10). Bromine (4 equiv, 0.25 mL) was added dropwise with stirring to compound **9** (220 mg, 1.14 mmol) in *t*-BuOH (3.5 mL) at 25 °C. After stirred for 1 h, the mixture was cooled to 20 °C, then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with 10% $NaHSO_3$, distilled water, brine, and dried over $MgSO_4$. The solvent was evaporated

in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (7:1, v/v) to afford **10** (200 mg, 85%) as colorless crystals; mp 102–103 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (9H, s), 3.97 (3H, s), 6.61 (1H, s), 7.32 (1H, d, J=1.8 Hz), 7.45 (1H, d, J=1.8 Hz), 9.82 (1H, s). ^{13}C NMR ($CDCl_3$) δ 29.1, 34.7, 56.3, 106.7, 125.3, 128.3, 135.6, 147.2, 150.3, 191.4. MS *m/z*: 208 (M^+), 193, 165. HRMS: $C_{12}H_{16}O_2$+H calcd 209.1172, found 209.1170.

4.1.5. Synthesis of ethyl (*E*)-3-(3-*tert*-butyl-4-hydroxy-5-methoxyphenyl)-propenoate (11). A solution of $Ph_3PCHCOOEt$ (2 equiv, 719 mg) in ethylene glycol dimethyl ether (20 mL) was added dropwise to the solution of **10** (215 mg, 1.03 mmol) in ethylene glycol dimethyl ether (10 mL), and the mixture was heated under reflux for 2 h. Then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (7:1, v/v) to afford **11** (276 mg, 96%) as white crystals; mp 69–70 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (3H, t, J=6.9 Hz), 1.40 (9H, s), 3.90 (3H, s), 4.26 (2H, q, J=6.9 Hz), 6.29 (1H, d, J=15.6 Hz), 6.30 (1H, s), 6.69 (1H, s), 7.09 (1H, s), 7.63 (1H, d, J=15.6 Hz). MS *m/z*: 278 (M^+), 263, 235, 217, 95. HRMS: $C_{16}H_{22}O_4$+Na calcd 301.1410, found 301.1414.

4.1.6. Synthesis of diethyl (*E*,*E*)-bis(3-*tert*-butyl-4-hydroxy-5-methoxybenzylidene)succinate (12). The compound **11** (200 mg, 0.719 mmol) in benzene (7.2 mL) was vigorously stirred with an aqueous solution (1.45 mL) containing potassium ferricyanide (600 mg) and potassium hydroxide (220 mg) for 0.5 h under nitrogen. The organic layer was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (5:1, v/v) to afford **12** (183 mg, 92%) as a yellow oil; IR (KBr) ν_{max}: 3412, 2957, 1366, 1700, 978 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.10 (6H, t, J=6.9 Hz), 1.34 (18H, s), 3.77 (6H, s), 4.14 (4H, q, J=6.9 Hz), 6.17 (2H, s), 7.03 (2H, s), 7.11 (2H, s), 7.85 (2H, s). MS *m/z*: 554 (M^+), 278, 57. HRMS: $C_{32}H_{42}O_8$+Na calcd 577.2772, found 577.2790.

4.1.7. Synthesis of diethyl bis(3-*tert*-butyl-4-hydroxy-5-methoxybenzyl)succinate (13). A mixture of compound **12** (200 mg, 0.36 mmol) and 10% Pd/C (5:1, substrate/catalyst) in EtOH (15 mL) was stirred at room temperature under hydrogen atmosphere for 24 h, Pd/C was filtrated and the solution was evaporated in vacuo. The residue was purified by column chromatography using benzene to afford **13a** (81 mg, 40%) and **13b** (119 mg, 59%); **13a**, white solid, mp 150–151 °C; IR (KBr) ν_{max}: 3526, 2956, 1726, 1367 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (6H, t, J=6.9 Hz), 1.37 (18H, s), 2.76–2.82 (4H, m), 3.01 (2H, d, J=3.9 Hz), 3.84 (6H, s), 4.01 (4H, q, J=6.9 Hz), 5.87 (2H, s), 6.54 (2H, s), 6.63 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 29.3, 34.3, 36.6, 50.4, 56.1, 60.4, 108.9, 119.3, 128.5, 135.9, 142.7, 146.6, 173.7. MS *m/z*: 558 (M^+), 279, 233, 193, 149, 57. HRMS: $C_{32}H_{46}O_8$+Na calcd 581.3085, found 581.3083. **13b**, yellow oil; IR (KBr) ν_{max}: 3526, 2956, 1730, 1595, 1372 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (6H, t, J=6.9 Hz), 1.36 (18H, s), 2.88 (2H, s), 2.92 (4H, s), 3.77 (6H, s), 4.08 (4H, q, J=6.9 Hz), 5.87 (2H, s), 6.43 (2H, s), 6.65 (2H, s). ^{13}C NMR ($CDCl_3$) δ 14.1, 29.3, 34.5, 35.7, 48.1, 55.9, 60.5, 108.8, 119.7, 128.2, 134.6, 142.6, 146.4, 173.7. MS *m/z*: 558 (M^+), 279, 193, 149, 57. HRMS: $C_{32}H_{46}O_8$+H calcd 559.3265, found 559.3267.

4.1.8. Synthesis of diethyl bis(4-hydroxy-3-methoxybenzyl)succinate (14). To a solution of compound **13** (**13a** and **13b**, 330 mg, 0.59 mmol) in benzene (20 mL) was added $AlCl_3$ (8 equiv, 631 mg) at 50 °C. The mixture was stirred at the same temperature for 1 h, and then the reaction was quenched with ice, extracted with benzene. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography using benzene and ethyl acetate (8:1, v/v) to afford **14** (208 mg, 79%); **14a**, 83 mg, colorless crystals, mp 180 °C; IR (KBr) ν_{max}: 3422, 2924, 1724, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (6H, t, J=6.9 Hz), 2.72–2.83 (4H, m), 2.98–2.99 (2H, m), 3.85 (6H, s), 4.02 (4H, q, J=6.9 Hz), 5.48 (2H, s), 6.64 (4H, s), 6.80 (2H, d, J=8.7 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 36.3, 50.2, 55.9, 60.5, 111.3, 114.1, 121.7, 130.2, 144.2, 146.3, 173.6. MS *m/z*: 446 (M^+), 223, 177, 137, 57. HRMS: $C_{24}H_{30}O_8$+Na calcd 469.1833, found 469.1848. **14b**, 125 mg, colorless oil; IR (KBr) ν_{max}: 3429, 2934, 1727, 1516 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (6H, t, J=7.2 Hz), 2.80–2.87 (3H, m), 2.91–2.96 (3H, m), 3.78 (6H, s), 4.10 (4H, q, J=7.2 Hz), 5.49 (2H, s), 6.48 (2H, d, J=1.8 Hz), 6.59 (2H, dd, J=1.8, 8.1 Hz), 6.79 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 14.1, 35.3, 47.5, 55.6, 60.6, 111.2, 114.0, 121.9, 130.5, 144.1, 146.3, 179.5. MS *m/z*: 446 (M^+), 277, 223, 177, 149, 137, 124, 91. HRMS: $C_{24}H_{30}O_8$+H calcd 447.2013, found 447.2021.

4.1.9. Synthesis of secoisolariciresinol (1). To a suspension of $LiAlH_4$ (1.2 equiv, 6.5 mg) in dry THF (10 mL), compound **14** (**14a** and **14b**, 65 mg, 0.15 mmol) was added at −15 °C, and stirred at same temperature for 2 h. Then the reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (1:1, v/v) to give the compound **1** (45 mg, 85%); **1** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (1:3, v/v) to afford **1a** (18 mg), colorless oil; **1b** (27 mg), white solid, mp 116–117 °C; **1b**, IR (KBr) ν_{max}: 3351, 2933, 1515 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.85 (2H, s), 2.64 (2H, dd, J=6.9, 13.5 Hz), 2.74 (2H, dd, J=8.1, 13.5 Hz), 3.54 (2H, dd, J=4.2, 12 Hz), 3.80–3.83 (2H, m), 3.81 (6H, s), 6.58 (2H, s), 6.62 (2H, d, J=8.4 Hz), 6.80 (2H, d, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 35.9, 43.8, 55.8, 60.8, 111.4, 114.1, 121.7, 132.4, 143.8, 146.4. MS *m/z*: 362 (M^+), 277, 189, 137. HRMS: $C_{20}H_{26}O_6$+NH_4 calcd 380.2068, found 380.2061.

4.1.10. Synthesis of dihydroguaiaretic acid (2). A solution of compound **1** (**1a** and **1b**, 420 mg, 1.16 mmol) in pyridine (1.50 mL) was stirred at 0 °C for 20 min, *p*-TsCl (8 equiv, 1.77 g) was added. The mixture was stirred at same temperature for other 4 h, and then the reaction was quenched with 2 N HCl (5 mL). The oil was separated, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated

in vacuo. The residue and $LiAlH_4$ (5 equiv, 182 mg) was added to the solution of dry THF (20 mL), and the mixture was refluxed for 6 h. The reaction was quenched with water, extracted with ethyl acetate, and the combined organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and a solution (15 mL) of potassium hydroxide (9.0 g) in H_2O (150 mL)–EtOH (150 mL) was added to the residue in three 5 mL portions at 15 min intervals. After reflux for 10 h, the solution was cooled, neutralized with acetic acid, and extracted with ether. The organic layers were washed with brine, dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (10:1, v/v) to afford **2** (188 mg, 49%); **2** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (9:1, v/v) to afford **2a** (75 mg) and **2b** (113 mg); **2a**, colorless crystals, mp 88–89 °C; IR (KBr) ν_{max}: 3445, 2925, 1513, 1458 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.84 (6H, d, J=6.3 Hz), 1.71–1.78 (4H, m), 2.28 (2H, dd, J=9.6, 13.5 Hz), 2.73 (2H, dd, J=5.1, 13.5 Hz), 3.86 (6H, s), 6.61 (2H, d, J=1.8 Hz), 6.65 (2H, d, J=8.4 Hz), 6.82 (2H, d, J=8.4 Hz). ^{13}C NMR ($CDCl_3$) δ 16.2, 30.9, 39.0, 39.2, 55.9, 111.5, 114.0, 121.8, 133.8, 143.7, 146.4. MS *m/z*: 330 (M^+), 208, 193, 165, 149, 137. HRMS: $C_{20}H_{26}O_4-H$ calcd 329.1758, found 329.1766. **2b**, white solid, mp 87–88 °C; IR (KBr) ν_{max}: 3425, 2925, 1513, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.82 (6H, d, J=6.3 Hz), 1.69–1.76 (4H, m), 2.38 (2H, dd, J=6.9, 13.5 Hz), 2.52 (2H, dd, J=6.9, 13.5 Hz), 3.81 (6H, s), 6.52 (2H, s), 6.58 (2H, d, J=8.1 Hz), 6.80 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 13.8, 37.4, 41.0, 55.7, 111.2, 113.8, 121.6, 133.6, 143.5, 146.2. MS *m/z*: 330 (M^+), 137. HRMS: $C_{20}H_{26}O_4-H$ calcd 329.1758, found 329.1759.

4.1.11. Synthesis of divanillyltetrahydrofuran (3). A solution of compound **1** (**1a** and **1b**, 165 mg, 0.46 mmol) in methanol (50 mL) containing 10 N HCl (0.5 mL) was refluxed for 18 h. The solvent was removed and the residue adsorbed on silica gel. Elution with petroleum ether and ethyl acetate (3:1, v/v) afforded **3** (151 mg, 96%); **3** was further purified by HPLC eluting with *n*-hexane and ethyl acetate (3:1, v/v) to afford **3a** (60 mg) and **3b** (91 mg); **3a**, white solid, mp 113–114 °C; IR (KBr) ν_{max}: 3375, 2929, 1603, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.47–2.54 (4H, m), 2.80–2.86 (2H, m), 3.64 (2H, dd, J=4.2, 8.1 Hz), 3.79 (2H, dd, J=4.2, 8.1 Hz), 3.87 (6H, s), 5.49 (2H, s), 6.65 (2H, d, J=1.2 Hz), 6.68 (2H, dd, J=1.2, 8.1 Hz), 6.85 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 33.1, 43.8, 55.9, 72.0, 111.2, 114.3, 121.2, 132.5, 143.8, 146.4. MS *m/z*: 344 (M^+), 189, 163, 137. HRMS: $C_{20}H_{24}O_5$ calcd 344.1618, found 344.1622. **3b**, colorless crystals, mp 134–135 °C; IR (KBr) ν_{max}: 3328, 2936, 1606, 1514 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13–2.20 (2H, m), 2.48–2.62 (4H, m), 3.53 (2H, dd, J=6.0, 8.7 Hz), 3.82 (6H, s), 3.92 (2H, dd, J=6.0, 8.7 Hz), 5.50 (2H, s), 6.50 (2H, d, J=1.5 Hz), 6.58 (2H, dd, J=1.5, 8.1 Hz), 6.80 (2H, d, J=8.1 Hz). ^{13}C NMR ($CDCl_3$) δ 39.2, 46.4, 55.7, 73.2, 111.0, 114.0, 121.3, 132.3, 143.8, 146.4. MS *m/z*: 344 (M^+), 137, 84. HRMS: $C_{20}H_{24}O_5-H$ calcd 343.1551, found 343.1555.

4.1.12. Synthesis of diethyl 1-(4-hydroxy-3-methoxyphenyl)-1,2-dihydro-6-methoxy-7-hydroxynaphthalene-2,3-dicarboxylate (15). To a solution of compound **12** (200 mg, 0.36 mmol) in benzene (20 mL) was added $AlCl_3$ (12 equiv, 578 mg) at 50 °C. The mixture was stirred at same temperature for 1 h, and then the reaction was quenched with ice, extracted with benzene. The combined organic layers were washed with brine, dried over Na_2SO_4. The solvent was evaporated in vacuo and the residue was purified by column chromatography using petroleum ether and ethyl acetate (1:1, v/v) to afford **15** (80 mg, 50%), white solid, mp 153 °C; IR (KBr) ν_{max}: 3402, 2931, 1697, 1512, 731 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.14 (3H, t, J=7.2 Hz), 1.29 (3H, t, J=7.2 Hz), 3.80 (3H, s), 3.91 (3H, s), 3.97 (1H, d, J=4.2 Hz), 4.08 (2H, q, J=7.2 Hz), 4.21 (2H, q, J=7.2 Hz), 4.53 (1H, d, J=4.2 Hz), 5.53 (1H, s), 5.84 (1H, s), 6.45 (1H, dd, J=8.1, 1.8 Hz), 6.63 (1H, d, J=1.8 Hz), 6.68 (1H, s), 6.73 (1H, d, J=8.1 Hz), 6.84 (1H, s), 7.64 (1H, s). ^{13}C NMR ($CDCl_3$) δ 14.0, 14.2, 45.7, 47.4, 55.8, 56.0, 60.7, 61.1, 110.1, 111.1, 114.1, 115.4, 120.5, 123.0, 123.9, 131.2, 134.3, 137.3, 144.3, 145.6, 146.3, 147.5, 166.7, 172.6. MS *m/z*: 442 (M^+), 368, 323, 69, 43. HRMS: $C_{24}H_{26}O_8$+H calcd 443.1700, found 443.1698.

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Synthesis and reactions of nitro derivatives of hydrogenated cardanol

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Abstract—3-*n*-Pentadecylphenol (hydrogenated cardanol) and its derivative 5-*n*-pentadecyl-2-*tert*-butylphenol can be nitrated using nitric acid in acetonitrile or methanol to give mono, di or trinitro products. 5-*n*-Pentadecyl-2-nitrophenol undergoes reductive carbonylation to give a benzoxazole-2-one derivative. An efficient catalytic oxidation reaction in the presence of $MeReO_3$ has also been studied.

1. Introduction

In recent years an increasing amount of work on cashew nut shell liquid derivatives has appeared in the literature. Cashew nut shell liquid (CNSL) is obtained as a by-product from mechanical processing for edible use of cashew kernel (*Anacardium occidentale* L.) and is a mixture of anacardic acid **1**, cardanol **2** and smaller amounts of cardol **3** and 2-methylcardol **4**.[1] Due to the easy thermal decarboxylation of anacardic acid **1**, the main component of distilled CNSL is cardanol **2** (yield up to 70–80% and purity up to 90%) as a mixture of saturated (3-*n*-pentadecylphenol), monoolefinic [3-(*n*-pentadeca-8-enyl)phenol], diolefinic [3-(*n*-pentadeca-8,11-dienyl)phenol], and triolefinic [3-(*n*-pentadeca-8,11,14-trienyl)phenol] long-chain phenols, with an average value of two double bonds per molecule. Cardol **3** and methylcardol **4** are present in smaller percentages (Fig. 1).[2]

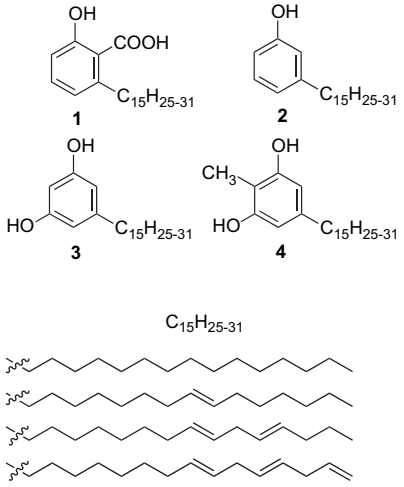

Figure 1. Components of CNSL.

World-wide cashew nut production is presently estimated to be 1,200,000 tons per annum and the availability of CNSL is 300,000–360,000 tons per annum. As the production of cashew nuts is rising every year the availability of up to 600,000 tons per annum of CNSL should be reached in the near future. Cardanol, upon catalytic hydrogenation, yields 3-*n*-pentadecylphenol (hydrogenated cardanol) and this unique alkyl phenol derivative is produced commercially in high purity.[3] Owing to the difficulty of synthesizing long-chain alkyl phenols with an aliphatic chain in the *meta* position, hydrogenated cardanol represents a simple and easily available entry to various derivatives useful for different purposes (e.g., antioxidants, flame-retardants, waterproofing agents, gum inhibitors for gasoline). Recently we have reported allylation and regioselective cyclocarbonylation[4] reactions on hydrogenated cardanol and the preparation of phthalocyanines,[5] porphyrins[6] and fullerene[7] derivatives of cardanol that possess lower melting points and higher solubility than similar products lacking long alkyl side-chains. Even azocrown ethers have been prepared from cardanol derivatives.[8] So these derivatives are an attractive

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renewable bio-source to develop new eco-friendly functional materials.

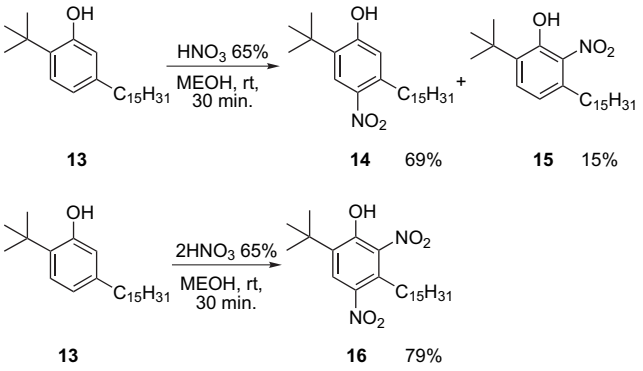
2. Results and discussion

2.1. Nitration of cardanol derivatives

In this paper we describe a mild and efficient protocol for the nitration of 3-*n*-pentadecylphenol **5** and its derivative 5-*n*-pentadecyl-2-*tert*-butylphenol **13**.[2] Nitration of cardanol derivatives has been carried out some time ago but only a few products[9] have been reported and a complete study of this interesting reaction has not been conducted until now. Nitro derivatives are useful materials and are very important intermediates in organic synthesis, especially in the preparation of amino derivatives. Some patents are related to preparation of 5-*n*-pentadecyl-2-nitrophenol **6** and 3-*n*-pentadecyl-4-nitrophenol **7** but the synthetic utility of other products from the nitration process has not been described.[10] Therefore, we undertook the study of reactions between hydrogenated cardanol and nitric acid.

The reactions proceeded smoothly at room temperature, under mild conditions, with a stoichiometric amount of nitric acid with easy work-up procedures. 3-*n*-Pentadecylphenol **5** reacted in 30 min at room temperature in acetonitrile or methanol with an equimolar amount of nitric acid (65%). After work-up procedures and chromatographic separations of the reaction mixture, 5-*n*-pentadecyl-2-nitrophenol **6** (38%), 3-*n*-pentadecyl-4-nitrophenol **7** (40%) and 3-*n*-pentadecyl-2-nitrophenol **8** (15%) were obtained. Under the same experimental conditions, 3-*n*-pentadecylphenol **5** reacted with nitric acid (65%) in a molar ratio 1:2 and 5-*n*-pentadecyl-2,4-dinitrophenol **9** was isolated in high yields (75%) along with small quantities of two other isomers 3-*n*-pentadecyl-2,4-dinitrophenol **10** (7%) and 3-*n*-pentadecyl-2,6-dinitrophenol **11** (1%) (GC–MS), due to steric hindrance of position 2 of 3-*n*-pentadecylphenol. When the ratio 3-*n*-pentadecylphenol/nitric acid (65%) was increased to 1:3 the only recovered reaction product was 3-*n*-pentadecyl-2,4,6-trinitrophenol **12** in high yields (86%) (Scheme 1).

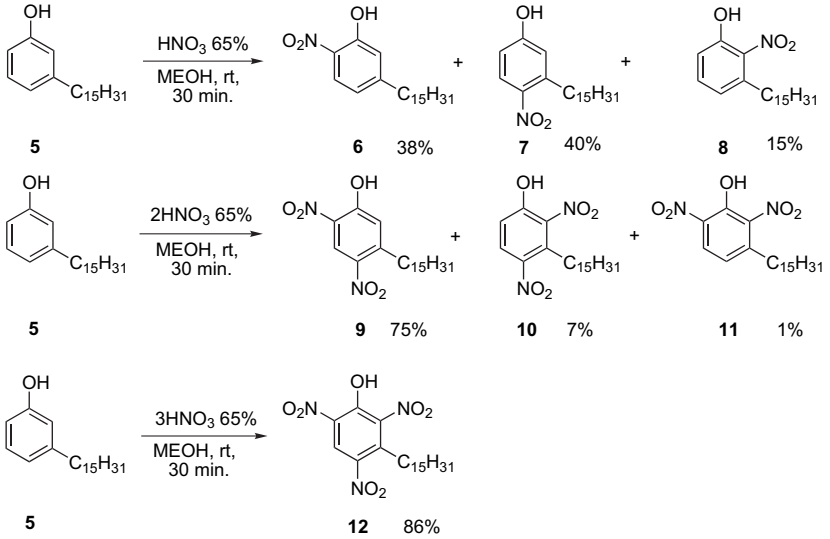
TGA/DSC on 3-*n*-pentadecyl-2,4,6-trinitrophenol **12** were carried out (see Section 4). 5-*n*-Pentadecyl-2-*tert*-butylphenol **13** reacted in 30 min at room temperature in acetonitrile or methanol with an equimolar amount of nitric acid (65%) affording a reaction mixture that after work-up procedures and chromatographic separations furnished 2-*tert*-butyl-5-*n*-pentadecyl-4-nitrophenol **14** (69%) and 3-*n*-pentadecyl-6-*tert*-butyl-2-nitrophenol **15** (15%). 5-*n*-Pentadecyl-2-*tert*-butylphenol **13** reacted with nitric acid (65%) in a molar ratio 1:2 affording 3-*n*-pentadecyl-6-*tert*-butyl-2,4-dinitrophenol **16** (79%) (Scheme 2).



Scheme 2.

2.2. $MeReO_3$ oxidation of cardanol derivatives

In spite of the high number of synthetic transformations reported for cardanol derivatives,[11] to the best of our knowledge there are few catalytic oxidative procedures. In this context, we described a convenient and efficient application of the catalytic system $MeReO_3/H_2O_2$ for the preparation of *ortho*- and *para*-benzoquinones from cardanol derivatives.[12] The regioselectivity of these oxidations was found to be dependent on the nature and position of substituents on the aromatic ring, *ortho*-benzoquinones being obtained only in the absence of an alkyl substituent on the C-2 position of the aromatic ring.



Scheme 1.

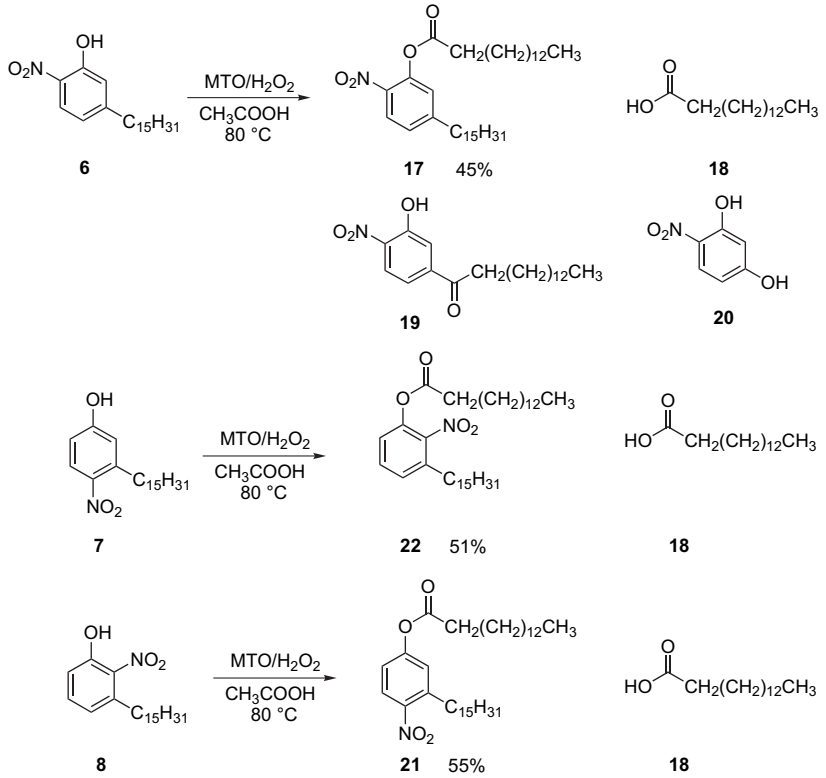
In the past few years methylrhenium trioxide ($MeReO_3$, MTO)[13] has been shown to possess interesting catalytic properties in oxidation reactions with environmental friendly hydrogen peroxide (H_2O_2) as an oxygen atom donor.[14] Methoxy-substituted benzenes are oxidized with the $MeReO_3/H_2O_2$ system in acetic acid to yield the corresponding alkoxy-substituted *para*-benzoquinones,[15] some of which show important biological activities.[16] Cardanol derivatives bearing bromine atoms as electron-withdrawing substituents were also found to be reactive substrates under these experimental conditions to give *para*-benzoquinone or catechol derivatives. A similar behaviour was observed with polymer supported rhenium catalysts based on the heterogenation of $MeReO_3$ on poly(4-vinylpyridine) 2% and 25% (PVP-2, PVP-25) cross-linked with divinylbenzene.[17] Higher conversions and yields of benzoquinones were obtained with PVP heterogeneous catalysts than with $MeReO_3$ in homogeneous phase, probably because of a support-mediated molecular recognition process based on hydrogen-bonding interactions between the pyridinyl moiety and the phenolic group of cardanol.[18]

Moreover, during the oxidation of cardanol derivatives with novel microencapsulated $MeReO_3$ systems, an unprecedented oxidative degradation of the aromatic moiety to biologically active γ-lactone derivatives was observed in the absence of C-2 substituents.[17]

We report here that $MeReO_3$ is an efficient and selective catalyst for the activation of H_2O_2 in the oxidation of relatively unreactive nitrocardanol derivatives. Because of the high value of the redox-potential of the aromatic moiety of these compounds, the oxidation proceeded mainly in the alkyl side-chain to give unexpected *O*-pentadeca-acyl cardanol derivatives probably by a side-chain intermolecular transfer process between two molecules of substrate.

Oxidations were performed by treating the appropriate substrate with an excess of H_2O_2 (8.0 equiv 35% aqueous solution) in acetic acid (1.0 mL) at 80 °C in the presence of catalytic amount of $MeReO_3$ (2% in weight of catalyst). Results of oxidations are reported in Scheme 3 and Table 1. The oxidation of 5-*n*-pentadecyl-2-nitrophenol **6** gives *O*-pentadecanoyl-5-*n*-pentadecyl-2-nitrophenol **17**, as the main reaction product, besides a low amount of pentadecanoic acid **18** as side-product (Table 1, entry 1).

Traces of aromatic ketone derivative **19** and 1,3-dihydroxy-6-nitrobenzene **20** were also detected in the reaction mixture by GC–MS analysis (see Scheme 3 for structures of compounds **19** and **20**) after derivatization with *N*,*O*-bis-trimethylsilyltrifluoroacetamide (BSTFA). It is reasonable to suggest that compound **17** can be formed by an intermolecular acyl transfer process from a first formed side-chain oxidized product. In particular, the reaction initially may proceed through oxidation of the reactive benzylic position to give **19**. The catalytic efficacy of $MeReO_3$ to afford a Bayer–Villinger rearrangement is known from the literature. In accordance with these data, ketone **19** can be further oxidized to corresponding aryl ester derivative (not shown), which can act as an electrophilic species transferring the acyl side-chain to a second molecule of substrate to give compounds **17** and **20**. In accordance with this hypothesis, treatment of a small amount of isolated ketone **19** with MTO under similar conditions afforded compounds **17** and **20** in detectable amounts. The hypothesized reaction



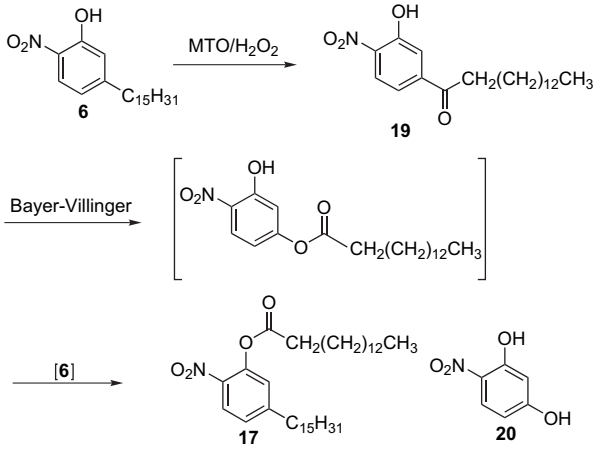
Scheme 3.

Table 1. Oxidation of nitrocardanol derivatives **6–8**, **15** with $MeReO_3$ and H_2O_2[a]

Entry	Substrate	H_2O_2 (equiv)	Conversion (%)	Product(s)	Yield(s)
1	**6**	6.0	75	**17**(**18**)	45(8)
2	**7**	6.0	55	**22**(**18**)	51(6)
3	**8**	6.0	65	**21**(**18**)	55(6)
4	**15**	6.0	70	**23**(**24**)	25(26)

[a] Reactions were performed with an excess of H_2O_2 (8.0 equiv) in CH_3COOH (1 mL) in the presence of 2% in weight of $MeReO_3$. Yields are calculated on converted substrate. The low mass-balance observed in some cases, is probably due to the formation of over-oxidation products not recovered under our experimental conditions.

pathway for the oxidation of **6** is schematically reported in Scheme 4.

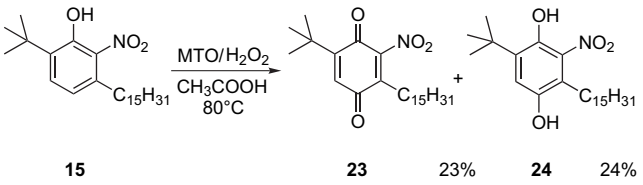


Scheme 4.

The low mass-balance observed for compound **20** is probably due to formation of high-polarity over-oxidation products not detectable under our experimental conditions. To the best of our knowledge this is one of the few examples of a multifunctional catalytic behaviour showed by $MeReO_3$ during the oxidation of natural substances with H_2O_2 as primary oxidant. To evaluate the generality of this transformation isomeric nitrocardanol derivatives 3-*n*-pentadecyl-4-nitrophenol **7** and 3-*n*-pentadecyl-2-nitrophenol **8** were oxidized under similar experimental conditions. Irrespective of the position of the nitro substituent on the aromatic ring, the corresponding *O*-acyl derivatives, *O*-pentadecanoyl-3-*n*-pentadecyl-4-nitrophenol **21** and *O*-pentadecanoyl-3-*n*-pentadecyl-2-nitrophenol **22**, were recovered as the main reaction products in acceptable yields (Table 1, entries 2 and 3).

In accordance with data previously obtained on the oxidation of cardanol derivatives with $MeReO_3$,[12] the presence of an alkyl substituent on the C-2 position of the aromatic ring modified the selectivity of the reaction.

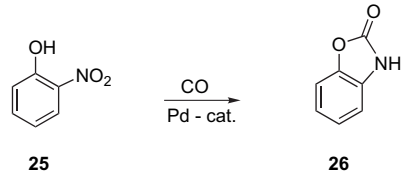
Thus, the oxidation of 3-*n*-pentadecyl-6-*tert*-butyl-2-nitrophenol **15**, performed under similar experimental conditions, gave the *para*-benzoquinone **23** and *para*-hydroquinone **24** as main products. (Scheme 5, Table 1, entry 4). In this case O-acylated products were not observed in the reaction mixture suggesting that the presence of the electron-donating alkyl substituent enhances the redox-potential of the aromatic ring, as would be expected.



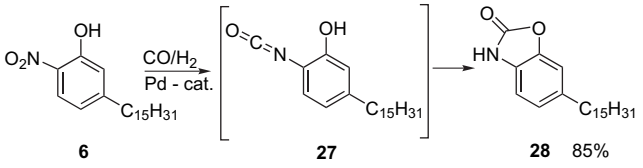
Scheme 5.

2.3. Reductive carbonylation of 5-*n*-pentadecyl-2-nitrophenol

Benzoxazolinones are a known class of commercially available compounds that are widely used in agriculture and industry. Traditionally, these compounds are produced by the intramolecular cyclization of phenyl *N*-(2-hydroxyphenyl) carbamate, which is produced by the reaction of *ortho*-aminophenol with phenyl chloroformate.[19] This route needs a large number of steps from commercially available starting materials. Various catalytic systems have been found for the preparation of benzoxazolinone in one step from readily available starting materials. For example, Fe/Pd as well as $Na_2[Fe(CO)_4]$ were used as catalysts for the reductive cyclocarbonylation of *ortho*-nitrophenol **25** to benzoxazol-2-one **26**,[20] more recently, a selenium-based catalyst has been used to perform this reaction (Scheme 6).[21] Recently, some of us reported that palladium(II) acetate $Pd(OAc)_2$ and 1,4-bis(diphenylphosphino)butane (dppb) catalyze the cyclocarbonylation of *o*-allyl phenol as well as *o*-allyl cardanol derivatives.[22] In this context, we report the cyclocarbonylation reaction of 5-*n*-pentadecyl-2-nitrophenol **6** carried out under mild conditions in the presence of the homogeneous catalytic system $Pd(OAc)_2$/dppb and a 1:1 mixture of CO/H_2 to produce the benzoxazol-2-one derivative **28** in good yield (85%) (Scheme 7). FTIR spectrum of 5-*n*-pentadecyl-2-nitrophenol **6** used as starting material shows characteristic bands centred at 1623, 1580, 1528 cm^{-1} (asymmetric stretch) and 1330 cm^{-1} (symmetric stretch) due to the NO_2 group. As expected, these signals are not present in the IR spectrum of the cyclocarbonylated product and a new strong peak characteristic of carbonyl compounds is found at 1742 cm^{-1}. In this reaction the formation of an isocyanate **27** as intermediate is presumed. The isocyanate **27** reacts further with the hydroxyl group to give the final product.



Scheme 6.



Scheme 7.

3. Conclusion

In the present paper we describe the reaction of 3-*n*-pentadecylphenol and 3-*n*-pentadecylphenol derivatives with nitric acid providing the corresponding nitro derivatives. The reaction occurred in mild conditions, with high yields and easy work-up procedures. The starting material with a long alkyl chain in *meta* position, not easily accessible directly by synthetic means, is a natural compound easily available from processing of cashew kernel (*A. occidentale* L.).

The nitro derivatives were processed with $MeReO_3$ and provided an interesting application of this oxidative system. One of these derivatives has been cyclocarbonylated to the corresponding benzoxazole-2-one in high yield.

4. Experimental

4.1. General

All solvents are ACS reagent grade and used without further purification. IRFT spectra were performed in Nujol mulls. Mass spectra EI were obtained at an ionizing voltage of 70 eV. ^{1}H NMR, ^{13}C NMR were recorded at 400 and 100 MHz, or 200 and 50 MHz, respectively, All NMR spectra were recorded in $CDCl_3$. Chemical shifts (δ_H) are reported in parts per million (ppm), relative to TMS as internal standard. All coupling constants (J) values are given in Hertz. Chemical shifts (δ_C) are reported in parts per million (ppm), relative to $CDCl_3$, as internal standard in a broad band decoupled mode. The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Gas-chromatography and mass spectrometry were performed by the use of HP5890 gas-chromatograph and by a Shimadzu GC–MS QP5050A spectrometer equipped with an Allthech® AT-20 column (0.25 mm, 30 m). TGA/DSC were carried out on a LABSYSTM TGA/DSC. Chromatographic purifications were performed on columns packed with Merck silica gel 60, 230–400 mesh for flash technique. Thin layer chromatography was carried out using Merck platen Kieselgel 60 F 25G. All new compounds showed satisfactory elemental analysis (C±0.35; H±0.30; N±0.30). Some overlaps in ^{13}C NMR of CH_2 resonances of long aliphatic chain occur.

4.1.1. General procedure for the nitration reactions. To a magnetically stirred solution of 3-*n*-pentadecylphenol **5** (1 mmol) in methanol (10 mL) a stoichiometric amount of nitric acid (65%) (1 mmol) in methanol (10 mL) was added dropwise over 30 min at room temperature. The reaction mixture was dried over anhydrous sodium sulfate, the solvent was evaporated under reduced pressure and then extracted with ethyl acetate (40 mL×3). The organic layer was washed with water and dried with sodium sulfate. After evaporation of the solvent, products **6–8** were separated by chromatography on a silica gel column (cyclohexane ethyl acetate mixtures) as oils.

The same procedure was used for preparation of products **14** and **15** from 5-*n*-pentadecyl-2-*tert*-butylphenol **13**.

For the synthesis of products **9–11**, **16** nitric acid (65%) (2 mmol) in methanol (20 mL) while for the synthesis of product **12** nitric acid (65%) (3 mmol) in methanol (30 mL) were used. The reactions can be carried out in acetonitrile and isolated reaction products can be crystallized from cyclohexane.

4.1.1.1. 5-*n*-Pentadecyl-2-nitrophenol 6. Bright yellow crystals. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz, *CH*$_3$), 1.19–1.38 (24H, m, *CH*$_2$), 1.61 (2H, m, ArCH$_2$*CH*$_2$), 2.62 (2H, t, J=7.6 Hz, Ar*CH*$_2$), 6.80 (1H, dd, J=8.8 Hz, 1.6 Hz, *H*-4), 6.94 (1H, d, J=1.6 Hz, *H*-6), 7.99 (1H, d, J=8.8 Hz, *H*-3), 10.61 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.5, 23.1, 27.3, 29.6, 29.8, 29.9, 30.1, 30.8, 32.3, 36.4, 119.1, 120.9, 125.0, 131.8, 154.6, 155.2. IR ν_{max}(Nujol) 3623, 1623, 1580, 1330 cm^{-1}. EIMS: *m*/*z* (relative intensity) 349 (M$^+$, 10), 332 (42), 314 (100). Anal. Calcd for $C_{21}H_{35}NO_3$ (349.51): C, 72.17; H, 10.09; N, 4.01. Found C, 72.23; H, 10.22; N, 4.18%.

4.1.1.2. 3-*n*-Pentadecyl-4-nitrophenol 7. Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.8 Hz, *CH*$_3$), 1.21–1.40 (24H, m, *CH*$_2$), 1.58–1.68 (2H, m, ArCH$_2$*CH*$_2$), 2.89 (2H, t, J=8.0 Hz, Ar*CH*$_2$), 5.88 (1H, s, *OH*), 6.71–6.78 (2H, m, *Ar*), 7.97 (1H, d, J=9.6 Hz, *H*-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 29.5, 29.7, 30.4, 31.9, 33.8, 113.5, 118.0, 128.0, 141.9, 142.2, 159.6. IR ν_{max}(Nujol) 3382, 1615, 1597, 1513, 1324 cm^{-1}. EIMS: *m*/*z* (relative intensity) 349 (M$^+$, 32), 332 (15), 314 (100). Anal. Calcd for $C_{21}H_{35}NO_3$ (349.51): C, 72.17; H, 10.09; N, 4.01. Found C, 72.31; H, 10.24; N, 3.92%.

4.1.1.3. 3-*n*-Pentadecyl-2-nitrophenol 8. Brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.7 Hz, *CH*$_3$), 1.20–1.45 (24H, m, *CH*$_2$), 1.52–1.64 (2H, m, ArCH$_2$*CH*$_2$), 2.90 (2H, t, J=8.0 Hz, Ar*CH*$_2$), 6.82 (1H, d, J=7.6 Hz, *H*-4), 6.98 (1H, dd, J=8.0 Hz, 1.2 Hz, *H*-6), 7.38 (1H, t, J=8.0 Hz, *H*-5), 9.94 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.9, 27.1, 29.6, 29.8, 29.9, 30.4, 30.8, 32.2, 34.7, 117.2, 123.0, 134.7, 135.5, 140.7, 154.5. IR ν_{max}(Nujol) 3190, 1609, 1589, 1533, 1345 cm^{-1}. EIMS: *m*/*z* (relative intensity) 349 (M$^+$, 15), 332 (35), 314 (100). Anal. Calcd for $C_{21}H_{35}NO_3$ (349.51): C, 72.17; H, 10.09; N, 4.01. Found C, 72.09; H, 10.21; N, 4.12%.

4.1.1.4. 5-*n*-Pentadecyl-2,4-dinitrophenol 9. White powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J=7.5 Hz, *CH*$_3$), 1.21–1.39 (24H, m, *CH*$_2$), 1.58–169 (2H, m, ArCH$_2$*CH*$_2$), 2.99 (2H, t, J=8.0 Hz, Ar*CH*$_2$), 7.13 (1H, s, *H*-6), 8.86 (1H, s, *H*-3), 10.79 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.9, 29.5, 29.6, 29.7, 29.8, 29.9, 30.4, 32.2, 34.0, 122.7, 123.6, 131.1, 141.5, 149.3, 157.2. IR ν_{max}(Nujol) 3294, 1633, 1582, 1540, 1342 cm^{-1}. EIMS: *m*/*z* (relative intensity) 394 (M$^+$, 12), 377 (100). Anal. Calcd for $C_{21}H_{34}N_2O_5$ (394.51): C, 63.93; H, 8.69; N, 7.10. Found C, 63.78; H, 8.79; N, 7.23%.

4.1.1.5. 3-*n*-Pentadecyl-2,4-dinitrophenol 10. White powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, J=6.6 Hz, *CH*$_3$), 1.17–1.35 (24H, m, *CH*$_2$), 1.58–1.65 (2H, m, ArCH$_2$*CH*$_2$), 2.98 (2H, t, J=8.0 Hz, Ar*CH*$_2$), 6.96 (1H, d, J=9.2 Hz, *H*-6), 8.15 (1H, d, J=9.2 Hz, *H*-5), 10.88 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 22.9,

27.1, 29.6, 29.7, 29.9, 30.3, 32.1, 34.9, 121.1, 126.1, 132.5, 142.1, 145.4, 147.5. IR ν_{max}(Nujol) 3256, 1618, 1585, 1546, 1349 cm^{-1}. EIMS: *m/z* (relative intensity) 394 (M^+, 12), 377 (100). Anal. Calcd for $C_{21}H_{34}N_2O_5$ (394.51): C, 63.93; H, 8.69; N, 7.10. Found C, 63.75; H, 8.82; N, 7.21%.

4.1.1.6. 3-*n*-Pentadecyl-2,4,6-trinitrophenol 12. Deep brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, *J*=7.6 Hz, CH_3), 1.24–1.46 (24H, m, CH_2), 1.57–1.66 (2H, m, $ArCH_2CH_2$), 2.91 (2H, t, *J*=8.0 Hz, $ArCH_2$), 8.97 (1H, s, *H*-5), 11.12 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.2, 22.8, 28.9, 29.2, 29.4, 29.6, 29.7, 29.9, 30.3, 32.0, 123.5, 131.2, 140.4, 140.6, 143.1, 149.5. IR ν_{max}(Nujol) 3273, 1635, 1593, 1536, 1356 cm^{-1}. EIMS: *m/z* (relative intensity) 440 (M^+, 56), 422 (15), 404 (100). Anal. Calcd for $C_{21}H_{33}N_3O_7$ (439.50): C, 57.39; H, 7.57; N, 9.56. Found C, 57.29; H, 7.65; N, 9.68%. TGA/DSC were carried out by controlled heating under a flow of dry air or nitrogen at a heating rate of 25 °C/min. Under a flow of dry air an enthalpy of −1074.91 and a total percentage weight lose of 36.5% was observed at 284 °C. Under a flow of nitrogen an enthalpy of −1169.35 and a total percentage weight lose of 32.3% was observed at 284 °C.

4.1.1.7. 2-*tert*-Butyl-5-*n*-pentadecyl-4-nitrophenol 14. White powder. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=7.2 Hz, CH_3), 1.18–1.36 (24H, m, CH_2), 1.41 (9H, s, $C(CH_3)_3$), 1.57–1.68 (2H, m, $ArCH_2CH_2$), 2.84 (2H, t, *J*=8.0 Hz, $ArCH_2$), 5.55 (1H, s, *OH*), 6.56 (1H, s, *H*-6), 7.99 (1H, s, *H*-3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 22.9, 29.4, 29.6, 29.8, 29.9, 30.7, 32.1, 33.4, 34.7, 119.2, 125.6, 135.2, 139.1, 142.0, 158.3. IR ν_{max}(Nujol) 3326, 1629, 1582, 1496, 1335 cm^{-1}. EIMS: *m/z* (relative intensity) 405 (M^+, 2), 388 (45), 375 (22), 357 (5), 169 (100). Anal. Calcd for $C_{25}H_{43}NO_3$ (405.61): C, 74.03; H, 10.69; N, 3.45. Found C, 74.11; H, 10.79; N, 3.36%.

4.1.1.8. 3-*n*-Pentadecyl-6-*tert*-butyl-2-nitrophenol 15. White powder. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, *J*=7.4 Hz, CH_3), 1.18–1.36 (24H, m, CH_2), 1.43 (9H, s, $C(CH_3)_3$), 1.56–1.64 (2H, m, $ArCH_2CH_2$), 2.84 (2H, t, *J*=8.0 Hz, $ArCH_2$), 6.75 (1H, d, *J*=8.0 Hz, *H*-5), 7.39 (1H, d, *J*=8.0 Hz, *H*-4), 10.56 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 29.2, 29.4, 29.6, 29.7, 30.5, 31.9, 34.4, 35.2, 122.0, 132.1, 136.2, 137.5, 138.2, 153.7. IR ν_{max}(Nujol) 3319, 1621, 1565, 1488, 1329 cm^{-1}. EIMS: *m/z* (relative intensity) 405 (M^+, 3), 388 (35), 375 (7), 169 (100). Anal. Calcd for $C_{25}H_{43}NO_3$ (405.61): C, 74.03; H, 10.69; N, 3.45. Found C, 74.16; H, 10.53; N, 3.36%.

4.1.1.9. 3-*n*-Pentadecyl-6-*tert*-butyl-2,4-dinitrophenol 16. White powder. ^1H NMR (400 MHz, $CDCl_3$): δ 0.87 (3H, t, *J*=7.5 Hz, CH_3), 1.20–1.35 (24H, m, CH_2), 1.44 (9H, s, $C(CH_3)_3$), 1.64 (2H, m, $ArCH_2CH_2$), 2.89 (2H, t, *J*=8.0 Hz, $ArCH_2$), 7.92 (1H, s, *H*-5), 9.63 (1H, s, *OH*). ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.6, 23.1, 28.8, 29.3, 29.4, 29.8, 29.9, 30.1, 30.3, 30.5, 32.3, 36.1, 127.8, 132.7, 137.9, 138.9, 143.1, 154.5. IR ν_{max}(Nujol) 3332, 1615, 1575, 1475, 1334 cm^{-1}. EIMS: *m/z* (relative intensity) 450 (M^+, 2), 435 (12), 434 (30), 433 (100). Anal. Calcd for $C_{25}H_{42}N_2O_5$ (450.61): C, 66.64; H, 9.39; N, 6.22. Found C, 66.55; H, 9.51; N, 6.30%.

4.1.2. General procedure for $MeReO_3$ oxidation of cardanol derivatives. To the suspension of the appropriate nitrocardanol derivative (1 mmol) and MTO (2% in weight) in acetic acid (1.0 mL) was added 35% hydrogen peroxide (ca. 8.0 mmol) in several batches. The reaction mixture was stirred at 80 °C under a nitrogen atmosphere for 4 days. The reaction was monitored by TLC (ethyl ester/ethyl acetate=9.5:0.5).

The reaction mixture was diluted with ethyl acetate (40 mL) and a small amount of MnO_2 was added to decompose the excess of H_2O_2. After filtration of MnO_2 the organic layer was washed with NaCl saturated solution (5 mL×3), dried with Na_2SO_4 and evaporated under reduced pressure. The products were obtained by chromatographic purification (cyclohexane ethyl acetate mixtures) and identified by spectroscopic analyses, mass spectroscopy and comparison with authentic samples.

4.1.2.1. *O*-Pentadecanoyl-5-*n*-pentadecyl-2-nitrophenol 17. Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 0.92 (6H, m, CH_3), 1.23–1.65 (50H, m, CH_2), 2.49–2.60 (2H, m, CO–CH_2), 2.91–3.05 (2H, m, $ArCH_2$), 6.80 (1H, d, *J*=10.0 Hz, *H*-4), 6.92 (1H, s, *H*-6), 8.0 (1H, d, *J*=10.0 Hz, *H*-3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 14.3, 22.5, 22.7, 25.0, 29.0, 29.3, 29.4, 29.5, 29.7, 31.9, 32.1, 32.5, 33.7, 35.8, 124.7, 125.3, 128.5, 139.2, 147.2, 148.0, 168.9. EIMS: *m/z* (relative intensity) 573 (M^+, 100), 558 (25), 544 (39), 376 (43), 348 (55). Anal. Calcd for $C_{36}H_{63}NO_4$ (573.88): C, 75.34; H, 11.06; N, 2.44. Found C, 75.37; H, 11.10; N, 2.39%.

4.1.2.2. *O*-Pentadecanoyl-3-*n*-pentadecyl-4-nitrophenol 21. Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 0.93 (6H, m, CH_3), 1.23–1.75 (50H, m, CH_2), 2.31–2.46 (2H, m, CO–CH_2), 2.84–2.99 (2H, m, $ArCH_2$), 6.71 (1H, s, *H*-2), 6.74 (1H, d, *J*=8.5 Hz, *H*-6), 7.97 (1H, d, *J*=8.5 Hz, *H*-5). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 22.5, 22.7, 25.0, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7, 29.8, 31.8, 31.9, 32.6, 33.5, 121.1, 121.9, 126.3, 132.7, 147.2, 156.7, 171.8. EIMS: *m/z* (relative intensity) 573 (M^+, 100), 558 (21), 544 (31), 376 (48), 348 (49). Anal. Calcd for $C_{36}H_{63}NO_4$ (573.88): C, 75.34; H, 11.06; N, 2.44. Found C, 75.38; H, 11.13; N, 2.38%.

4.1.2.3. *O*-Pentadecanoyl-3-*n*-pentadecyl-2-nitrophenol 22. Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 0.80–0.92 (6H, m, CH_3), 1.23–1.70 (50H, m, CH_2), 2.24–2.38 (2H, m, CO–CH_2), 2.80–2.96 (2H, m, $ArCH_2$), 6.77–6.84 (1H, m, *Ar*), 6.86–6.95 (1H, m, *Ar*), 7.26–7.35 (1H, m, *Ar*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.1, 14.3, 22.7, 25.0, 29.0, 29.3, 29.4, 29.5, 29.6, 29.7, 31.8, 31.9, 32.6, 33.7, 118.2, 129.3, 132.7, 132.9, 143.0, 147.2, 168.9. EIMS: *m/z* (relative intensity) 573 (M^+, 100), 558 (21), 544 (55), 530 (45), 376 (48), 348 (37). Anal. Calcd for $C_{36}H_{63}NO_4$ (573.88): C, 75.36; H, 11.06; N, 2.44. Found C, 75.39; H, 11.12; N, 2.34%.

4.1.2.4. *para*-Benzoquinone 23. Yellow oil. ^1H NMR (200 MHz, $CDCl_3$): δ 0.75–0.87 (3H, m, CH_3), 1.15–1.34 (24H, m, CH_2), 1.28(9H, s, $C(CH_3)_3$), 1.45–1.68 (2H, m, $ArCH_2CH_2$), 2.29–255 (2H, m, $ArCH_2$), 6.51–6.62 (1H, s, *Ar*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.3, 22.7, 25.6, 29.0,

29.1, 29.3, 29.4, 29.5, 29.6, 29.8, 31.9, 35.8, 132.8, 147.1, 147.4, 160.6, 175.4, 177.7. EIMS: *m*/*z* (relative intensity) 419 (M^+, 100), 404 (71), 390 (46), 376 (41), 362 (39). Anal. Calcd for $C_{25}H_{41}NO_4$ (419.6): C, 71.56; H, 9.85; N, 3.34. Found C, 71.60; H, 9.79; N, 3.41%.

4.1.2.5. *para*-Hydroquinone 24. Yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.82–0.95 (3H, m, CH_3), 1.18–1.35 (24H, m, CH_2), 1.37 (9H, s, $C(CH_3)_3$), 1.48–1.69 (2H, m, $ArCH_2CH_2$), 2.50–2.68 (2H, m, $ArCH_2$), 6.67 (1H, s, *Ar*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.2, 22.7, 25.4, 29.3, 29.4, 29.5, 29.6, 29.8, 30.0, 30.3, 31.9, 33.3, 113.1, 116.1, 130.6, 137.4, 143.9, 148.8. EIMS: *m*/*z* (relative intensity) 421 (M^+, 100), 406 (63), 392 (51), 378 (48), 364 (37). Anal. Calcd for $C_{25}H_{43}NO_4$ (421.6): C, 71.22; H, 10.28; N, 3.32. Found C, 71.24; H, 10.21; N, 3.39%

4.1.3. Procedure for the cyclocarbonylation reaction. Palladium(II) acetate (0.01 mmol) and dppb (0.04 mmol) were dissolved in of dry toluene (5 mL) and 5-*n*-pentadecyl-2-nitrophenol **6** (1 mmol) was added. The autoclave was purged three times with CO and pressurized with CO (300 psi) and H_2 (300 psi). The reaction mixture was heated with stirring for 24 h at 100 °C (oil bath temperature). The reaction mixture was cooled to room temperature, the solution was concentrated and the residue was extracted with ether. The benzoxazol-2-one **28** was purified by chromatography using petroleum ether and diethyl ether as eluant.

White solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.88 (3H, t, J=6.5 Hz, CH_3), 1.15–2.30 (26H, m, CH_2), 2.63 (2H, t, J=7.5 Hz, $ArCH_2$), 7.03 (1H, s, *Ar*), 7.25–8.00, (2H, m, *Ar*). ^{13}C NMR (50 MHz, $CDCl_3$): δ 14.5, 23.1, 29.6, 29.8, 29.9, 30.0, 30.1, 32.2, 32.4, 36.3, 110.1, 124.1, 129.2, 131.1, 132.3, 144.6, 157.0. IR ν_{max}(Nujol) 3277, 1742, 1498, 1255, 1170 cm^{-1}. EIMS: *m*/*z* (relative intensity) 345 (M^+, 59), 317 (7), 162 (12), 148 (100). Anal. Calcd for $C_{22}H_{35}NO_2$ (345.52): C, 76.47; H, 10.21; N, 4.05. Found C, 76.61; H, 10.32; N, 3.92%.

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Cyclization and rearrangement products from coupling reactions between terminal *o*-alkynylphenols or *o*-ethynyl(hydroxymethyl)benzene and 6-halopurines

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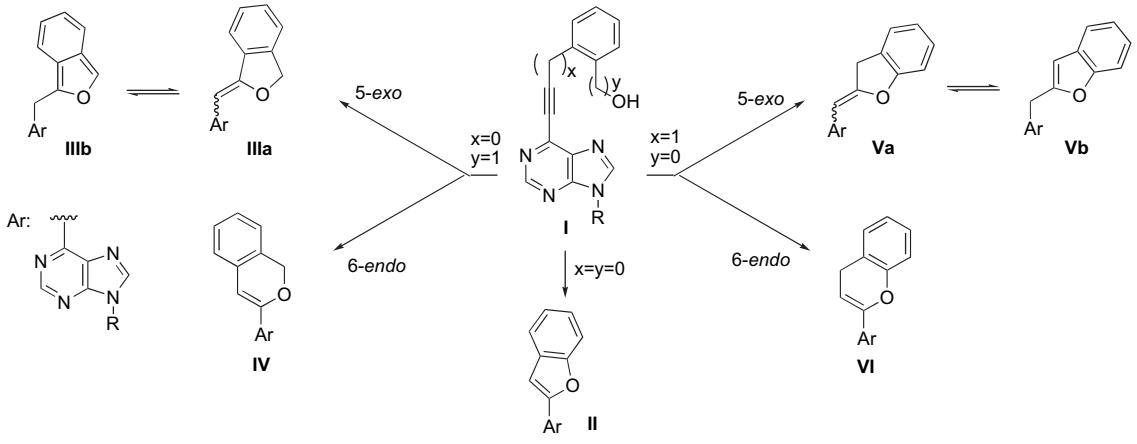
Abstract—Cyclization reactions on 6-[(2-hydroxyphenyl)ethynyl]purines, 6-[(2-hydroxymethylphenyl)ethynyl]purines and 6-[(2-hydroxyphenyl)propyn-1-yl]purines have been studied. 6-(2-Benzofuryl)purines are readily available via a one-pot Sonogashira coupling–cyclization between 6-iodopurine and 2-ethynylphenol. When the same reaction was performed with *o*-(hydroxymethyl)ethynylbenzene, 6-[isobenzofuran-1(3*H*)-ylidenemethyl]purine was formed, mainly as the (*E*)-isomer. Acid catalyzed isomerization of the (*E*)-compound afforded the (*Z*)-isomer. The latter compound was also formed from a two-step reaction; Sonogashira coupling with *O*-silylated alkyne followed by deprotection and subsequent 5-*exo* cyclization. Sonogashira coupling between 6-halopurines and 2-propynylphenol gave only the alkyne coupling product and no cyclization took place. However, the Sonogashira product was unexpectedly rearranged to 6-(3-phenoxypropa-1,2-dienyl)purines under basic conditions. Theoretical calculations demonstrated that the allenes are more stable than their alkyne isomers.

1. Introduction

During our synthetic studies toward potential plant growth hormone analogs,[1] we found that 6-(hydroxyalkynyl)purines ring close by an *exo-dig* attack from the hydroxy group on the triple bond.[1d] The electron deficient purine activates the alkyne function for nucleophilic attack. We have previously studied addition of nucleophiles to alkenylpurines.[2] Purines carrying different carbon substituents in the 6-position are associated with a wide variety of biological effects, like antimycobacterial activity,[3] cytotoxic effects,[4] a(nta)-gonist activity toward adenosine receptors,[5] inhibition of 15-lipoxygenase,[6] and antiviral activity[7,4f] in addition to the above-mentioned ability to stimulate plant growth.[1] In order to increase the synthetic methodologies for constructing 6-substituted purines, we decided to study the cyclizations of alkynylpurines with the general structure **I** and to explore the possibility of forming benzofuryl derivatives **II**, **III**, and **V** by 5-*exo* cyclization, or isomeric 6-*endo* products **IV** and **VI** (Scheme 1).



Scheme 1. Cyclization reactions studied herein.

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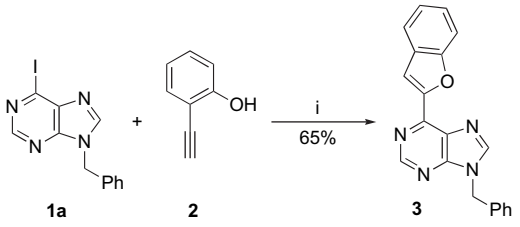
2. Results and discussion

Benzo[*b*]furans and indoles may be formed by Pd(0) and/or Cu(I)-mediated reactions of 2-alkynylphenols.[8] 2-Aryl- or 2-vinylbenzo[*b*]furans have been prepared by a one-pot Sonogashira coupling–cyclization when ethynylphenol **2** was reacted with aryl- or vinyl iodides under solventless microwave-enhanced Sonogashira coupling conditions, but only moderate yields were achieved due to polymerization reactions.[9] The 6-(2-benzofuryl)purine **3** (Scheme 2) exhibits antimycobacterial activity and has previously been prepared by Stille coupling on 6-halopurine.[3d] 6-(2-Benzofuryl)purine riboside has been prepared by Suzuki coupling in quite modest yield.[4f] We have determined that 6-iodopurine **1a** reacts with ethynylphenol **2** under standard Sonogashira conditions to give 2-benzofurylpurine **3** in a yield almost identical to what have been obtained previously,[3d] but the reaction described herein takes place under more environmentally benign conditions and utilizes less expensive starting materials, since the use of an organotin compound in stoichiometric amounts is avoided (Scheme 2).



Scheme 2. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NH$, DMF, 60 °C.

6-Iodopurine **1a** was reacted with terminal alkynes **4**. When the acetylene carried a free hydroxy group (**4a**), cyclization took place under Sonogashira conditions and the (*E*)-5-*exo* product **5** was formed together with minor amounts of the (*Z*)-isomer **7** (Scheme 3). NMR spectroscopic analyses indicated that compound **5** exists as an enol ether with the CH_2-group inside the newly formed ring, and the presence of an aromatic benzo[*c*]furyl substituent (product type **IIIb**, Scheme 1) could easily be excluded. Also other studies of 2-alkylbenzo[*c*]furans have shown that equilibria like **IIIa**–**IIIb** (Scheme 1) lies in favor of the benzenoid tautomer **IIIa**.[10]

Structure elucidation of compound **5** was initially based on NOESY correlation between H-2 in the purine ring and one of the hydrogens in the benzofuryl substituent (Scheme 3). The distance between the H-2 and the benzene ring would have been much larger in the (*Z*)-isomer **7** or in the 6-*endo* cyclized isomer (comp. **IV**, Scheme 1).

It was interesting to note that the chemical shift for the benzofuryl proton correlating to H-2 in the NOESY spectrum was shifted significantly downfield (δ 9.84 ppm). This might be explained by the close proximity to N-1 in the purine. The only difference found in the ^1H–^{15}N HMBC spectra of compound **5** and isomer **7** (Scheme 3) discussed below was a correlation between N-1 and the proton shifted downfield in the benzofuran ring of compound **5**. This confirms the close proximity of those two atoms and a hydrogen bond between them forming a pseudo 7-membered ring (Fig. 1). Not only is the hydrogen shifted downfield, also a 5.8 ppm up-field shift was observed for N-1 in compound **5** relative to the N-1 shift in the isomer **7**. The chemical shift values found for N-3, N-7, and N-9 in the two isomers were virtually identical. To the best of our knowledge, a persistent C–H···N bond in solution, detected by ^1H–^{15}N HMBC spectroscopy, has not been reported before, but it is now established that scalar couplings can be observed across H-bonds.[11] The correlation between N-1 and the benzofuryl signal at 9.84 ppm,

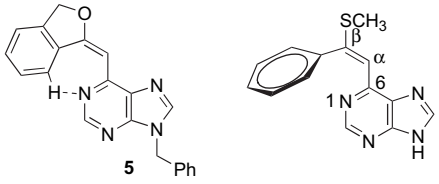
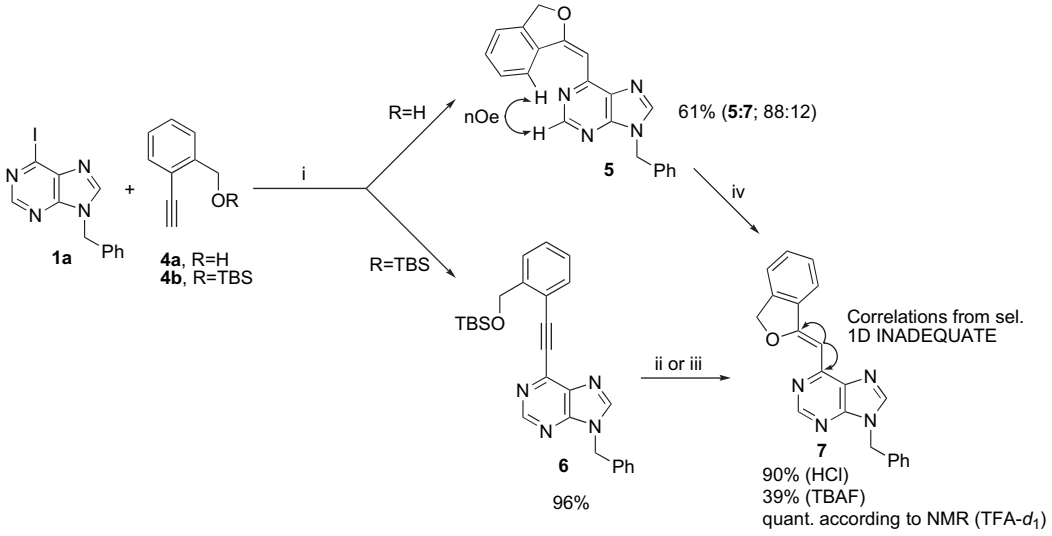


Figure 1. Structure of compound **5** with an intramolecular C–H···N bond and the more flexible 6-styrylpurine[13] where no intramolecular H-bond was observed.



Scheme 3. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NH$, DMF, 60 °C; (ii) HCl (aq), EtOH; (iii) TBAF, THF; (iv) TFA-d_1, $CDCl_3$.

seen in the ^{1}H–^{15}N HMBC spectrum of compound **5**, is a strong indication of a C–H···N bond, which may be the reason for the high chemical shift value for the benzofuryl proton.

The (*E*)-benzofurylalkylidene compound **5** readily isomerizes to the corresponding (*Z*)-isomer **7** (see below) and the intramolecular H-bond appears to be a consequence of the rigidity of compound **5**. No abnormalities in the ^{1}H NMR spectra indicating a C–H···N bond could be seen in spectra reported for a series of 6-styrylpurines[12] where there is free rotation between the phenyl and double bond. In the 6-styrylpurine shown in Fig. 1, the torsion angle N1–C-6–Cα–Cβ was only 6.7° in the crystal structures, but the angle between the phenyl and purine ring was 117°.[13]

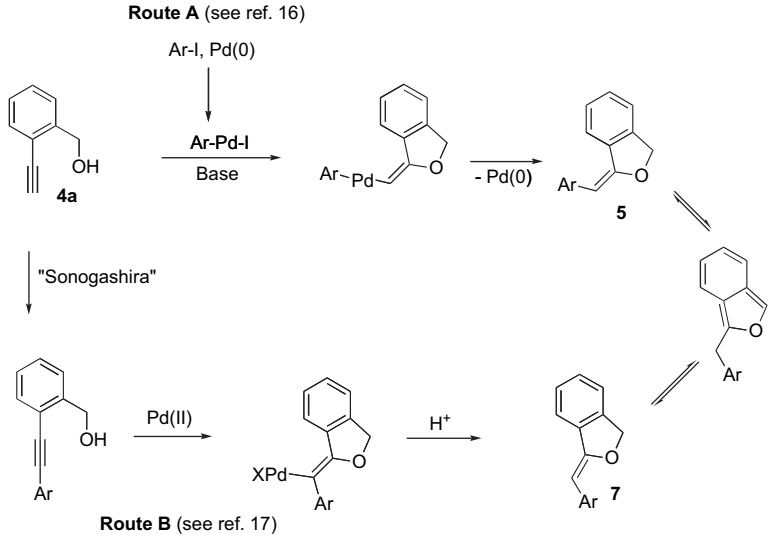
When the TBS-protected alcohol **4b** was employed in the Sonogashira reaction, the alkyne **6** was isolated in nearly quantitative yield (Scheme 3). Cyclization took place during deprotection. Both acidic and TBAF mediated cleavage of the silyl ether gave the (*Z*)-5-*exo* cyclized product **7**. The regioselectivity in cyclizations of compounds related to the general structure **I** (*x*=0, *y*=1, Scheme 1) is difficult to predict. Under basic conditions the alkoxy anion generally attacks the triple bond in related non-purine compounds to form 5-*exo* products,[14] but there are examples of rearrangement to the 6-*endo* isomer during work-up.[14a] Ring formation in the presence of TBAF appears to be sensitive to sterical hindrance; with relatively bulky alkyls on the alkyne the 6-*endo* product is formed, otherwise 5-*exo* cyclization is favored.[15] PdI_2 also promotes cyclization of alkynes related to **I** (*x*=0, *y*=1, Scheme 1). In these reactions the regiochemical outcome is sensitive to the solvent used.[16]

The ^{1}H–^{15}N HMBC spectrum, optimized for 10 Hz $^{2}J/^{3}J$ couplings of compound **7** was, with exception of the intramolecular H-bond in compound **5**, identical with the ^{1}H–^{15}N HMBC spectrum of the (*E*)-isomer **5**. In both spectra correlation between the CH═ in the side chain and N-1 was easily seen, an indication that both compounds were 5-membered rings, and that the theoretically possible 6-*endo* cyclized isochromene (type **IV** product; Scheme 1) was not formed. Selective 1D INADEQUATE (SELINQUATE) NMR, optimized for ^{1}J(C,C) proved unambiguously the 5-membered ring structure of compound **7**. When the *C*H═ in the side chain was irradiated, correlations to the two neighboring carbons, C-6 in the purine and the ═*C*–O, in the newly formed ring was observed (Scheme 3).

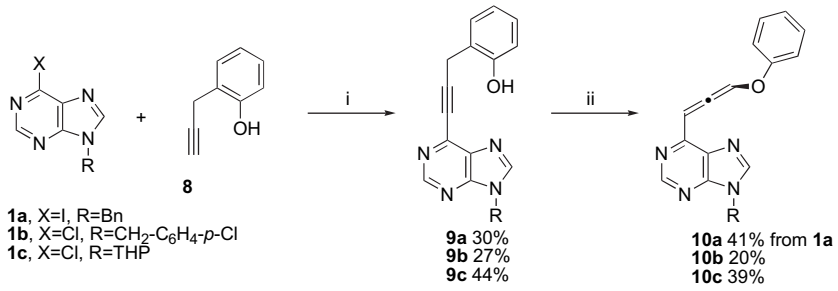
Based on the mechanism proposed for cycloisomerization of 2-alkynylbenzyl alcohols[16,17] and the isomerization experiments described below, it seems reasonable that compound **5** is formed by cyclization followed by cross-coupling (Scheme 4, route A) rather than the alternative route B. The latter route may explain the formation of the by-product **7** (Scheme 4), but compound **7** is also available from isomerization of the (*E*)-isomer **5**. CuI was present in the synthesis of compound **5**. The copper salt is of course required in the Sonogashira coupling in route B, and may replace Pd(II) in the cyclization in route B, but the possible role of CuI in route A is not clarified.

Complete isomerization of compound **5** to isomer **7** was observed in less than 5 min by NMR spectroscopy, when a drop of TFA-d_1 was added to a $CDCl_3$ solution of pure (*E*)-isomer **5**. The isomerization of pure (*E*)-**5** also took place, although slowly, in pure $CDCl_3$. After one day 8% of the (*Z*)-isomer **7** was formed and after 26 days 87% of compound **7** was present in the mixture as judged by ^{1}H NMR. In CD_2Cl_2 and CD_3OD, the conversion of compound **5** to isomer **7** was 53 and 62%, respectively, after 26 days. The (*Z*)-compound **7** was completely stable under acidic conditions. The elusive *o*-quinonoid tautomer of compounds **5** and **7** shown in Scheme 4, could not be observed in the NMR spectra from the isomerization studies, and related *o*-quinonoid isobenzofurans are reported to be highly unstable.[10]

Compounds **5** and **7** were tested as antimycobacterials and both isomers exhibited MIC values of 6.25 μg/mL against *Mycobacterium tuberculosis*. Compound **5** may have isomerized to isomer **7** during determination of antibacterial effect. The activity against *M. tuberculosis* found for compound **7** is



Scheme 4. Possible mechanisms for the formation of the isomers **5** and **7**.



Scheme 5. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60–80 °C; (ii) CuI, Et_3N, Δ.

comparable with that reported for the benzofuryl derivative **3**,[3d] but none of these compounds are as active as our most promising antimycobacterial purines.[3]

The alkyne **8** (Scheme 5) is reported to react with aryl iodides in the presence of BuLi and a Pd(II) precatalyst to give 5-*exo* products (type **V**, Scheme 1), a reaction somewhat like route B in Scheme 3.[17] However, the application of these conditions in reaction between halopurine **1c** and the acetylene derivative **8** was not successful. Compound **9c** was prepared in moderate yield by standard Sonogashira conditions and several unsuccessful attempts were made to cyclize this compound. When refluxed in Et_3N in the presence of catalytic amounts of CuI and $(Ph_3P)_2PdCl_2$, still no cyclization occurred, but an unexpected rearrangement to the allene **10c** took place. We found that the reaction took place in Et_3N without any additives, but the yield of compound **10c** was somewhat higher when the reaction was carried out in the presence of CuI. Addition of a Pd-catalyst [generated from Pd(II) or Pd(0)] actually had a negative effect on the yield of allene. Compound **10c** was isolated in 39% when **9c** was refluxed in Et_3N in the presence of catalytic CuI. Allenes **10a** and **10b** were formed by the same reaction sequence. Compound **10a** could also be isolated directly from the Sonogashira coupling after prolonged reaction time. Allenes **10** decomposed when exposed to light in $CHCl_3$ solution and the low stability of the allenes may explain the only moderate isolated yields. The allenes **10** carry both an electron withdrawing and an electron donating group and high reactivity has also been previously reported for 'push–pull' substituted allenes.[18]

NMR spectroscopy as well as synthesis by a different route (see Scheme 7 below) confirmed the unexpected allene structure of compounds **10**. Compound **10c** possesses a mono substituted benzene ring and the ^1H and ^{13}C NMR signals (see Section 4) for the benzene ring indicated that an RO– substituent was connected to the phenyl ring. The phenoxy- and purinyl moieties were separated by a CH–C–CH linkage. Furthermore, the direct coupling constants between C and H in this fragment were found to be ca. 175 Hz, a strong indication that both CH carbons are sp^2 hybridized and that the phenyl- and purine rings were separated by the allenyloxy fragment. It is worth mentioning that 'unusual' ^{13}C NMR shifts were observed especially for the central allene carbon and C-2, C-4, and C-6 in the purine ring, all these ^{13}C resonances were shifted considerably up-field (Fig. 2). Up-field shifts for central allene carbons have been observed before when the allene carries alkoxy group(s) acting as π-donors.[18] However, the low up-field shifts found for several purine carbon resonances indicate that the purine ring behaves as a π-acceptor, which should lead to a deshielding of the central allene carbon. In 'push–pull' substituted allenes described before, the effects from the donors and acceptors often cancel each other with respect to the ^{13}C NMR shift of the central allene carbon.[18]

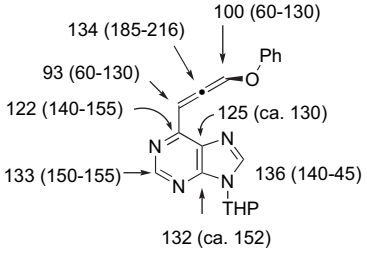
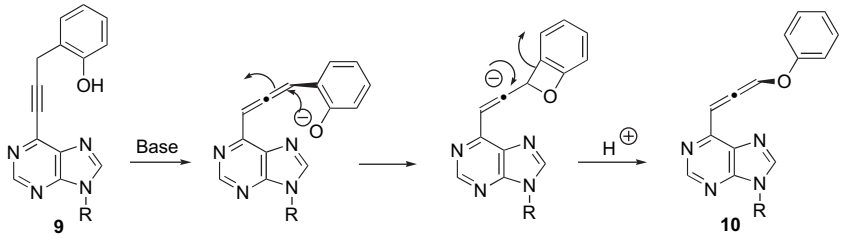
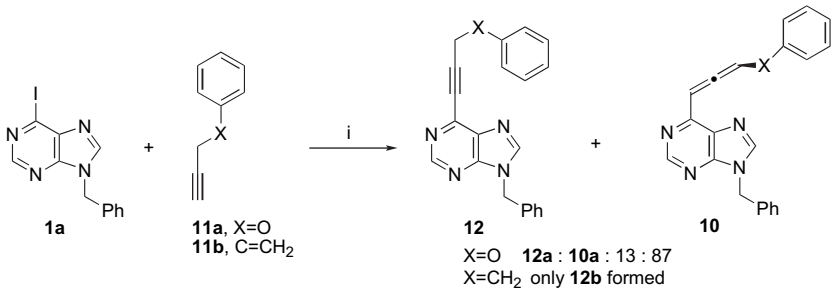


Figure 2. Structure of the phenoxy allene **10c**. Selected ^{13}C NMR shifts for compound **10c** are shown, typical shift ranges for purine ring carbons in 6-alkenyl or alkynylpurines,[1,2,6] and allene carbons[18] are shown in brackets.

A tentative mechanism for allene formation without CuI, is detailed in Scheme 6. The presence of a 4-membered ring intermediate seems reasonable given that the carbon–oxygen bond is formed by attack from the phenolate anion on an allene isomer of **9**, even though allenes are normally attacked



Scheme 6. Tentative mechanism for the formation of compounds **10**.



Scheme 7. Reagents and conditions: (i) $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-Pr})_2NR$, DMF, 60 °C.

by nucleophiles at the central carbon. The favorable influence of CuI on the rearrangement is currently not understood.

In order to further confirm the structure of the allenes **10**, purine **1a** was reacted with the alkyne **11a** and the allene **10a** was isolated together with the alkyne **13a** (13%) after chromatography (Scheme 7). Theoretical calculations have shown that an alkoxy group will stabilize an allene,[19] and propargyl ethers can be isomerized to alkoxyallenes under basic conditions, but generally strong bases like Bu^tOK or RLi, are employed.[20] Formation of the allene **10a** under moderately basic Sonogashira conditions indicates that the 6-purinyl moiety facilitate allene formation. When the 3-phenoxypropyn-1-yl functionality was introduced in the less electron deficient purine 2-position, the expected alkyne was formed.[21]

Electronic structure calculations were carried out to further investigate the formation of the allene **10a**, rather than the expected alkyne **12a**, in Scheme 7. First, the reactants **1a** and **11a** were optimized individually before assembling the two products **12a** and **10a** from these fragments. As both the resulting compounds are highly flexible, a thorough search of the conformational space was necessary. The equilibrium structures and the gas-phase molecular energies were determined by locating the global minimum of the potential energy surface (PES) of each isolated product. A large number of starting geometries were generated, and subsequently optimized, by systematically rotating key dihedral angles in the two product structures. For compound **12a** nine conformers were found, whereas a total of 15 different conformers were found for compound **10a**. Frequency calculations were then carried out for the handful of conformers of each system possessing the lowest energy, serving both to verify that the geometries indeed corresponded to stable structures and to estimate the zero-point vibrational energy of each system. The two equilibrium structures are shown in Figure 3, and it was found that the molecular energy of the allene **10a** is 27 kJ/mol lower than the expected Sonogashira alkynylation product **12a**. By adding the zero-point vibrational energy, the energy difference increases very

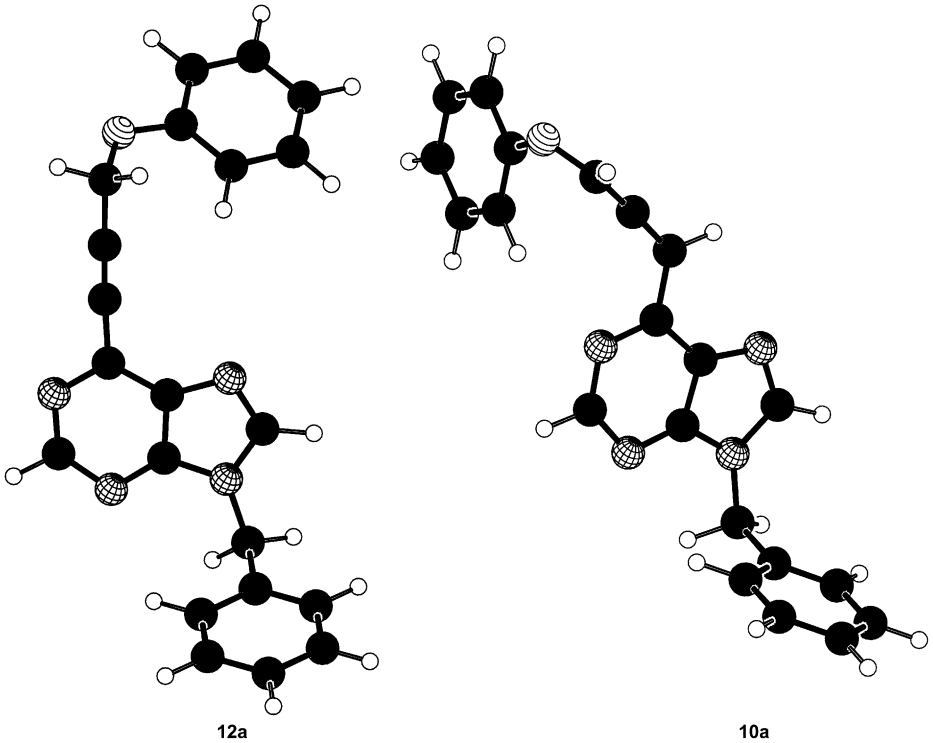
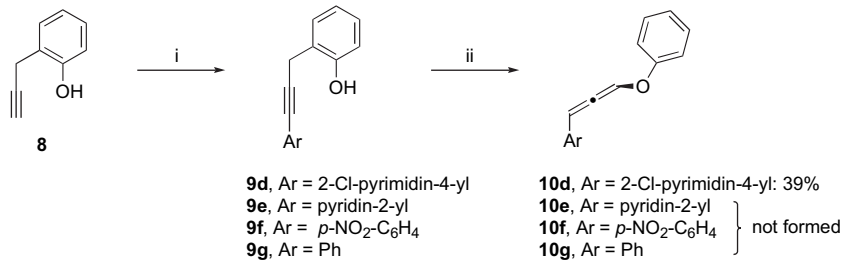


Figure 3. The gas-phase equilibrium structure of the expected Sonogashira product **12a** and the observed product **10a** as calculated at the B3LYP/6-31G(d,p) level of theory. Carbon, hydrogen, nitrogen, and oxygen atoms are shown in black, in white, with grids, and with lines, respectively.

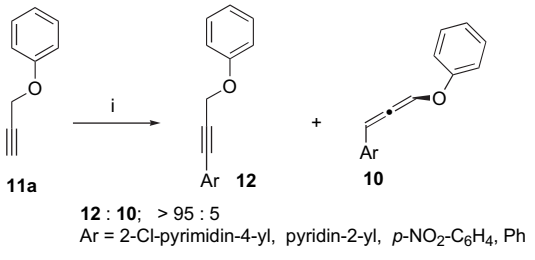


Scheme 8. Reagents and conditions: (i) ArX, $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60 °C; (ii) CuI, Et_3N, Δ.

slightly to 28 kJ/mol. One may also estimate the standard enthalpy of formation for the two compounds, and the allene is again found to be 28 kJ/mol more stable than the alkyne. While not yielding a huge energy difference, the theoretical calculations clearly indicate that of the two compounds, the allene is energetically favorable. The theoretical results are thus in very good agreement with the experimental findings.

The rearrangement of compounds **9** to the allenes **10** (Scheme 5 above) was highly unexpected and we decided to look into the scopes and limitations of the reaction. Even though allenes often has been regarded as chemical curiosities, they may be useful synthetic intermediates[22,23] and there are quite a few examples of pharmacologically active allenes including allene natural products.[24] Our hypothesis was that the allene formation is especially favorable when the allene carries both powerful electron withdrawing and electron donating groups. Coupling between purine **1a** and alkyne **11b** gave only the alkyne **12b** (Scheme 7). The alkyne **8** was reacted with different aryl halides or heteroaryl halides to give compounds **9d**–**9g**. Only the alkyne **9d** rearranged to the allene under basic conditions confirming that a highly electron withdrawing group is required for the reaction to take place (Scheme 8).

Finally, we reacted alkyne **11a** with the same aryl- or heteroaryl halides as used in the reactions described in Scheme 9. In all cases examined the 'normal' Sonogashira product **12** was formed and no allenes **10** could be detected, not even in the synthesis of pyrimidine **12d** even though the allene **10d** could be formed by rearrangement (Scheme 8).



Scheme 9. Reagents and conditions: (i) ArX, $(Ph_3P)_2PdCl_2$, CuI, $(i\text{-}Pr)_2NR$, DMF, 60 °C.

3. Conclusions

6-(2-Benzofuryl)purines are readily available by one-pot Sonogashira coupling–cyclization between 6-iodopurine and 2-ethynylphenol. When the same reaction is performed with *o*-(hydroxymethyl)ethynylbenzene, 6-(isobenzofurylidenemethyl)purine was formed, mainly as the (*E*)-isomer. The pure (*Z*)-isomer was available from a two-step reaction; Sonogashira coupling with *O*-silylated alkyne followed by acidic or TBAF mediated deprotection and subsequent 5-*exo* cyclization. The less stable *o*-quinonoid tautomer 6-(isobenzofurylmethyl)purine could not be detected, neither could formation of a 6-*endo* cyclized isochromene product. In the (*E*)-isomer of the 6-(isobenzofurylidenemethyl)-purine, NMR spectroscopy indicates the presence of an intramolecular C–H···N bond between N-1 in the purine and H-7 in the isobenzofurane.

Sonogashira coupling between 6-halopurines and 2-propynylphenol gave only the alkyne coupling product and no cyclization took place. However, the Sonogashira product was unexpectedly rearranged to 6-(3-phenoxypropa-1,2-dienyl)-purines, when refluxed in Et_3N. The yields were somewhat improved in the presence of CuI. Only allenes with both a powerful electron withdrawing and electron releasing substituent on the allene fragment was formed by this novel rearrangement.

4. Experimental

4.1. General

The ^1H NMR spectra were acquired on a Bruker Avance AV 600 spectrometer, a Bruker Avance DRX 500 spectrometer, a Bruker Avance DPX 300 spectrometer or a Bruker Avance DPX 200 spectrometer at 600, 500, 300 or 200 MHz, respectively. The ^1H decoupled ^{13}C NMR spectra were recorded at 150, 125, 75 or 50 MHz using the above-mentioned spectrometers. Assignments of ^1H and ^{13}C resonances are inferred from 1D ^1H NMR, 1D ^{13}C NMR, APT, DEPT and/or from 2D NMR (gs-COSY, gs-HMQC, gs-HMBC, NOESY) spectral data. ^{15}N NMR data were acquired at 50 MHz on the Bruker Avance DRX 500 with a 5 mm TXI ($^1H/^{13}C$, ^{15}N–^2H) Triple Resonance Inverse probe, equipped with Z-gradient coil, by applying 2D NMR experiments based on gradient pulse selection and inverse detection methods: gs-[^1H, ^{15}N] HMBC, optimized for $^2J/^3J$ $^{15}N/^1H$-couplings of 10 Hz (Bruker pulse program: *inv4gplplrndqf*, ^{15}N-pulses via F2-channel, relaxation delay, *d*1: 1.5 s, acquisition time, aq: 0.17 s, delay for evolution of long range couplings, *d*6: 0.1 s). ^{15}N chemical shifts are reported relative to external $Me^{15}NO_2$ at 0 ppm ($MeNO_2$ dissolved in the respective deuterated solvent in ratio 9:1). The selective 1D INADEQUATE (SELINQUATE) spectrum for verification of

the 5-membered ring structure of product **7** was acquired on the Bruker Avance AV 600 with a 5 mm CP–TCI ($^{1}H/^{13}C$, ^{15}N–^{2}H) Triple Resonance Inverse Cryo probe (cold ^{13}C coil and preamplifier). In order to decrease the relaxation times especially for the quaternary ^{13}C atoms and thereby to reduce the experiment time, 130 mg of product **7** was dissolved in 0.6 mL nonafluoro-*tert*-butyl alcohol (perfluoro-tertiarybutanol, 'artificial blood').[25] 5% DMSO-d_6 was added for the lock and the solution was saturated with oxygen at room temperature. Bruker pulse program: *selina*. A Gaussian shape cascade with 1024 data points (*SPNAM1*: Q5.1000) of 10 ms length (*p11*) and 32 dB attenuation (*sp1*, which was calibrated for our specific spectrometer probe), corresponding to 90° excitation was used as the ^{13}C transmitter soft pulse. The acquisition was optimized for ^{1}J(C,C) couplings of 60 Hz (*CNST3*), corresponding to $d4$=4.17 ms. Relaxation delay ($d1$): 4 s, acquisition time (aq): 0.3 s. The experimental time was 62 h with 50,000 scans applied. IR spectra were recorded at a Perkin–Elmer Spectrum One instrument. MS spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage and are presented as *m/z* (% rel int.). CH_4 was employed as the ionization gas for chemical ionization (CI). Electrospray MS spectra were recorded with a Bruker Apex 47e FT-ICR mass spectrometer. Elemental analyses were performed by Ilse Beetz Mikroanalytisches Laboratorium, Kronach, Germany. Melting points are uncorrected. DMF, CH_2Cl_2, triethylamine, and diisopropylamine were distilled from CaH_2. The following compounds were prepared by literature methods: **1a**,[26] **1b**,[3c] **1c**,[27] **2**,[9] **4b**,[28] **8**.[29] All other reagents were commercially available and used as received. All quantum chemical calculations were performed using Gaussian 03.[30] Both geometry optimizations and frequency calculations were carried out at the DFT level of theory, employing the B3LYP-functional in conjunction with the 6-31G(d,p) basis set and the 'ultrafine' grid. The chosen computational method is well established and it gives sufficiently accurate results for this study at a reasonable computational cost. Antimycobacterial activities were determined as described before.[3]

4.1.1. 6-(2-Benzo[*b*]furyl)-9-benzyl-9*H*-purine (3). Diisopropylamine (848 μL, 6.00 mmol) was added to a stirred solution of 9-benzyl-6-iodo-9*H*-purine (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL). The mixture was heated at 60 °C, and 2-ethynylphenol (142 mg, 1.20 mmol) in DMF (1 mL) was added over 2 h and the reaction mixture was stirred for additional 3 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:9); yield 211 mg (65%) off-white crystalline solid, mp 200–202 °C (lit.[3d] 202–203 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.08 (s, 1H, H-2), 8.29 (s, 1H, H-3 in benzofuryl), 8.13 (s, 1H, H-8), 7.70–7.72 (m, 2H in Ar), 7.28–7.40 (m, 7H, Ar), 5.48 (s, 2H, CH_2).

4.1.2. (*E*)-9-Benzyl-6-[isobenzofuran-1(3*H*)-ylidenemethyl]-9*H*-purine (5). 9-Benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol) was added to a stirred solution of $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) under N_2-atm. The reaction mixture was heated to 60 °C and compound **4a** (159 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 1 h. The resulting mixture was stirred at 60 °C for 4 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (2:1); yield 206 mg (61%, *E*/*Z* ratio: 88:12), 100 mg of the isomeric mixture was purified by flash chromatography silica gel eluting with $CHCl_3$–EtOAc (2:1); yield 79 mg pure (*E*)-isomer, yellow crystals, mp 170–173 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ 9.84 (d, *J* 7.9 Hz, 1H, benzofuran), 8.88 (s, 1H, H-2), 8.59 (s, 1H, H-8), 7.59–7.53 (m, 3H, benzofuran), 7.34–7.27 (m, 5H, Ph), 6.82 (s, 1H, CH=), 5.53 (s, 2H, OCH_2), 5.48 (s, 2H, NCH_2); ^{13}C NMR (150 MHz, DMSO-d_6): δ 166.0 (benzofuran), 153.3 (C-6), 151.5 (C-2), 150.2 (C-4), 144.5 (benzofuran), 144.4 (C-8), 136.7 (Ph), 131.4 (benzofuran), 130.0 (benzofuran), 129.6 (C-5), 128.7 (Ph), 127.86 (benzofuran), 127.85 (benzofuran), 127.8 (Ph), 127.6 (Ph), 121.4 (benzofuran), 94.3 (CH=), 73.7 (OCH_2), 46.3 (NCH_2); ^{15}N NMR (50 MHz, $Me^{13}NO_2$): δ −217.0 (N-9), −137.4 (br, N-3 and N-7), −114.9 (N-1); IR (KBr) ν_{max} 1621 (s), 1578 (s), 1469 (m), 1444 (m), 1401 (m), 1088 (m), 982 (m) cm^{-1}; EIMS *m/z* (rel %): 340 (96, M^+), 240 (100), 91 (71); HRMS (EI) found 340.1327, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.3. 9-Benzyl-6-{[2-({[(1,1-Dimethylethyl)dimethylsilyl]oxy}methyl)phenyl]ethynyl}-9*H*-purine (6). 9-Benzyl-6-iodo-9*H*-purine **1a** (168 mg, 0.500 mmol) was added to a stirred solution of $(PPh_3)_2PdCl_2$ (18 mg, 0.025 mmol), CuI (9 mg, 0.05 mmol), and diisopropylamine (427 μL, 3.00 mmol) in DMF (5 mL) under N_2-atm. The reaction mixture was heated to 60 °C and compound **4b** (148 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 1.5 h. The resulting mixture was stirred at 60 °C for 22 h before evaporation. The product was isolated by flash chromatography on silica gel eluting with $CHCl_3$–EtOAc (1:1); yield 219 mg (96%), pale brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.97 (s, 1H, H-2), 8.07 (s, 1H, H-8), 7.64–7.61 (m, 3H, Ph), 7.43–7.21 (m, 6H, Ph), 5.44 (s, 2H, OCH_2), 5.12 (s, 2H, NCH_2), 0.94 (s, 9H, *t*-Bu), 0.12 [s, 6H, $Si(CH_3)_2$]; ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.6 (C-2), 151.6 (C-4), 145.0 (C-8), 144.9 (Ph), 142.0 (C-6), 134.9 (C-5), 134.4 (Ph), 132.6 (Ph), 130.1 (Ph), 129.2 (Ph), 128.7 (Ph), 127.8 (Ph), 126.4 (Ph), 125.7 (Ph), 117.9 (Ph), 95.0 (C≡), 88.9 (C≡), 63.2 (OCH_2), 47.4 (NCH_2), 26.0 (CH_3 in *t*-Bu), 18.4 (C in *t*-Bu), −5.3 [$Si(CH_3)_2$]; IR (CCl_4) ν_{max} 3069 (w), 304 (w), 2956 (m), 2930 (m), 2886 (m), 2857 (m), 2213 (m), 1748 (w), 1579 (s) cm^{-1}; CIMS *m/z* (rel %): 455 (76, M+1), 397 (100), 91 (34); HRMS (ESI) found 455.2250, calcd for $C_{27}H_{30}N_4OSi$+H 455.2261.

4.1.4. (*Z*)-9-Benzyl-6-[isobenzofuran-1(3*H*)-ylidenemethyl]-9*H*-purine (7). Method A: The TBS-protected alcohol **6** (200 mg, 0.44 mmol) was dissolved in EtOH (10 mL) and aq HCl (5 mL, 1 M) was added dropwise. The resulting mixture was stirred at ambient temperature for 6 h and quenched by addition of $NaHCO_3$ to neutral pH before evaporation. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (9:1); yield 99 mg (90%), pale yellow crystals, mp 207–208 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.03 (s, 1H, H-2), 7.94 (s, 1H, H-8), 7.85–7.81 (m, 1H, benzofuran), 7.48–7.26 (m, 8H, Ph and benzofuran), 6.84 (s, 1H, CH=), 5.73 (s, 2H, OCH_2), 5.41 (s, 2H, NCH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 163.5 (C-2 in benzofuran), 153.3 (C-6), 152.1 (C-2), 150.3 (C-4),

144.2 (C-8), 141.5 (C in benzofuran), 136.8 (C-1 in Ph), 133.4 (C in benzofuran), 130.9 (C in benzofuran), 129.5 (C-5), 128.7 (C in benzofuran), 128.6 (C in benzofuran), 127.9 (C in benzofuran), 127.6 (C in Ph), 120.0 (C in benzofuran), 121.4 (C in benzofuran), 88.0 (CH═), 76.2 (CH_2 in benzofuran), 46.3 (NCH_2); ^{15}N NMR (50 MHz, Me$^{13}NO_2$): δ −217.6 (N-9), −137.3 (br, N-3 and N-7), −109.1 (N-1); IR (KBr) ν_{max} 1635 (s), 1577 (s), 1452 (m), 1398 (m), 1296 (m), 1052 (m), 975 (m) cm^{-1}; EIMS *m/z* (rel %): 340 (97, M$^+$), 249 (100), 91 (34); HRMS (EI) found 340.1321, calcd for $C_{21}H_{16}N_4O$ 340.1324.

Method B: The TBS-protected alcohol **6** (153 mg, 0.34 mmol) was dissolved in THF (5 mL), a solution of tetrabutylammonium fluoride (440 μL, 0.1 mM in THF) was added and the resulting mixture was stirred for 4 h at ambient temperature under N_2-atm. The reaction mixture was evaporated on silica gel and the product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (9:1); yield 44 mg (39%); data, see above.

4.1.5. 2-[3-(9-Benzyl-9*H*-purin-6-yl)-2-propynyl]phenol (9a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (169 mg, 0.50 mmol), diisopropylamine (427 μL, 3.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) under N_2-atm was heated to 60 °C. 2-(Prop-2-ynyl)phenol **8** (82 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for 2 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (1:1); yield 50 mg (30%), yellow oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.96 (s, 1H, H-2), 8.11 (s, 1H, H-8), 7.38–7.24 (m, 6H, Ph), 7.07–6.96 (m, 3H, Ph), 5.44 (s, 2H, CH_2), 5.06 (s, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 157.6 (C-6), 152.7 (C-2), 151.7 (C-4), 145.3 (C-8), 140.8 (Ph), 134.7 (Ph), 134.3 (C-5), 129.5 (Ph), 129.2 (2×C in Ph), 128.7 (Ph), 127.8 (Ph), 121.6 (Ph), 114.9 (2×C in Ph), 93.2 (C≡), 81.4 (C≡), 56.3 (CH_2), 47.4 (NCH_2); IR (neat) ν_{max} 3063 (m), 2987 (m), 1593 (s), 1494 (s), 1403 (s) cm^{-1}; EIMS *m/z* (rel %): 340 (81, M$^+$), 247 (54), 91 (100); HRMS (EI) found 340.1313, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.6. 2-{3-[9-(4-Chlorobenzyl)-9*H*-purin-6-yl]-2-propynyl}phenol (9b). A mixture of 6-chloro-9-[(4-chlorophenyl)methyl]-9*H*-purine **1b** (140 mg, 0.500 mmol), diisopropyl(ethyl)amine (424 μL, 3.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) was heated to 80 °C under N_2-atm. 2-(Prop-2-ynyl)-phenol **8** (82 mg, 0.60 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 3.5 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:1); yield 50 mg (27%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.92 (s, 1H, H-2), 8.07 (s, 1H, H-8), 7.32–7.20 (m, 5H, Ph), 7.03 (m, 3H, Ph), 5.38 (s, 2H, CH_2), 5.03 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.6 (C-6), 152.8 (C-2), 151.6 (C-4), 145.1 (C-8), 141.0 (Ph), 134.8 (Ph), 134.4 (C-5), 133.2 (Ph), 129.5 (Ph), 129.2 (Ph), 121.7 (Ph), 115.0 (Ph), 93.5 (C≡), 81.4 (C≡), 56.4 (CH_2), 46.8 (CH_2); IR (neat) ν_{max} 3420 (br), 3063 (m), 2239 (w), 1897 (w), 1593 (s), 1495 (s), 1437 (s), 1403 (s) cm^{-1}; EIMS *m/z* (rel %): 376/374 (26/87, M$^+$), 249 (100), 125 (96); HRMS (EI) found 374.0946, calcd for $C_{21}H_{15}N_4OCl$ 374.0934.

4.1.7. 2-[3-(9-Tetrahydropyran-2-yl-9*H*-purin-6-yl)-2-propynyl]phenol (9c). A mixture of 6-chloro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine **1c** (476 mg, 2.00 mmol), diisopropyl(ethyl)amine (2.08 mL, 12.0 mmol), $(PPh_3)_2PdCl_2$ (140 mg, 0.20 mmol), and CuI (76 mg, 0.40 mmol) in DMF (8 mL) was heated to 60 °C under N_2-atm. 2-(Prop-2-ynyl)phenol **8** (344 mg, 2.40 mmol) in DMF (4 mL) was added dropwise over 5.5 h, and the resulting mixture was stirred for another 0.5 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–$CHCl_3$ (1:1); yield 294 mg (44%), yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.89 (s, 1H, H-2), 8.31 (s, 1H, H-8), 7.29–7.24 (m, 2H, Ph), 7.02–6.92 (m, 2H, Ph), 5.75 (dd, *J* 9.8 and 2.6 Hz, 1H, H-2 in THP), 5.02 (s, 2H, CH_2), 4.13 (dd, *J* 11.5 and 3.8 Hz, 1H, H-6$_a$ in THP), 3.74 (dt, *J* 11.5 and 2.6 Hz, 1H, H-6$_b$ in THP), 2.09–2.02 (m, 3H, THP), 1.75–1.63 (m, 3H, THP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (Ph), 152.4 (C-2), 150.7 (C-4), 143.3 (C-8), 140.6 (C-6), 134.5 (C-5), 129.4 (Ph), 121.5 (Ph), 114.8 (Ph), 93.1 (C≡), 82.0 (C-2 in THP), 81.4 (C≡), 68.6 (C-6 in THP), 56.2 (CH_2), 31.6 (THP), 24.7 (THP), 22.6 (THP); IR (neat) ν_{max} 3446 (br), 3102 (m), 3060 (m), 2947 (s), 2859 (s), 2240 (m), 1735 (w), 1583 (s), 1494 (s), 1441 (s), 1403 (s) cm^{-1}; CIMS (CH_4) *m/z* (rel %): 335 (14, M+1), 251 (100); HRMS (CI) found 335.1510, calcd for $C_{19}H_{19}N_4O_2$+H 335.1508.

4.1.8. 2-[3-(2-Chloropyrimidin-4-yl)-2-propynyl]phenol (9d). A mixture of 2,4-dichloropyrimidine (149 mg, 1.00 mmol), diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), and CuI (19 mg, 0.10 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. 2-(Prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 2 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (4:1); yield 44 mg (18%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, *J* 5.1 Hz, 1H, H-6), 7.29–7.21 (m, 3H, Ph H-5), 6.99–6.93 (m, 2H, Ph), 4.89 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.2 (C-2), 159.6 (C-6), 157.3 (Ph), 152.3 (C-4), 129.6 (2×C in Ph), 121.9 (Ph), 121.8 (C-5), 114.8 (2×C in Ph), 91.1 (C≡), 83.2 (C≡), 56.0 (CH_2); IR (neat) ν_{max} 3043 (w), 2917 (w), 2237 (w), 1561 (s), 1495 (m) cm^{-1}; EIMS *m/z* (rel %): 246/244 (42/100, M$^+$), 215/217 (71/26), 151 (47); HRMS (EI) found 244.0394, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.9. 2-[3-(Pyridin-2-yl)-2-propynyl]phenol (9e). 2-Bromopyridine (158 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (70 mg, 0.10 mmol), CuI (38 mg, 0.20 mmol) diisopropyl(ethyl)-amine (1.04 mL, 6.00 mmol), and 2-(prop-2-ynyl)phenol **6** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (1:1); yield 123 mg (59%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* 4.5 Hz, 1H, Ar), 7.60–7.57 (m, 1H, Ar), 7.41–7.38 (m, 1H, Ar), 7.32–7.27 (m, 2H, Ar), 7.24–7.21 (m, 1H, Ar), 7.03–6.95 (m, 2H, Ar), 4.91 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (Ar), 150.0 (Ar), 142.5 (Ar), 136.1 (Ar), 129.5 (Ar), 127.3 (Ar), 123.2 (Ar), 121.5 (Ar), 114.9 (Ar), 86.2 (C≡), 83.9 (C≡), 56.3 (CH_2); IR (CCl_4) ν_{max} 3066

(w), 1599 (m), 1583 (s), 1495 (s) cm^{-1}; EIMS *m/z* (rel %): 209 (74, M^+), 116 (100); HRMS (EI) found 209.0839, calcd for $C_{14}H_{11}NO$ 209.0841; Anal. found: C, 80.16; H, 5.60; N, 7.00. $C_{14}H_{11}NO$ requires C, 80.36; H, 5.30; N, 6.69%.

4.1.10. 2-[3-(*p*-Nitrophenyl)-2-propynyl]phenol (9f). 1-Bromo-4-nitrobenzene (202 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (70 mg, 0.10 mmol), CuI (38 mg, 0.20 mmol), diisopropyl-(ethyl)amine (1.04 mL, 6.00 mmol), and 2-(prop-2-ynyl)-phenol **8** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (95:5); yield 166 mg (66%), mp 83–85 °C, off-white crystals. ^1H NMR (300 MHz, $CDCl_3$): δ 8.17–8.14 (m, 2H, Ph), 7.58–7.54 (m, 2H, Ph), 7.35–7.29 (m, 2H, Ph), 7.03–6.98 (m, 2H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.5 (Ph), 147.3 (Ph), 132.5 (Ph), 129.5 (Ph), 129.1 (Ph), 123.5 (Ph), 121.7 (Ph), 114.9 (Ph), 89.3 (C≡), 85.1 (C≡), 56.3 (CH_2); IR (KBr) ν_{max} 3415 (br), 3107 (w), 2856 (w), 1592 (s), 1519 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 253 (63, M^+), 160 (100), 130 (99); HRMS (EI) found 253.0737, calcd for $C_{15}H_{11}NO_3$ 253.0738; Anal. found: C, 71.11; H, 4.38. $C_{15}H_{11}NO_3$ requires C, 71.14; H, 4.38%.

4.1.11. 2-(3-Phenyl-2-propynyl)phenol (9g). Iodobenzene (114 μL, 1.00 mmol), $(PPh_3)_2PdCl_2$ (71 mg, 0.100 mmol), CuI (38 mg, 0.20 mmol), diisopropylamine (0.84 mL, 6.0 mmol), and 2-(prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) was reacted as described for **9b** above. The product was isolated by flash chromatography on silica gel eluting with hexane–acetone (199:1); yield 169 mg (81%), mp 44–45 °C, pale yellow crystals. ^1H NMR (300 MHz, $CDCl_3$): δ 7.46–7.42 (m, 2H, Ph), 7.34–7.28 (m, 4H, Ph), 7.05–6.97 (m, 3H, Ph), 4.91 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2 (Ph), 132.2 (Ph), 129.9 (Ph), 129.1 (Ph), 128.7 (Ph), 122.7 (Ph), 121.6 (Ph), 115.4 (Ph), 87.6 (C≡), 84.4 (C≡), 57.1 (CH_2); IR (KBr) ν_{max} 3436 (br), 3050 (w), 2964 (w), 2930 (w), 2196 (w), 1598 (m), 1586 (m), 1489 (s) cm^{-1}; EIMS *m/z* (rel %): 208 (19, M^+), 115 (100); HRMS (EI) found 208.0886, calcd for $C_{15}H_{12}O$ 208.0888; Anal. found: C, 86.30; H, 5.72. $C_{15}H_{12}O$ requires C, 86.51; H, 5.81%.

4.1.12. 9-Benzyl-6-(3-phenoxypropa-1,2-dienyl)-9H-purine (10a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) was stirred under N_2-atm at 60 °C, and 2-(prop-2-ynyl)phenol **8** (163 mg, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h. The mixture was stirred for another 24 h at 60 °C. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (3:2); yield 139 mg (41%), mp 83–85 °C, yellow crystals. ^1H NMR (500 MHz, CD_3OD): δ 8.43 (s, 1H, H-2), 8.04 (s, 1H, H-8), 7.32–7.28 (m, 7H, Ph), 7.08–7.00 (m, 1H, Ph), 6.99–6.98 (m, 2H, Ph), 6.59 (d, *J* 3.9 Hz, 1H, =CH), 6.33 (d, *J* 3.9 Hz, 1H, =CH), 5.41 (s, 2H, NCH_2); ^{13}C NMR (125 MHz, CD_3OD): δ 159.1 (Ph), 140.0 (C-8), 137.9 (Ph), 135.6 (Ph), 134.6 (C-4), 133.6 (C-2), 131.1 (Ph), 129.9 (Ph), 129.1 (Ph and =C=), 128.8 (Ph), 125.5 (Ph), 124.8 (C-5), 123.4 (C-6), 116.9 (Ph), 101.4 (CH= in allene), 94.1 (CH= in allene), 49.0 (NCH_2); IR (neat) ν_{max} 3108 (w), 2943 (w), 1639 (m), 1556 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 340 (88, M^+), 263 (42), 91 (100); HRMS (EI) found 340.1320, calcd for $C_{21}H_{16}N_4O$ 340.1324.

4.1.13. 9-(4-Chlorobenzyl)-6-(3-phenoxypropa-1,2-dienyl)-9*H*-purine (10b). A mixture of compound **9b** (50 mg, 0.14 mmol) and CuI (3 mg, 0.014 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 24 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (2:1); yield 10 mg (20%), brownish oil. ^1H NMR (600 MHz, CD_3OD): δ 8.40 (s, 1H, H-2), 7.73 (s, 1H, H-8), 7.32–7.27 (m, 4H, Ph), 7.20 (m, 2H, Ph), 7.10 (m, 1H, Ph), 7.00 (m, 2H, Ph), 6.65 (dd, *J* 3.9 and 0.7 Hz, 1H, =CH), 6.35 (d, *J* 3.9 Hz, 1H, =CH), 5.41 (s, 2H, NCH_2); ^{13}C NMR (150 MHz, CD_3OD): δ 157.7 (Ph), 137.9 (C-8), 134.5 (Ph), 133.8 (Ph), 133.6 (C-4), 134.2 (=C=), 132.2 (C-2), 129.9 (Ph), 129.3 (Ph), 128.2 (Ph), 125.3 (C-5), 123.7 (Ph), 122.8 (C-6), 115.8 (Ph), 100.7 (=CH in allene), 93.1 (=CH in allene), 46.9 (NCH_2); EIMS *m/z* (rel %): 376/374 (37/100, M^+), 299/297 (15/45), 127/125 (21/65); HRMS (EI) found 374.0930, calcd for $C_{21}H_{15}N_4OCl$ 374.0934.

4.1.14. 6-(3-Phenoxypropa-1,2-dienyl)-9-(tetrahydropyran-2-yl)-9*H*-purine (10c). A mixture of compound **9c** (140 mg, 0.42 mmol) and CuI (8 mg, 0.042 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 16 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–EtOH (99:1); yield 54 mg (39%), yellow oil. ^1H NMR (500 MHz, $CDCl_3$): δ 8.39 (s, 1H, H-2), 7.96 (s, 1H, H-8), 7.31–7.28 (m, 2H, Ph), 7.09–7.06 (m, 1H, Ph), 6.99–6.97 (m, 2H, Ph), 6.64 (dd, *J* 3.9 and 0.8 Hz, 1H, CH=), 6.35 (d, *J* 3.9 Hz, 1H, CH=), 5.68–5.66 (m, 1H, H-2 in THP), 4.15 (dd, *J* 11.7 and 2.3 Hz, 1H, H-6_a in THP), 3.74 (dt, *J* 11.7 and 2.3 Hz, 1H, H-6_b in THP), 2.11–2.02 (m, 3H, THP), 1.76–1.62 (m, 3H, THP); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (Ph), 136.2 (C-8), 133.6 (=C=), 132.6 (C-2), 132.0 (C-4), 129.9 (Ph), 125.1 (C-5), 122.0 (C-6), 123.6 (Ph), 115.7 (Ph), 100.8 (=CH in allene), 93.1 (=CH in allene), 82.1 (C-2 in THP), 68.7 (THP), 31.7 (THP), 24.9 (THP), 22.9 (THP); IR (neat) ν_{max} 2947 (m), 2858 (m), 1641 (m), 1579 (m), 1552 (s), 1490 (s) cm^{-1}; EIMS *m/z* (rel %): 334 (24, M^+), 250 (100), 173 (89); HRMS (EI) found 334.1432, calcd for $C_{19}H_{19}N_4O_2$ 334.1430.

4.1.15. 2-Chloro-4-(3-phenoxypropa-1,2-dienyl)-pyrimidine (10d). A mixture of compound **9d** (44 mg, 0.18 mmol) and CuI (4 mg, 0.018 mmol) in Et_3N (5 mL) was refluxed under N_2-atm for 26 h. The compound was isolated by flash chromatography on a silica gel eluting with hexane–EtOAc (4:1); yield 17 mg, (39%), pale yellow oil. ^1H NMR (500 MHz, CD_3OD): δ 8.56 (d, *J* 1.3 Hz, 1H, H-6), 7.37–7.34 (m, 3H, H-5 and 2H in Ph), 7.15–7.12 (m, 1H, Ph), 7.04–7.02 (m, 2H, Ph), 6.43 (s, 2H, 2×CH= in allene); ^{13}C NMR (125 MHz, CD_3OD): δ 158.6 (Ph), 136.1 (C-6), 135.2 (=C=), 134.5 (C-2), 131.2 (Ph), 127.2 (C-4), 125.2 (Ph), 117.2 (Ph), 113.0 (C-5), 103.8 (CH= in allene), 98.7 (CH= in allene); EIMS *m/z* (rel %): 246/244 (25/72, M^+), 169/167 (36/100); HRMS (EI) found 244.0402, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.16. 9-Benzyl-6-(3-phenoxy-1-propynyl)-9*H*-purine (12a). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg,

1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropylamine (854 μL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C. Phenyl propargyl ether (154 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 7 h. The product was isolated by flash chromatography on silica gel eluting with EtOAc–hexane (3:1); yield 145 mg (43%) as a 13:87 mixture of **12a** and **10a**, NMR data for **12a**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.93 (s, 1H, H-2), 8.06 (s, 1H, H-8), 7.33–7.00 (m, 10H, Ph), 5.47 (s, 2H, NCH_2), 5.03 (s, 2H, OCH_2).

4.1.17. 9 Benzyl-6-(4-phenyl-1-butynyl)-9*H*-purine (12b). A mixture of 9-benzyl-6-iodo-9*H*-purine **1a** (336 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. 4-Phenyl-1-butyne (169 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 4 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (1:1); yield 289 (86%), pale brownish oil. ^{1}H NMR (300 MHz, CD_3OD): δ 8.81 (s, 1H, H-2), 8.55 (s, 1H, H-8), 7.35–7.15 (m, 10H, Ph), 5.50 (s, 2H, NCH_2), 3.02–2.98 (m, 2H, CH_2), 2.90–2.84 (m, 2H, CH_2); ^{13}C NMR (75 MHz, CD_3OD): δ 153.3 (C-2), 152.8 (C-4), 148.2 (C-8), 142.6 (Ph), 141.6 (C-6), 137.0 (Ph), 135.1 (C-5), 130.0 (Ph), 129.5 (Ph), 129.4 (Ph), 129.0 (Ph), 127.5 (Ph), 102.5 (C≡), 76.9 (C≡), 48.3 (NCH_2), 35.3 (CH_2), 22.7 (CH_2), one C in Ph was hidden; IR (neat) ν_{max} 3088 (m), 2930 (m), 2862 (m), 2233 (s), 1734 (w), 1710 (w), 1582 (s), 1497 (s) cm^{-1}; EIMS *m/z* (rel %): 338 (72, M^+), 247 (51), 91 (100); HRMS (EI) found 338.1529, calcd for $C_{22}H_{18}N_4$ 338.1531.

4.1.18. 2-Chloro-4-(3-phenoxy-1-propynyl)pyrimidine (12c). A mixture of 2,4-dichloropyrimidine (149 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (4:1); yield 74 mg (30%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.57 (d, *J* 5.0 Hz, 1H, H-6), 7.33 (m, 3H, Ph and H-5), 7.03–6.96 (m, 3H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 161.6 (C-2), 159.6 (C-6), 157.4 (C in Ph), 152.3 (C-4), 129.6 (CH in Ph), 122.0 (C-5), 121.8 (CH in Ph), 114.8 (CH in Ph), 91.1 (C≡), 83.2 (C≡), 56.0 (CH_2); IR (CCl_4) ν_{max} 3043 (w), 2959 (w), 2926 (w), 2860 (w), 2237 (w), 1599 (s), 1590 (s), 1495 (s) cm^{-1}; EIMS *m/z* (rel %): 246/244 (33/100, M^+), 151 (11); HRMS (EI) found 244.0402, calcd for $C_{13}H_9N_2OCl$ 244.0403.

4.1.19. 2-(3-Phenoxy-1-propynyl)pyridine (12d). A mixture of 2-bromopyridine (96 μL, 1.0 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 3 h, and the resulting mixture was stirred for another 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (2:1), yield 79 mg (38%), brownish oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.55 (d, *J* 4.4 Hz, 1H, H-6), 7.61–7.58 (m, 1H, H-3), 7.41–7.39 (m, 1H, H-4), 7.32–7.27 (m, 2H, Ph), 7.24–7.22 (m, 1H, H-5), 7.03–6.95 (m, 3H, Ph), 4.92 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.7 (C in Ph), 150.6 (C-6), 142.5 (C-2), 136.1 (C-3), 129.5 (CH in Ph), 127.3 (C-4), 123.2 (C-5), 121.5 (CH in Ph), 114.9 (CH in Ph), 86.2 (C≡), 84.0 (C≡), 56.3 (CH_2); IR (CCl_4) ν_{max} 3065 (w), 2918 (w), 2862 (w), 1599 (s), 1583 (s), 1495 (s), 1464 (s) cm^{-1}; EIMS *m/z* (rel %): 209 (96, M^+), 116 (100); HRMS (EI) found 209.0831, calcd for $C_{14}H_{11}NO$ 209.0841; Anal. Found: C, 80.35; H, 5.41; N, 6.62. $C_{14}H_{11}NO$ requires C, 80.36; H, 5.30; N 6.69%.

4.1.20. 1-Nitro-4-(3-phenoxy-1-propynyl)benzene (12e). A mixture of 1-bromo-4-nitrobenzene (202 mg, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2.5 h, and the resulting mixture was stirred for 2.5 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (9:1); yield 175 mg (69%), off-white crystals, mp 87–89 °C (lit.[31] 76–77 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18–8.14 (m, 2H, Ph), 7.57–7.54 (m, 2H, Ph), 7.34–7.24 (m, 2H, Ph), 7.02–6.98 (m, 3H, Ph), 4.93 (s, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.0 (C in Ph), 147.8 (C in Ph), 133.0 (CH in Ph), 130.0 (CH in Ph), 129.5 (C in Ph), 124.0 (CH in Ph), 122.2 (CH in Ph), 115.3 (CH in Ph), 89.7 (C≡), 85.6 (C≡), 56.8 (CH_2); EIMS *m/z* (rel %): 253 (97, M^+), 160 (100); HRMS (EI) found 253.0733, calcd for $C_{15}H_{11}NO_3$ 253.0738.

4.1.21. (3-Phenoxy-1-propynyl)benzene (12f). A mixture of iodobenzene (112 μL, 1.00 mmol), $(PPh_3)_2PdCl_2$ (35 mg, 0.05 mmol), CuI (19 mg, 0.10 mmol), and diisopropyl(ethyl)amine (1.02 mL, 6.00 mmol) in DMF (5 mL) was heated to 60 °C under N_2-atm. Phenyl propargyl ether (158 μL, 1.20 mmol) in DMF (1 mL) was added dropwise over 2 h, and the resulting mixture was stirred for 3 h. The product was isolated by flash chromatography on silica gel eluting with hexane–EtOAc (9:1); yield 208 mg (quant.), off-white crystals, mp 44–45 °C (lit.[31] 44 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44–7.41 (m, 2H, Ph), 7.33–7.24 (m, 5H, Ph), 7.04–6.96 (m, 3H, Ph), 4.91 (CH_2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.8 (Ph), 131.8 (Ph), 129.5 (Ph), 128.6 (Ph), 128.3 (Ph), 122.3 (Ph), 121.4 (Ph), 115.0 (Ph), 87.1 (C≡), 83.9 (C≡), 56.6 (CH_2); EIMS *m/z* (rel %): 208 (40, M^+), 115 (100); HRMS (EI) found 208.0885, calcd for $C_{15}H_{12}O$ 208.0888.

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