ELSEVIER

Tetrahedron

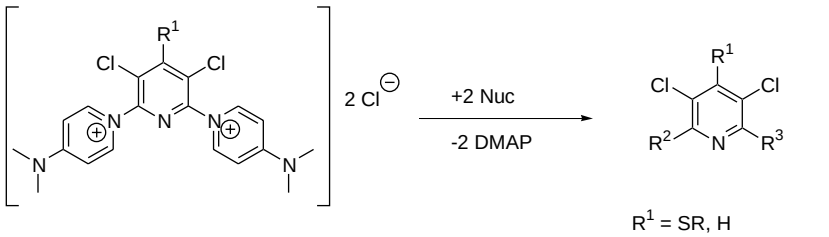
Tetrahedron Vol. 62, No. 8, 2006

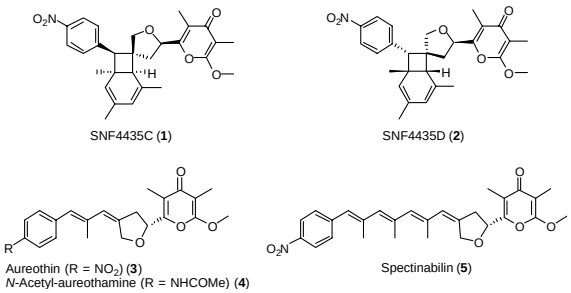
Contents

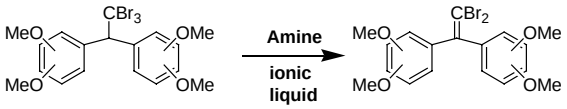
REPORT

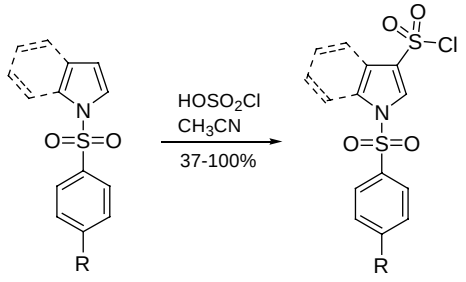
Asymmetric domino reactions are reviewed for the first time. The first part of the review deals with asymmetric domino reactions based on the use of chiral auxiliaries, covering the classification and characteristics of these reactions together with the most important applications. This compilation clearly demonstrates that the concept of asymmetric domino reactions has emerged as a powerful tool in asymmetric synthetic chemistry.

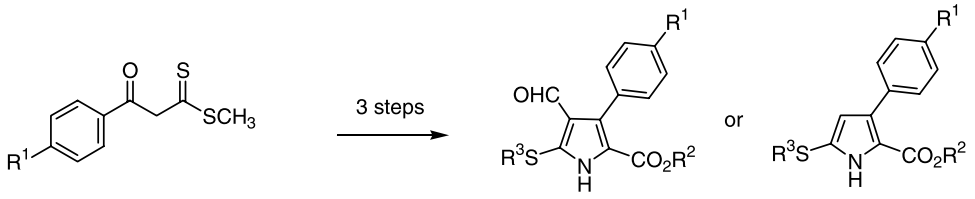
ARTICLES

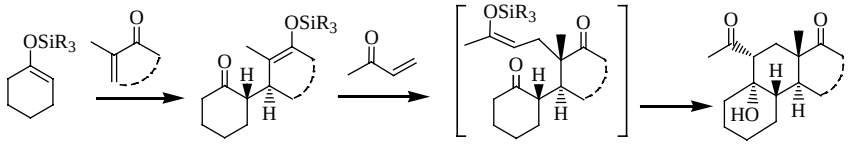


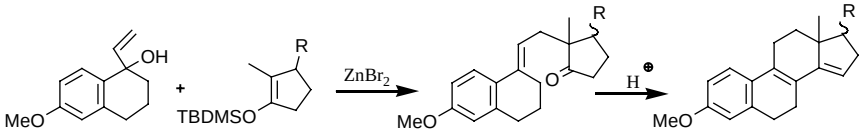


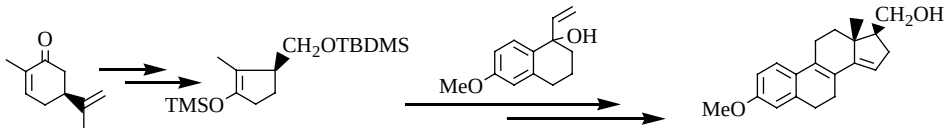


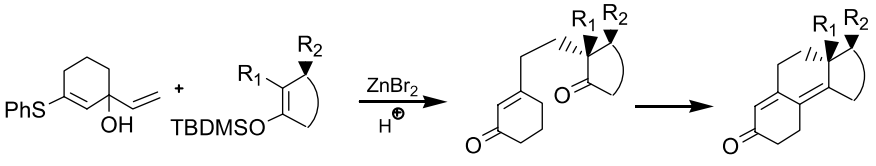


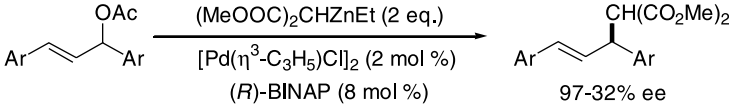


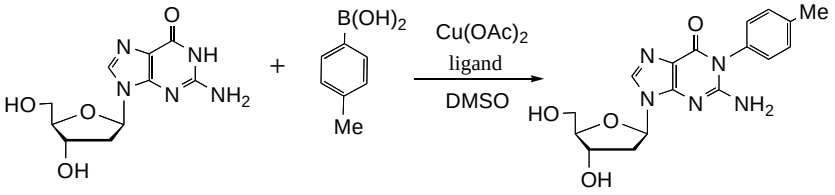


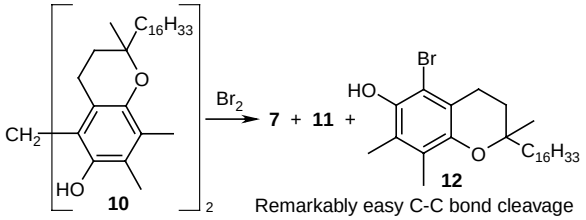




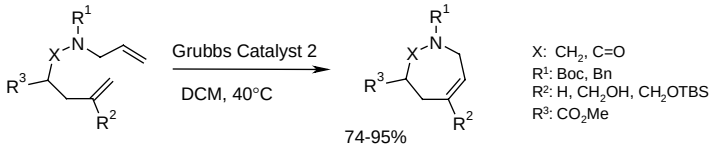


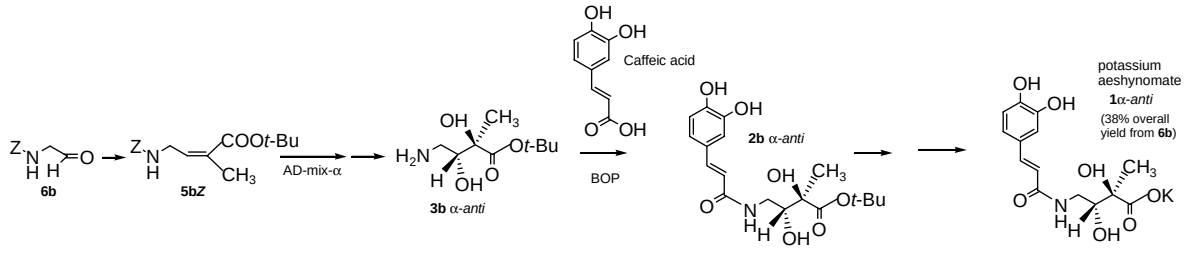


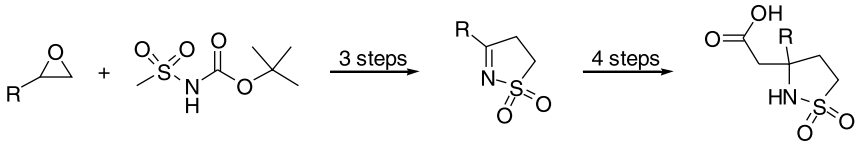




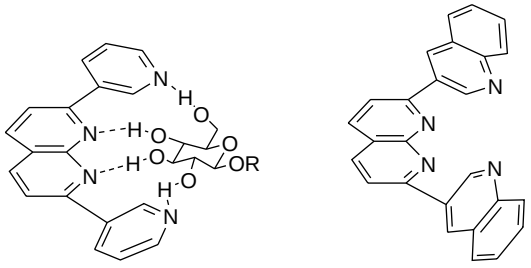
Bromination of ethano-dimer **6** afforded the pyrano-spirodimer **7** quantitatively, while methano-dimer **10** gave a product mixture, including furano-spirodimer **11**, pyrano-spirodimer **7**, and 5-bromo-γ-tocopherol (**12**), the latter being formed in an unusual dealkylation step.



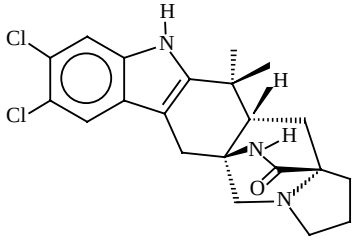


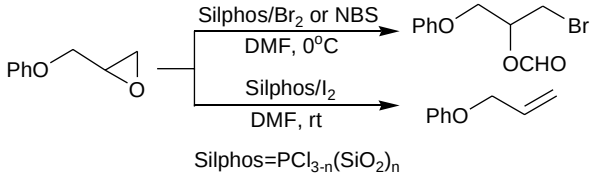


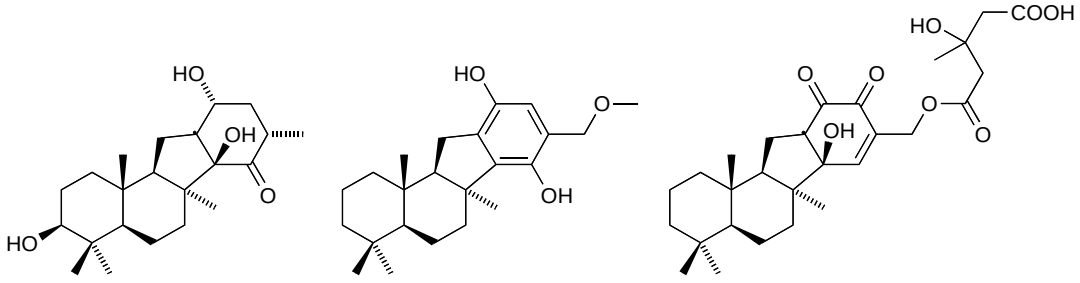
The recognition capabilities of two molecular receptors toward monosaccharides were evaluated. The binding processes were studied by UV–vis, fluorescence and ^{1}H NMR spectrophotometric titrations as well as electrospray ionization mass spectroscopy. The binding strength between the two receptors and examined monosaccharides was comparable to that for many other hydrogen-bonding host molecules previously reported.

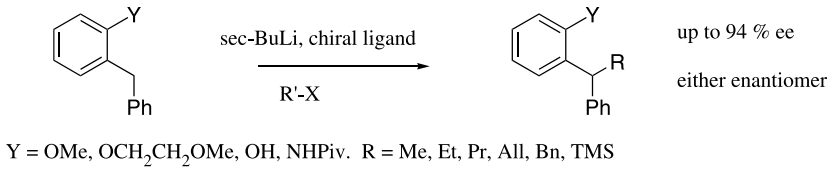


Malbrancheamide (**1**) is a novel indole alkaloid whose structure was unequivocally established by NMR, MS and X-ray studies. It caused moderate inhibition of radicle growth of *Amaranthus hypochondriacus* ($IC_{50}=0.37$ μM) and inhibited the activation of the calmodulin (CaM)-dependent enzyme PDE1 ($IC_{50}=3.65\pm0.74$ μM). The inhibition mechanism was competitive with respect to CaM according to a kinetic analysis ($Ki=47.4\pm5.63$ μM).

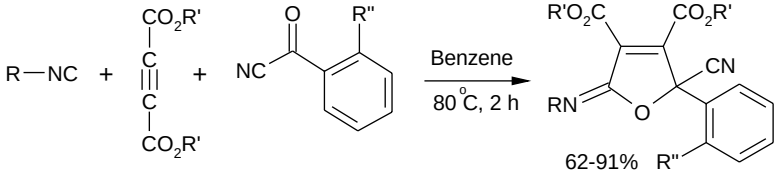


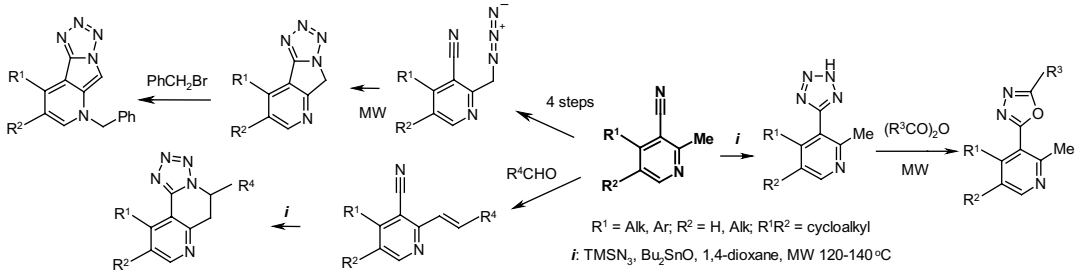


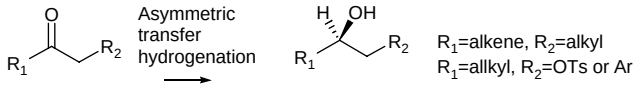


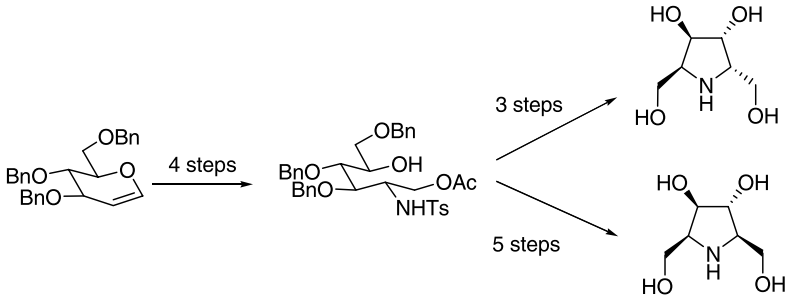


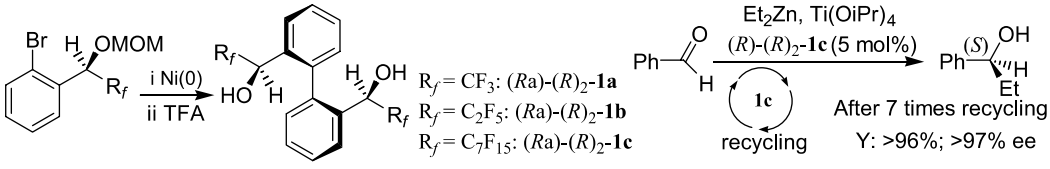
Y = OMe, OCH_2CH_2OMe, OH, NHPiv. R = Me, Et, Pr, All, Bn, TMS

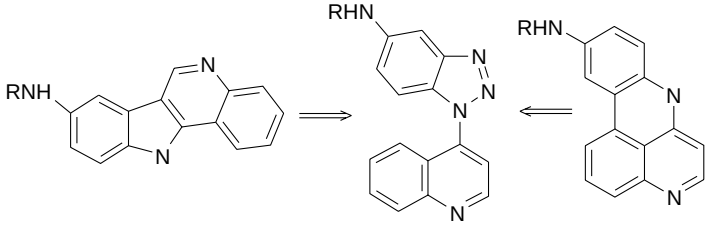












The synthesis of original thiazoloindolo[3,2-*c*]quinoline and quinolinoquinoline rings system was investigated from benzotriazoles following a microwave-assisted Graebe–Ullmann cyclization.

OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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

ELSEVIER

ISSN 0040-4020

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1619–1665

Tetrahedron report number 750

Asymmetric domino reactions. Part A: Reactions based on the use of chiral auxiliaries

Hélène Pellissier*

UMR no. 6180, Faculté des Sciences de Saint-Jérôme, Avenue Esc. Normandie-Niemen, 13397 Marseille Cedex 20, France

Received 24 September 2005

Available online 2 December 2005

In memory of Cyril and Valérie Pellissier

Contents

Keywords: Asymmetric domino reactions; Chiral auxiliary; Asymmetric synthesis.

Abbreviations used: Ac, acetyl; Acac, acetylacetone; AIBN, 2,2′-azobisisobutyronitrile; Ala, alanine; Ar, aryl; BAIB, bisacetoxyiodobenzene; BINAP, 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl; $BF_3 \cdot Et_2O$, boron trifluoride etherate; BHT, 2,6-di-*tert*-butyl-4-methylphenol; Bipc*2*, diisopinocampheylborane; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu, butyl; Bz, benzoyl; c, cyclo; Cbz, benzyloxycarbonyl; COD, cyclooctadiene; Cp, cyclopentadienyl; CSA, 10-camphorsulphonic acid; dba, (*E*,*E*)-dibenzylideneacetone; DBU, 1,8-dazabicyclo[5.4.0]undec-7-ene; DCA, 9,10-dicyanoanthracene; DDQ, 2,3-dichloro-5,6-dicyanobenzoquinone; de, diastereomeric excess; DMF, dimethylformamide; DMSO, dimethylsulphoxide; dppp, 1,3-bis(diphenylphosphino)propane; dr, diastereomeric ratio; ee, enantiomeric excess; Et, ethyl; Gly, glycine; Hex, hexyl; HFIP, hexafluoro-2-propanol; HMDS, bis(trimethylsilyl)amide; HMTA, hexamethylenetetramine; IBX, *o*-iodoxybenzoic acid; Ipc, isopinocampheyl; LA, Lewis acid; LDA, lithium diisopropylamide; MAPh, Methyl aluminium bis(2,6-diphenylphenoxide); MCPBA, 3-chloroperoxybenzoic acid; Me, methyl; Ms, mesyl; MOM, methoxymethyl; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NIS, *N*-iodosuccinimide; Np, naphthyl; PCC, pyridinium chlorochromate; Pent, pentyl; Ph, phenyl; Pht, phthalimido; Piv, pivaloyl; PMB, *p*-methoxybenzoyl; PMP, *p*-methoxyphenyl; PNB, *p*-nitrobenzyl; PPA, polyphosphoric acid; Pr, propyl; py, pyridine; TBDMS, *tert*-butyldimethylsilyl; TBDPS, *tert*-butyldiphenylsilyl; TEMPO, 2,2,6,6-tetramethyl-1-piperidinyloxy; Tf, trifluoromethanesulphonyl; TFA, trifluoroacetic acid; TFE, trifluoroethanol; TfOH, triflic acid; TFSA, trifluoromethanesulphonic acid; THF, tetrahydrofuran; THP, tetrahydropyranyl; TIPS, triisopropylsilyl; TMP, 2,4,6-trimethoxyphenyl; TMS, trimethylsilyl; TMSOTf, trimethylsilyl trifluoromethanesulphonate; Tol, toluene; Tr, triphenylmethyl(trityl); Troc, 2,2,2-trichloroethoxycarbonyl; Ts, 4-toluenesulphonyl(tosyl); TsOH, *p*-toluenesulphonic acid.

* Tel.: +33 4 91 28 27 65; e-mail: h.pellissier@univ.u-3mrs.fr

doi:10.1016/j.tet.2005.10.040

1. Introduction

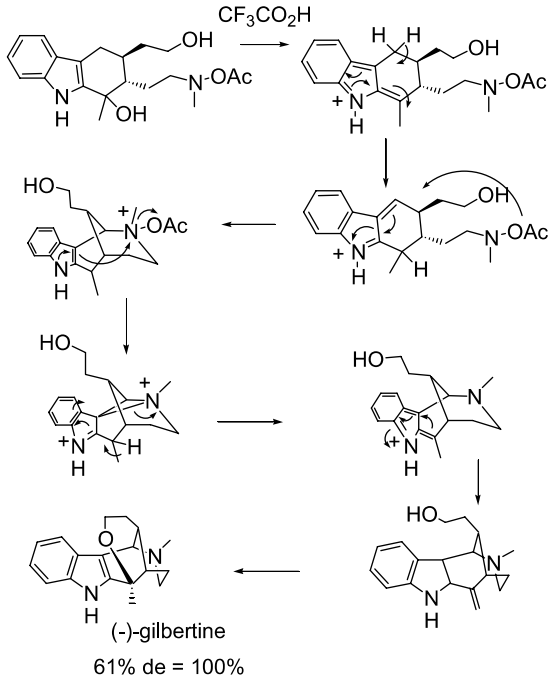
A main issue in modern synthetic organic chemistry, which deals with the preparation of natural products, pharmaceuticals, diagnostics, agrochemicals, and other important materials, is the improvement of efficiency, the avoidance of toxic reagents, the reduction of waste, and the responsible treatment of our resources. One of the ways to fulfil these goals is the development and use of domino processes, which consist of several bond-forming reactions and which allow the highly efficient synthesis of complex molecules starting from simple substrates. The relationship between structural complexity and the number of steps in a synthesis must be improved. Multistep syntheses with more than 20 steps have to be avoided, because they are neither economically nor ecologically justifiable. Thus, modern syntheses must deal carefully with our resources and our time, must reduce the amount of waste formed, should use catalytic transformations and, finally, must avoid all toxic reagents and solvents. Tietze has defined a domino reaction as involving two or more bond-forming transformations, which take place under the same reaction conditions, without adding additional reagents and catalysts, and in which the subsequent reactions result as a consequence of the functionality formed by bond formation or fragmentation in the previous step.[1] Domino reactions can be classified according to the mechanism of the single steps, which may be of the same, or of different, types (cationic, anionic, radical, pericyclic, or transition-metal-catalysed transformations). The quality and importance of a domino reaction can be correlated to the number of bonds generated in such a process and the increase of complexity. They can be performed as single-, two- and multicomponent transformations. Thus, most, but not all, of the known multicomponent processes can be defined as a subgroup of domino reactions. The use of domino and domino multicomponent reactions in asymmetric synthesis is increasing constantly. Such single-step reactions allow the synthesis of a wide range of structurally diverse compounds in an efficient and economic way by using processes that are reasonably simple. They allow the efficient synthesis of complex molecules from simple substrates in an ecologically and economically favourable manner. The reactions can be performed in solution, as well as on solid support, and provide facile access to highly diverse molecules; in addition, their use in automated synthesis is possible.[2] These processes are sometimes also called cascade or tandem reactions. The use of such terms should, however, be avoided because they do not correspond to the proper meaning of these transformations and, more importantly, these expressions are used in many other connections and must make data bank searches very difficult. In contrast, the expression 'domino' is unambiguous. While it is desirable that the whole process proceeds without changing the conditions, raising the temperature or adding a reagent may be allowed. Domino reactions have gained wide acceptance, because they increase synthetic efficiency by decreasing the number of laboratory operations required and the quantities of chemicals and solvents used. The proliferation of domino reactions is evidenced by the number of recent reviews covering the literature through 1992.[3] The asymmetric aspect of the domino methodology has not yet, however, been reviewed (except for multicomponent reactions)[4] and, with this review, the author would like to fill this gap. It is difficult to organise a review that covers such a diverse array of transformations. As in previous reviews, the domino reactions are catalogued on the basis of the reaction intermediates or, in some cases, the reaction types involved in the first two synthetic steps. It is, of course, impossible to locate all the published examples of asymmetric domino reactions, since many are incorporated in total syntheses advertised under different keywords. The cases cited in this review, which is divided into two parts, have been selected to highlight the most promising applications of asymmetric domino reactions to organic synthesis. To facilitate presentation, the work is divided into two parts: (A) domino reactions using chiral auxiliaries; and (B) domino reactions catalysed by chiral catalysts, and asymmetric biocatalysed domino reactions. Each part is then subdivided, taking as a basis the reaction type of the first two synthetic steps. Since this review covers such a diverse array of reactions, it was difficult to organise and, therefore, for a few examples involving multicomponent reactions, it was decided to make these appear in a given section, whereas they could also be included in sections devoted to asymmetric multicomponent reactions. In addition, it must be noted that procedures needing the evaporation under vacuum of a solvent or a reagent in excess, before the second step of the domino process, have been deliberately excluded.

2. Chiral auxiliaries

2.1. Cationic sequences

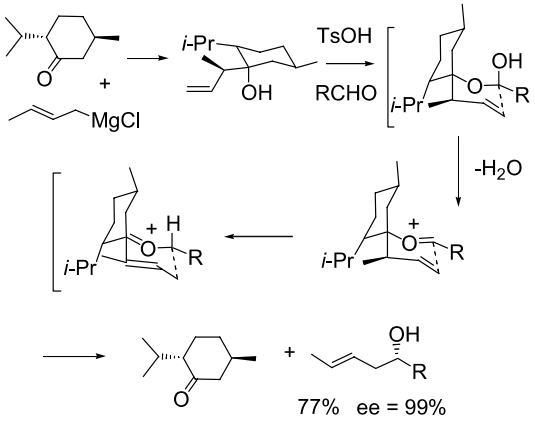
Cationic-mediated reactions constitute one of the oldest known subsets of domino reactions. In this process, a carbocation is formed, either formally or in reality. This carbocation can be formed by elimination, or by addition of a positive particle such as a proton. The carbocation then reacts with a nucleophile to form a new carbocation that undergoes one or more comparable further transformations in a cationic–cationic process, finally being trapped by a nucleophile or stabilised by elimination of a proton. The biomimetic cyclisation of polyenes is of great biological importance. An application of the acid-catalysed cyclisation of polyenes for the biomimetic synthesis of steroids was studied by Johnson et al. who demonstrated the effectiveness of a C-8 fluoro atom as a cation-stabilising auxiliary for enhancing the polyene cyclisations.[5] Various cationic cascade cyclisations have been developed[6] such as that applied to the first enantioselective synthesis of (−)-gilbertine (Scheme 1).[7]

A domino Ferrier rearrangement cyclisation has been used to prepare chiral pyrano[2,3-*b*][1]benzopyrans by a one pot cation-mediated process. Reaction of 2-*C*-acetoxymethylgalactal with *p*-chlorophenol in the presence of $BF_3 \cdot Et_2O$ resulted in an exocyclic Ferrier rearrangement, followed by an intramolecular cyclisation to the chiral pyrano[2,3-*b*]-[1]benzopyran.[8] In 1994, Nicolaou et al. reported the synthesis of the core scaffold of zaragozic acid A, based on an acid-catalysed rearrangement of a tricyclic ketal lactone.[9] Optically active strychnan- and aspidospermatan-type alkaloids have been synthesised by Kuehne et al. starting from an enantiopure tryptophan derivative. The key



Scheme 1. Synthesis of (−)-gilbertine via cationic cascade cyclisation.

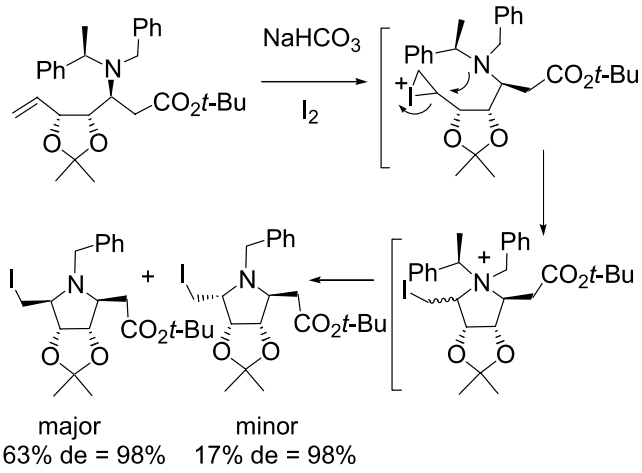
sequence involved a cascade of a condensation, a [3,3]-sigmatropic rearrangement and a termination by a Mannich-type cyclisation.[10] On the other hand, an asymmetric menthone-monitored crotylation of aldehydes was developed by Nokami et al.[11] The reaction mechanism was rationalised as the initial formation of a hemi-acetal, after which an acid-catalysed dehydration an oxonium ion was generated, and this rearranged, adopting a chair-like transition state in an oxonia-Cope-type [3,3]-sigmatropic process (Scheme 2).



Scheme 2. Asymmetric menthone-monitored crotylation of aldehydes.

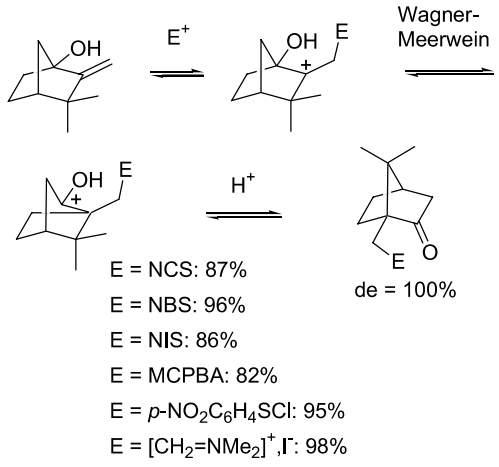
In 2004, Davies et al. provided a direct route for the asymmetric synthesis of polyhydroxylated pyrrolidines from homochiral β-amino acid derivatives, based on an iodine-mediated ring-closing alkene iodoamination with concomitant *N*-debenzylation (Scheme 3).[12]

Cerero et al. have demonstrated that valuable chiral sources of C(10)-substituted camphors or fenchones could be straightforwardly obtained by treatment of an appropriate,



Scheme 3. Asymmetric synthesis of polyhydroxylated pyrrolidines.

easily obtainable, camphor- or fenchone-derived 2-methyl-enenorbornan-1-ol with an electrophilic reagent. The process took place via a domino regioselective carbon–carbon double-bond addition stereocontrolled Wagner-Meerwein rearrangement (Scheme 4).[13]

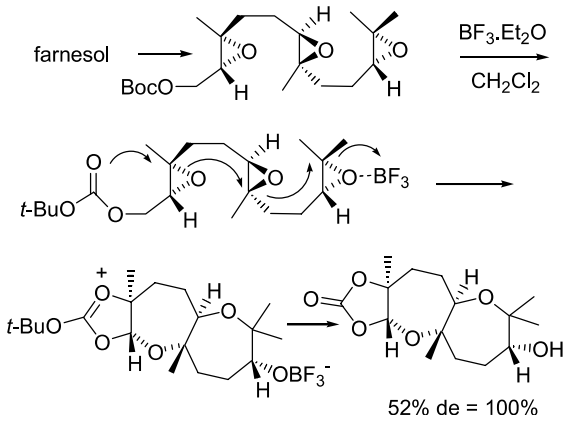


Scheme 4. Asymmetric domino carbon–carbon double-bond addition Wagner-Meerwein rearrangement reaction.

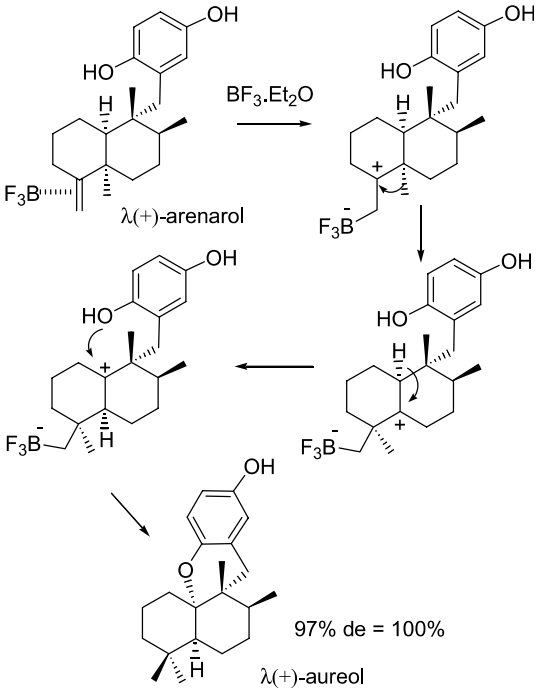
In 2002, McDonald et al. reported the *endo*-oxacyclisations of polyepoxides derived from various acyclic terpenoid polyalkenes, including geraniol, farnesol, and geranylgeraniol, providing an efficient and stereoselective synthesis of substituted oxepanes and fused polyoxepanes.[14] This domino *endo*-regioselective and trans-stereoselective oxacyclisation of 1,5-, 1,5,9-, and 1,5,9,13-polyepoxides was promoted by boron trifluoride-etherate (Scheme 5).

Another domino boron trifluoride-etherate-promoted reaction was developed by Katoh et al. involving a rearrangement cyclisation reaction of (+)-arenarol to form (+)-aureol (Scheme 6).[15]

In addition, these authors reported a total synthesis of the tetracyclic core of (+)-stachyflin, a potent anti-influenza A virus agent, which featured a boron trifluoride-etherate-induced domino epoxide-opening rearrangement cyclisation reaction as the key step (Scheme 7).[16]



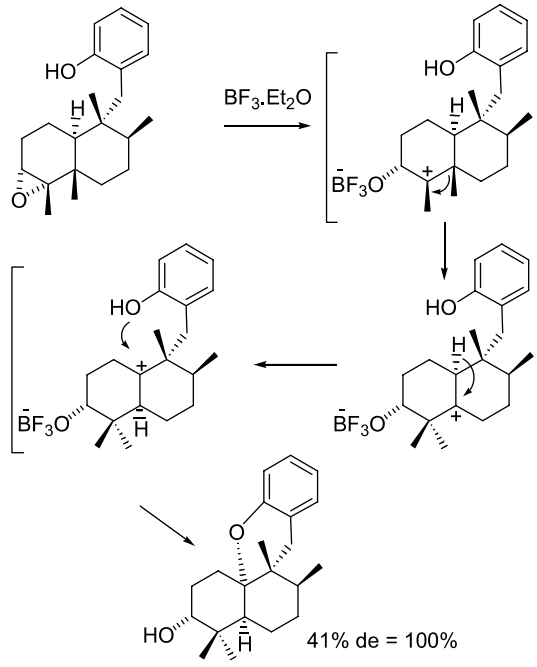
Scheme 5. Asymmetric domino *endo*-oxacyclisations reaction of polyepoxides.



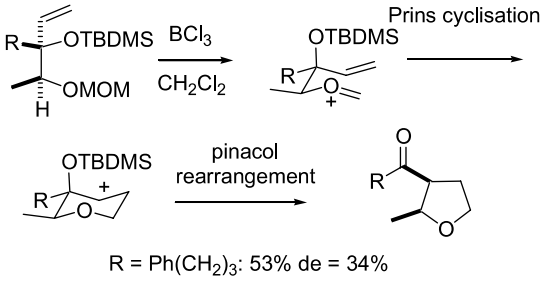
Scheme 6. Asymmetric domino rearrangement cyclisation reaction of (+)-arenarol.

Overman's group began their involvement with domino reactions in 1979, with the invention of the aza-Cope–Mannich reaction for synthesising substituted pyrrolidines.[17] In subsequent years, this transformation has been shown to be of exceptional value for the stereocontrolled synthesis of alkaloid natural products such as (−)-strychnine.[18] Another domino process that has been of considerable interest in the same group was the acid-promoted pinacol-terminated Prins cyclisation reaction (Scheme 8).[19] This latter domino reaction has been the key strategic element in the total synthesis of heterocyclic and carbocyclic natural products such as (−)-citreoviral,[20] cladiellin and briarellin diterpenes,[21] (−)-magellanine and (+)-magellaninone,[22] and shahamin K.[23]

On the other hand, Fadel et al. have developed an easy and efficient one pot synthesis of enantiopure (+)-1-amino-2-methylcyclopropanephosphonic acid and its antipode from

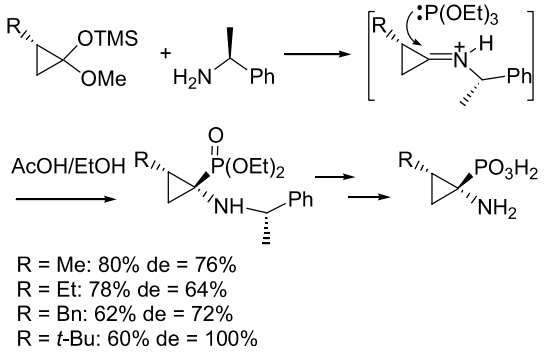


Scheme 7. Asymmetric domino epoxide-opening rearrangement cyclisation reaction.



Scheme 8. Asymmetric domino pinacol-terminated Prins cyclisation reaction.

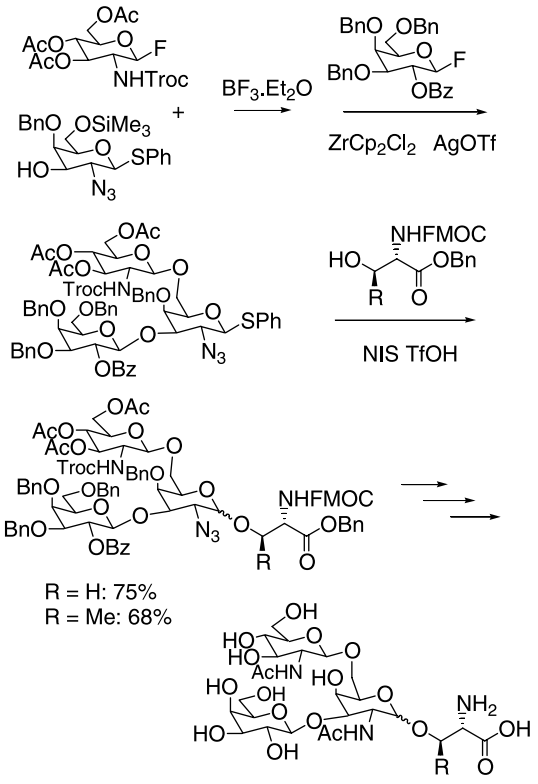
the readily available racemic methylcyclopropanone acetal.[24] This latter compound added a chiral amine to give the corresponding iminium intermediate, which then underwent triethyl phosphite addition to furnish the final aminophosphonate (Scheme 9).



Scheme 9. Asymmetric one pot synthesis of 1-amino-2-methylcyclopropanephosphonic acid.

The one pot sequential glycosylation is based on sequential activation of glycosyl donors to provide linear oligosaccharides. Although this methodology implies the successive

addition of the glycosyl donors, it could be considered as a powerful domino process. This procedure has recently been applied to the synthesis of F1α antigen,[25] phytoalexin-elicitor active heptasaccharide,[26] and core 2 class branched glycosylamino acids (Scheme 10).[27]

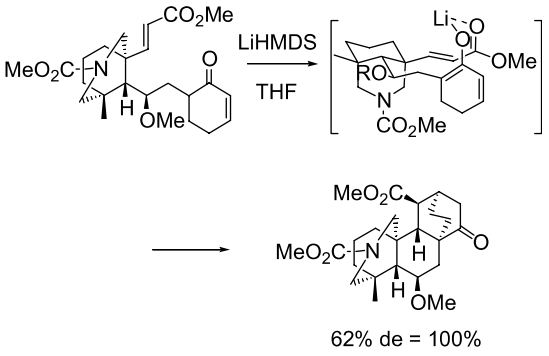


Scheme 10. Synthesis of core 2 class glycosylamino acids via one pot sequential glycosylation.

2.2. Anionic primary step

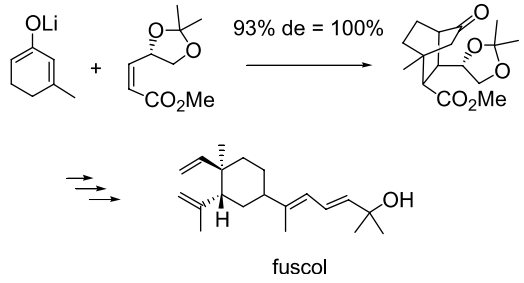
The largest family of domino reactions involves anionic intermediates. In reactions of this type, the primary step is the formation of an anion or a nucleophile. The majority of cases involve the deprotonation of a CH group with the formation of a carbanion, which then reacts with an electrophile to form a new anionic functionality. This anion then attacks another electrophile in an anionic–anionic process. The sequence is completed by reaction with an electrophile, for example, a proton, or, by elimination of an X^- group. In the case of an anionic–pericyclic process, the anion formed in the anionic step is converted into a compound containing a multiple bond, which is then capable of undergoing a pericyclic reaction. Finally, a third class of anionic domino reactions is constituted by reactions in which the second step is neither an anionic nor a pericyclic process. The family of domino reactions involving anionic intermediates has been used extensively in total syntheses.

2.2.1. Anionic–anionic reactions. A large fraction of anionic–anionic processes involve either a Michael-initiated or -terminated process and generate a cyclic structure. The Michael–Michael domino reaction is a powerful tool in forging ring systems common to many natural products. Several elegant applications of the asymmetric intramolecular double Michael reaction have been described by Fukumoto et al. such as the synthesis of oxygenated derivatives of the diterpene alkaloid, atisine (Scheme 11),[28] and the first total synthesis of the naturally occurring enantiomer of tylophorine.[29]



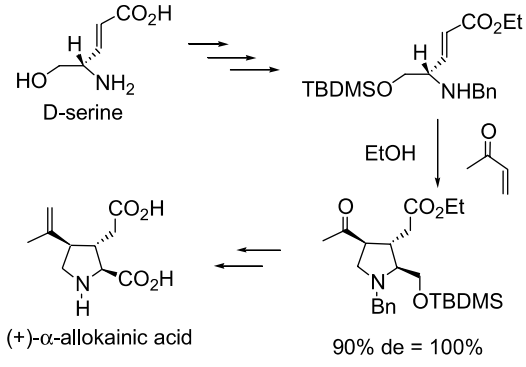
Scheme 11. Asymmetric intramolecular double Michael reaction.

A number of intermolecular versions of this domino reaction have been developed involving various chiral auxiliaries.[30] In a beautiful example, depicted in Scheme 12, this procedure was used as the first step of an enantioselective synthesis of the diterpene, fuscol.[31]



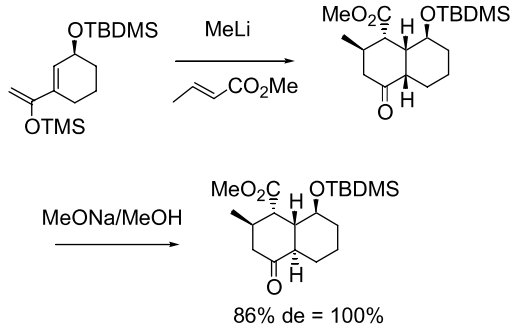
Scheme 12. Synthesis of fuscol via asymmetric intermolecular double Michael reaction.

In 1990, Benetti et al. reported a concise enantioselective route to (+)- and (−)-α-allokainic acid from D- and L-serine, respectively, based on the asymmetric domino Michael reaction methodology (Scheme 13).[32] In addition, an enantioselective synthesis of (−)-meroquinene was accomplished by these authors by the use of (−)-menthyl (*E*)-5-(*N*-benzylamino)-2-pentenoate as the chiral auxiliary.[33]



Scheme 13. Synthesis of (+)-α-allokainic acid via asymmetric intermolecular double Michael reaction.

In 1993, Hagiwara et al. studied the reaction of kinetic enolates or trimethylsilyl enol ethers of 1-acetylcyclohexenes with various acrylates of chiral alcohols such as (−)-menthol or (−)-binaphthol.[34] Application of these double Michael reactions has enabled the syntheses of ε-cadinene, khusitone and khusilal to be accomplished. In addition, the total syntheses of (+)-compactin and the phytotoxins, solanapyrones D and E, were achieved by employing a double Michael reaction of (*R*)-1-acetyl-3-(*tert*-butyldimethylsiloxy)cyclohexene with methyl crotonate as the key reaction (Scheme 14).[35,36] On the other hand, a double Michael reaction between nitromethane, a chiral α,β-unsaturated ketone, 16-dehydropregnenolone acetate, and different alkyl acrylates was reported in 2004, providing the corresponding 1,7-dicarbonyl compounds in only modest stereoselectivity.[37]



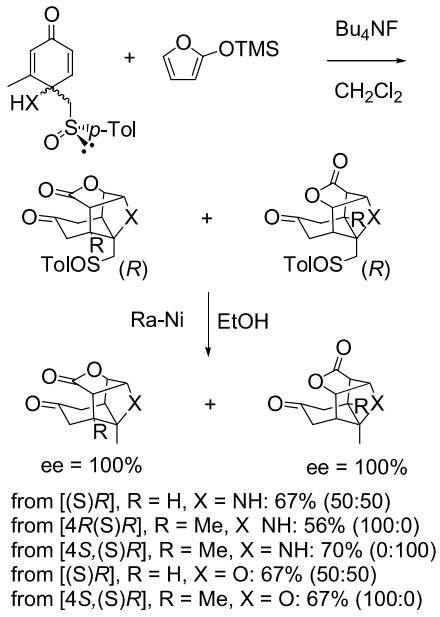
Scheme 14. Synthesis of the decalin portion of phytotoxins, solanapyrones D and E, based on domino Michael strategy.

In 2002, Carreno et al. reported the achievement of a highly stereoselective synthesis of various tetracyclic cage compounds bearing two heterocyclic rings through the reaction between [(*S*)*R*]-4-amino- or 4-hydroxy-4-[(*p*-tolylsulphinyl)-methyl]cyclohexa-2,5-dienone derivatives and 2-(trimethylsilyloxy)furan. This combination provided a short and simple access to optically pure heterotetracyclic cage compounds, not accessible by other methods, through a one pot, domino, and triple-conjugate addition process (Scheme 15).[38]

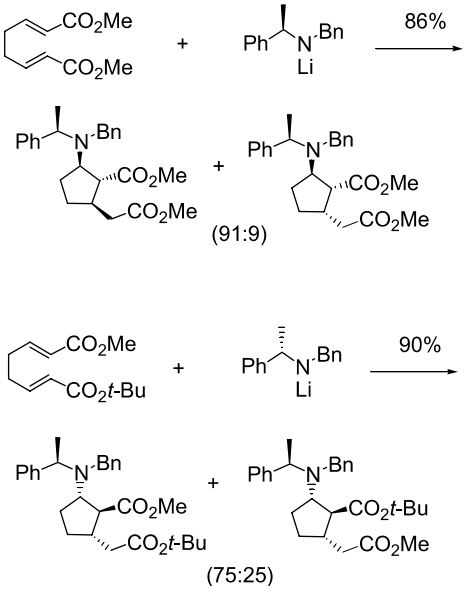
The asymmetric synthesis of orthogonally functionalised 2-*N*-benzyl-*N*-α-methylbenzylamino-5-carboxymethyl-cyclopentane-1-carboxylates was achieved by a domino reaction involving an asymmetric Michael addition and a subsequent 5-*exo*-*trig* intramolecular cyclisation (Scheme 16).[39] Very recently, this reaction has been extended to a range of diester derivatives of (*E*,*E*)-nona-2,7-dienedioic acid, providing the corresponding cyclohexanic 1,2-*anti*-1,6-*anti*-cyclic β-amino esters in >95% diastereoisomeric excesses.[40]

Chan et al. have studied the condensation of secondary amines onto chiral acetylenic sulphoxides followed by acid-induced cyclisation, providing an approach to the enantioselective syntheses of pentacyclic yohimbine alkaloids (Scheme 17) and structures of the tetrahydroisoquinoline skeleton such as (*S*)-(−)-carnegine.[41]

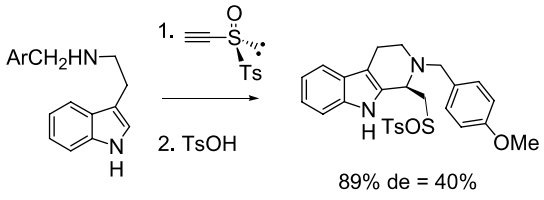
The domino Michael addition S_N2 reaction is also known as the Michael-initiated ring closure (MIRC) reaction. Enders et al. have recorded excellent enantioselectivities in Michael S_N2 reactions of hydrazones, for example, deprotonation of hydrazone, depicted in Scheme 18, followed by reaction with methyl (*E*)-6-bromo-2-hexenoate afforded the



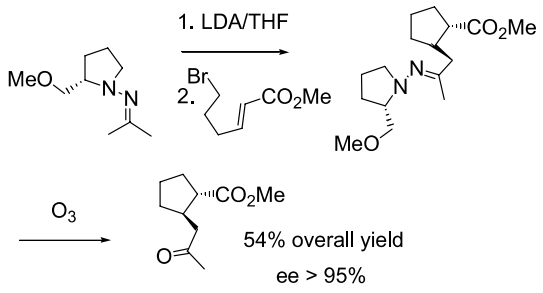
Scheme 15. Synthesis of heterocyclic cage compounds by domino triple-conjugate addition process.



Scheme 16. Asymmetric synthesis of polyfunctionalised cyclopentane derivatives by domino Michael reactions.



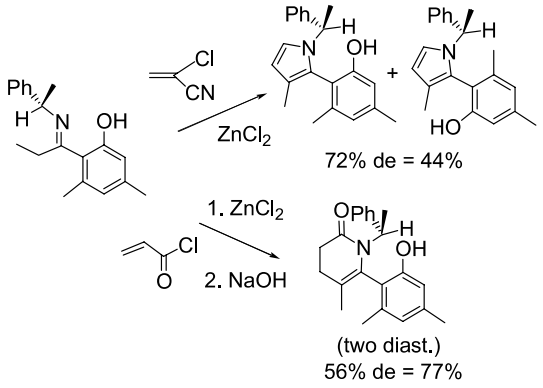
Scheme 17. Asymmetric domino Michael acid-induced cyclisation of amine to chiral acetylenic sulphoxide.



Scheme 18. Asymmetric MIRC reaction of hydrazone.

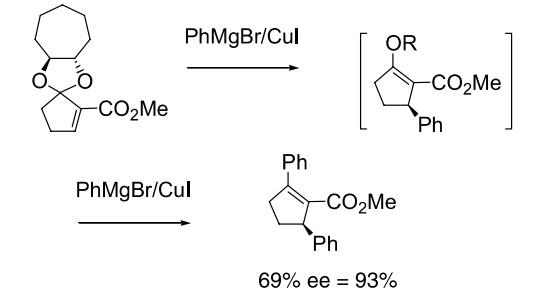
corresponding MIRC product.[42] Another asymmetric MIRC was studied by Little et al. involving a series of chiral esters of ω-bromo-2-alkenoic acids.[43]

More recently, new classes of atropisomeric compounds consisting of five- or six-membered azaheterocycles bearing an aryl substituent have been prepared from chiral imines, through an efficient asymmetric domino Michael reaction azacyclisation process (Scheme 19).[44]



Scheme 19. Asymmetric domino Michael reaction azacyclisation process of chiral imines.

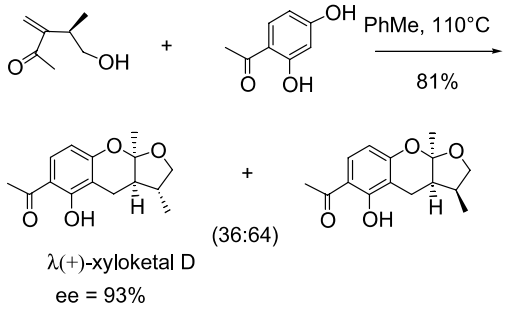
An intriguing asymmetric domino reaction initiated by an organometallic species was the double conjugate addition elimination from the reaction of PhMgBr/CuI with the chiral ketal depicted in Scheme 20.[45]



Scheme 20. Asymmetric domino double conjugate addition elimination process.

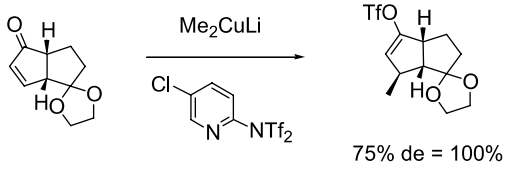
In 1995, Chen et al. reported the synthesis of enantiomerically pure 5-(*l*-menthyloxy)-3,4-dibromo-2(5*H*)-furanone and its asymmetric domino Michael addition elimination reaction in the presence of thiols and amines, providing a series of new chiral polyfunctionalised furanones.[46]

A number of asymmetric domino reactions consist of a Michael addition followed by an electrophilic trapping reaction. Thus, Hruby described in 1993 examples of asymmetric 1,4-conjugate addition of organocuprates to prochiral α,β-unsaturated 4-(*S*)-phenyl-*N*-crotonyl-oxazolidinone, followed by electrophilic bromination, furnishing precursors of unusual amino acids.[47] On the other hand, the alkylation by allyl halides of the intermediate enolate, prepared in situ by the conjugate addition of di-*p*-tolylcuprate to chiral (*p*-tolylsulphinyl)pyrrolyl cinnamoyl amide, gave the (2*R*,3*R*)-adducts as the major products with 81–94% de.[48] The key step of the total synthesis of (+)-kalkitoxin, reported in 2004 by White et al. was the installation of the *anti–anti* methyl stereotriad by means of a domino asymmetric conjugate addition of an organocopper species to an α,β-unsaturated *N*-acyl oxazolidin-2-one, followed in situ by α-methylation of the resultant enolate.[49] In order to form partially modified retropeptide mimetics incorporating a trifluoroalanine surrogate, a novel highly stereoselective domino aza-Michael addition enolate protonation was elaborated from the reaction between α-amino esters and *N*-(α-trifluoromethyl)acryloyl-α-amino esters.[50] Krohn et al. demonstrated in 2004 that heating optically active 5-hydroxy-4-methyl-3-methylenepentan-2-one (*R*) in toluene with 2,4-dihydroxyacetophenone led to the one pot formation of (+)-xyloketal D via a domino reaction involving a Michael addition, followed by a spontaneous ketal formation (Scheme 21).[51]



Scheme 21. Asymmetric domino Michael addition ketal formation reaction.

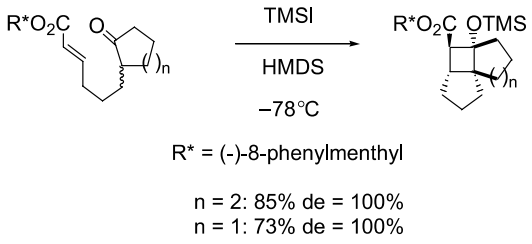
The first enantioselective total synthesis of cylindramide reported in 2005 by Laschat et al. was based on a Michael addition of Me_2CuLi to a chiral bicyclic enone, followed by in situ trapping with the Commins reagent (Scheme 22).[52]



Scheme 22. Asymmetric domino Michael addition trapping reaction with Commins reagent.

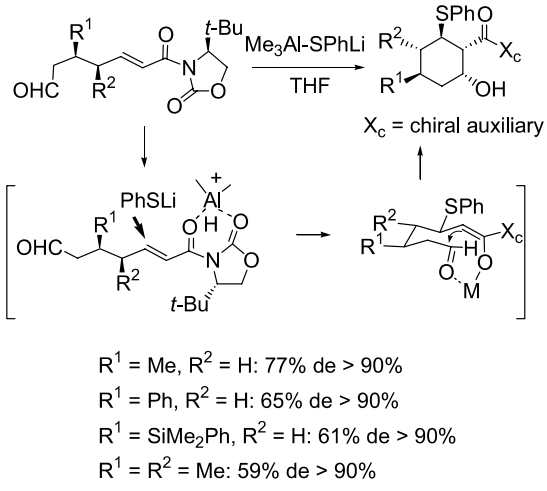
An asymmetric domino three-component synthesis of β-lactams was based on Michael addition of lithium dialkylcuprates with chiral Michael acceptors, for example, Oppolzer's *N*-enoyl-2,10-camphorsultams or Evans' *N*-enoyl-4-phenyl-1,3-oxazolidin-2-ones, and *N*-(methoxycarbonylmethylidene)(4-methoxyphenyl)amine to afford

the corresponding *cis*-3-alkyl-4-methoxycarbonyl-1-(4-methoxyphenyl)azetidin-2-ones in yields of 40–67% and ees of 91–99%.[53] An extremely potent synthetic methodology to obtain optically pure tricyclic cyclobutanes was provided by the development of the asymmetric modification of the intramolecular version of the Michael aldol reaction using (−)-phenylmenthyl enoates as chiral auxiliaries (Scheme 23).[54]



Scheme 23. Asymmetric intramolecular Michael aldol reaction of (−)-phenylmenthyl enoates.

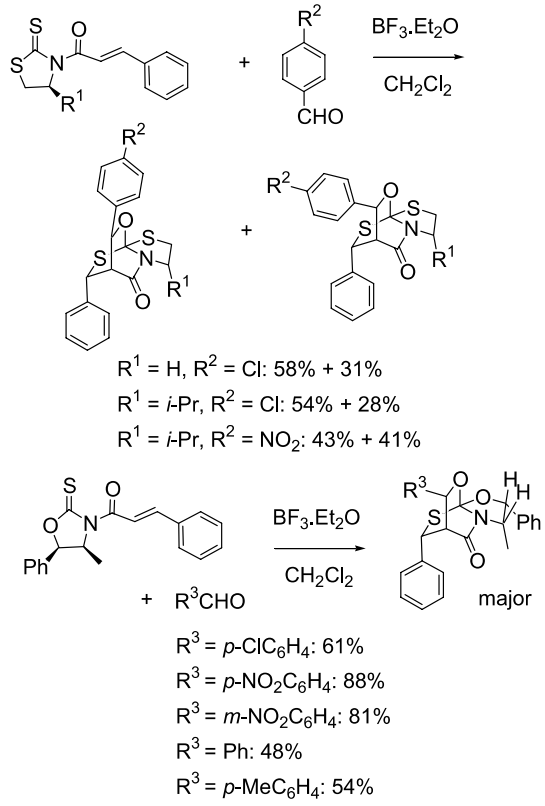
Another domino Michael aldol reaction was reported by Schneider et al. involving chiral 7-oxo-2-enimides as chiral auxiliaries, which yielded, upon treatment with organocopper or organoaluminium reagents, the corresponding functionalised cyclohexanes (Scheme 24).[55] The same chiral auxiliaries were also engaged in asymmetric domino Michael Mannich reactions in the presence of amines.[55b]



Scheme 24. Asymmetric domino Michael aldol reaction of chiral 7-oxo-2-enimides.

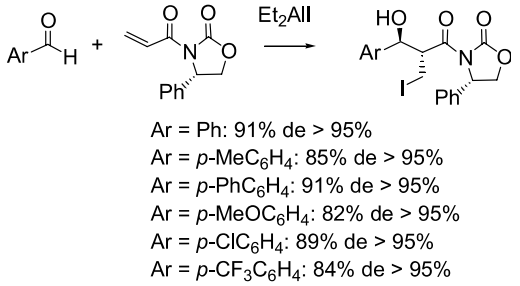
In 2003, Kataoka et al. reported the asymmetric domino Michael aldol reaction of chiral *N*-cinnamoyl-1,3-thiazolidine-2-thione and its 1,3-oxazolidine congener with aldehydes in the presence of $BF_3 \cdot Et_2O$.[56] This method was easy to use and gave unusual heterotricyclic compounds with three consecutive chiral centres and a chiral carbon centre bound to four heteroatoms (Scheme 25).

In 2003, Tomioka et al. developed asymmetric domino Michael aldol cyclisation reactions of ω-oxo-α,β-unsaturated esters with the lithium thiolate of 10-mercapto-isoborneol methyl ether providing, after reductive desulphurisation, the corresponding optically pure 2-hydroxycycloalkane-carboxylates.[57] The first effective



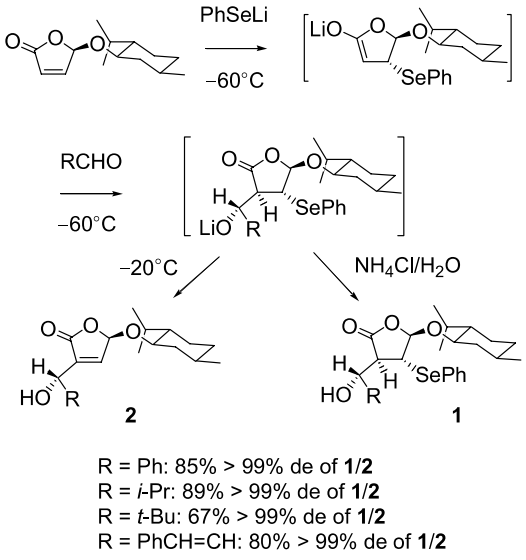
Scheme 25. Asymmetric domino Michael aldol reaction of *N*-enoylthioamides.

asymmetric domino halo aldol reaction using Evans' oxazolidinones as chiral auxiliaries has been established for domino I–C/C–C bond formations. This novel asymmetric reaction provided a practical approach to a variety of halo aldols of a non-Evans' type that could not be easily synthesised by other methods (Scheme 26).[58]



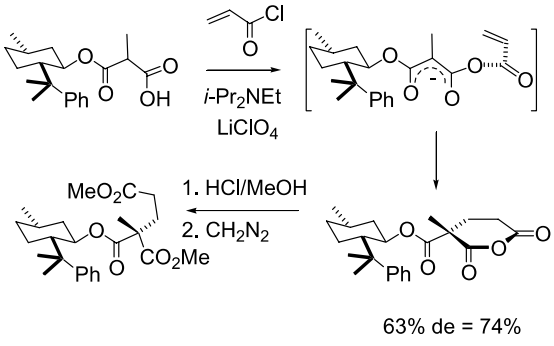
Scheme 26. Asymmetric domino halo aldol reaction.

The Baylis–Hillman reaction involves the tertiary amine-catalysed addition of an acrylate to an aldehyde. Michael addition of the catalyst to the acrylate is followed by an aldol addition and subsequent elimination, which regenerates the catalytic nucleophile. An asymmetric version of this domino reaction was reported by Leahy et al. in 1997 using camphor-based acrylates.[59] More recently, Jauch has proposed a new protocol for this enantioselective reaction, based on chirality transfer in a lithium phenylselenide-induced domino Michael aldol-retro Michael reaction (Scheme 27).[60] This three-component reaction could also be included in Section 2.7.



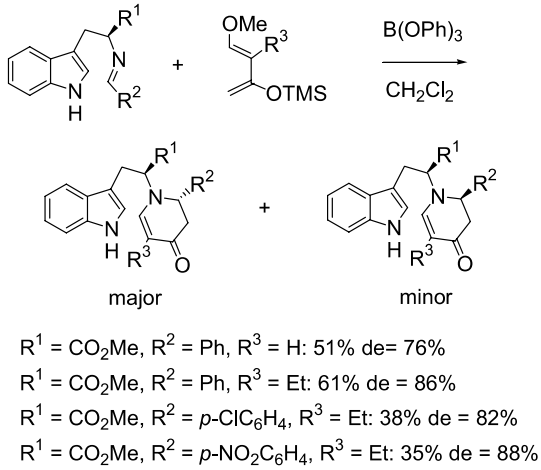
Scheme 27. Asymmetric Baylis–Hillman reaction.

Several asymmetric Michael-terminated processes involving chiral auxiliaries are known in the literature such as the enantioselective construction of a quaternary stereogenic centre via domino acid anhydride formation-intramolecular Michael reaction reported by Fukumoto et al.[61] Scheme 28 shows the reaction between the chiral half ester and acryloyl chloride, which has been applied to the total synthesis of *Hunteria* and *Aspidosperma* indole alkaloids. Another example of an asymmetric Michael-terminated reaction was the domino Horner–Emmons Michael reaction of the hemi-aminal derived from *N*-Boc-protected pyroglutamic esters with stabilised phosphonates, giving enantiomerically pure 5-substituted prolinates through a 1,4-asymmetric induction process.[62]



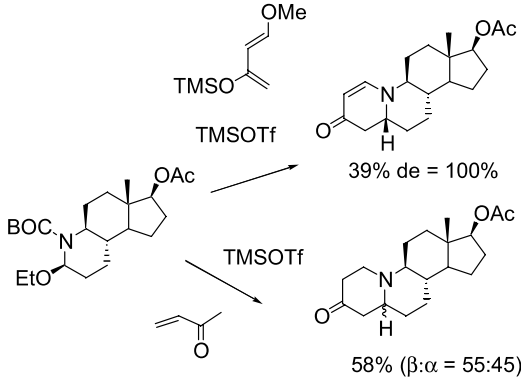
Scheme 28. Asymmetric domino acid anhydride formation-intramolecular Michael reaction.

Waldmann et al. have developed asymmetric variants of the domino Mannich Michael reaction such as those involving amino acid ester imines as mediators of chirality with Danishefsky's diene, delivering the corresponding chiral enaminones.[63] This methodology was applied to the synthesis of highly functionalised tetracyclic indole bases embodying the basic skeleton of yohimbine- and reserpine-type alkaloids.[64] Thus, Schiff bases derived from tryptophan methyl ester reacted with differently substituted electron-rich siloxydienes in the presence of boric acid esters to give the corresponding optically pure enaminones, which were further converted into highly functionalised indoloquinolizines (Scheme 29).



Scheme 29. Asymmetric domino Mannich Michael reaction of chiral Schiff bases derived from tryptophan.

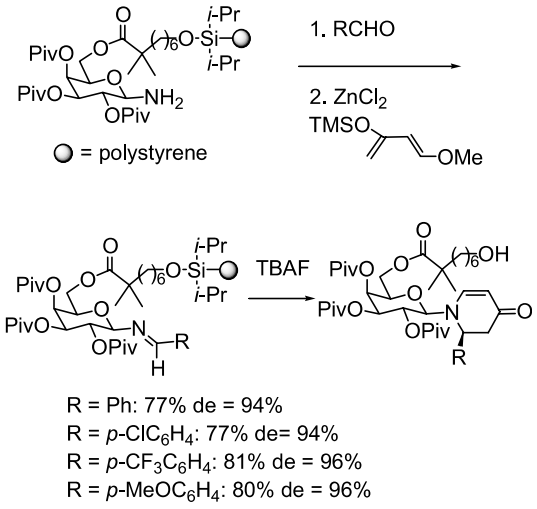
A concise route to 19-nor-10-azasteroids, a new class of steroid 5α-reductase inhibitors, was based on a domino Mannich Michael mechanism, in which the A-ring construction of azasteroids occurred by reaction between the in situ-generated *N*-(acyloxy)-iminium ion and 2-(silyloxy)-1,3-butadiene or methyl vinyl ketone (Scheme 30).[65]



Scheme 30. Synthesis of azasteroids through domino Mannich Michael reaction.

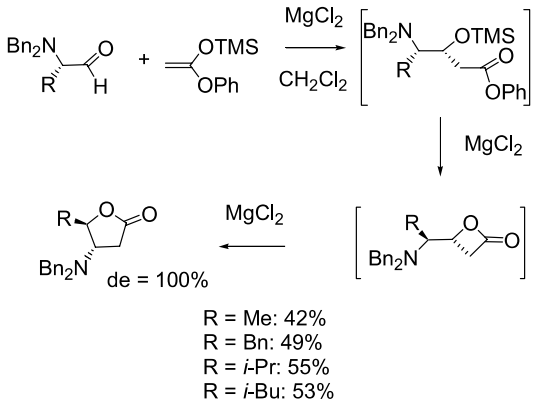
In 1997, Kunz et al. showed that aldimines of 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactosylamine reacted with 1-methoxy-3-trimethylsilyloxy-buta-1,3-diene in a Mannich Michael reaction, giving rise to the corresponding optically active 2-substituted *N*-galactosyl-5,6-dehydropiperidin-4-ones.[66] More recently, this author has developed a solid-phase synthesis of chiral piperidine derivatives through a diastereoselective domino Mannich Michael reaction performed with an immobilised glycosylamine as auxiliary (Scheme 31).[67] This three-component reaction could also be included in Section 2.7.

An asymmetric domino aldolisation lactonisation dyotropic rearrangement reaction of chiral α-amino aldehydes was performed by Reetz et al. in the presence of 1-phenoxy-1-trimethylsiloxy-ethylene, all three reactions being catalysed



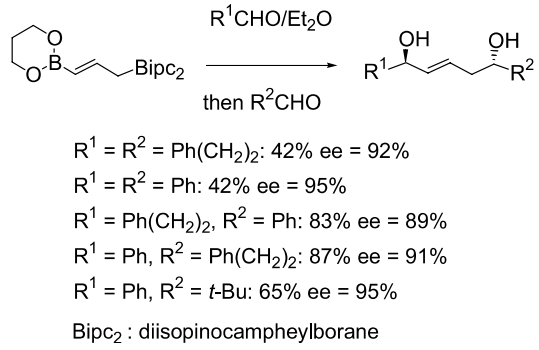
Scheme 31. Solid-phase asymmetric domino Mannich Michael reaction.

by $MgCl_2$, thus providing optically pure 4-substituted 3-amino-γ-lactones (Scheme 32).[68]



Scheme 32. Asymmetric domino aldolisation lactonisation dyotropic rearrangement reaction of α-amino aldehydes.

Another asymmetric domino aldolisation lactonisation reaction occurred when the lithium enolate of 1-octanoylbenzotriazole was treated with (*S*)-3-(2-methoxy-prop-2-oxy)tetradecanal, providing the corresponding enantiomerically pure β-lactones, key intermediates for the enzyme inhibitors, tetrahydrolipstatin and tetrahydroesterastin.[69] In addition, enantiomerically pure α-mesyloxyaldehydes were prepared by Rosini et al. through a domino nitroaldol cyclisation reaction starting from D-mannitol.[70] In 1992, Meyers et al. reported an efficient one pot synthesis of chiral 7-substituted indolines via intramolecular cyclisation of in situ-generated (2-phenyl)formamidines with in situ-generated benzynes.[71] The synthesis of enantiopure 1,3,5-triols was performed by Tietze et al. in a domino fashion, consisting of a bisalkylation of lithiated 2-trialkylsilyl-1,3-dithianes with chiral epoxides.[72] On the other hand, a simple and efficient one pot method was developed to give chiral homoallylic amines and amino acids from the respective aldehydes in high stereoselectivity via an indium-mediated allylation of in situ-generated chiral imines.[73] In 1997, Warrener et al. reported an asymmetric synthesis of protoberberine alkaloids via a domino nucleophilic addition and intramolecular cyclisation of a chiral *o*-toluamide anion with 3,4-dihydroisoquinoline with ees >96%.[74] A series of one pot aromatic vicarious nucleophilic substitutions of hydrogen asymmetric alkylation reactions were described by Lawrence et al. in which the enolates of several chiral cyclohexylphenylsulphanylacetates reacted readily with 3-chloronitrobenzene, followed by subsequent stereoselective alkylation.[75] In 1998, Otera et al. developed a one pot access to chiral cyclopropanolactones based on the CsF-induced condensation of malonate with glycidyl nosylate, followed by intramolecular attack of the substituted malonate moiety on the oxirane ring with high enantiopurity (ee =92–99%).[76] A one pot double allylboration reaction sequence was described by Roush et al. allowing the enantioselective synthesis of 1,5-*anti*- and 1,5-*syn*-diols (Scheme 33).[77] This three-component reaction could also be included in Section 2.7.

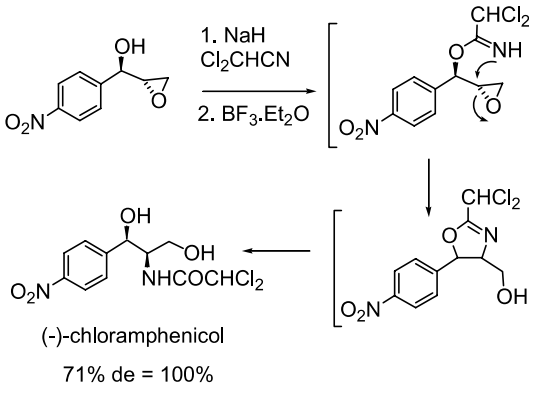


Scheme 33. Asymmetric domino double allylboration reaction.

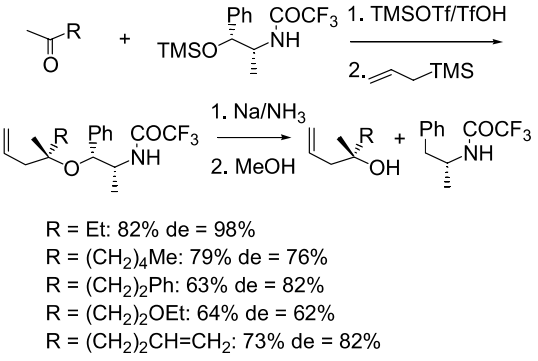
In 2003, Inomata reported a continuous nucleophilic addition with several organometallic reagents to chiral tricyclic lactones, providing the corresponding γ-substituted butenolides with tertiary and quaternary asymmetric centres.[78] A unique fragmentation–cyclisation cascade was developed by Nicolaou with the aim tof synthesising tetrahydrofurans fashioning the central portion of the antibiotic, efrotomycin.[79] This author elaborated another anionic cascade sequence involving eight intermediates, enabling generation of the coveted maleic anhydride portion of the CP(coat protein)-molecules.[80] In 2004, Rao et al. reported a short enantioselective synthesis of (−)-chloramphenicol on the basis of a $BF_3 \cdot Et_2O$-mediated cascade reaction, involving the intramolecular opening of chiral epoxydichloroimidates and in situ oxazoline hydrolysis (Scheme 34).[81]

In 1995, Tietze et al. reported an enantioselective synthesis of tertiary homoallylic alcohols via the diastereoselective addition of allylsilanes to ketones in the presence of the trimethylsilyl ether of (1*R*,2*R*)-*N*-(trifluoroacetyl)norpseudoephedrin and TMSOTf (Scheme 35).[82] This reaction, the Sakurai allylation process, has also been performed in the presence of aldehydes instead of ketones.[83] This reaction could also be included in Section 2.7, since it involves three components.

A domino-type reaction sequence consisting of an enantioselective intramolecular carbolithiation of chiral 6-phenylhex-5-enyl carbamates and a highly stereospecific retro-[1,4]-Brook rearrangement was reported in 1999,

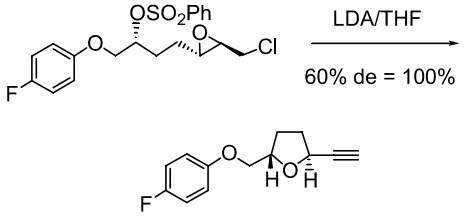


Scheme 34. Synthesis of (−)-chloramphenicol via $BF_3 \cdot Et_2O$-mediated cascade reaction.



Scheme 35. Asymmetric domino synthesis of tertiary homoallylic alcohols.

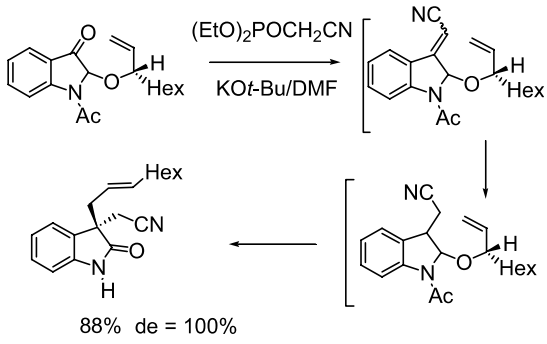
providing the corresponding carbocycles with high enantiomeric excesses (ee >96%).[84] The key step of a novel total synthesis of CMI-977, a potent anti-asthmatic lead drug, was a domino double elimination of a chiral α-chlorooxirane and concomitant intramolecular nucleophilic substitution (Scheme 36).[85]



Scheme 36. Asymmetric domino double elimination intramolecular nucleophilic substitution reaction.

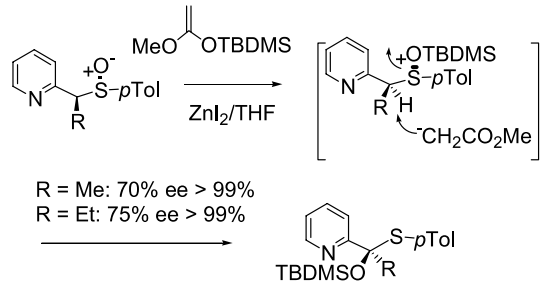
Starting from a chiral 2-allyloxyindolin-3-one, Kawasaki et al. developed an enantioselective total synthesis of (−)-pseudophrynaminol through a domino olefination, isomerisation, and asymmetric Claisen rearrangement reaction (Scheme 37).[86]

In 2004, Csàkÿ et al. reported an asymmetric synthesis of cyclopentenones with benzylic α-quaternary carbon stereogenic centres from furans, involving a one pot alkylation elimination sequence of a chiral β-hydroxycyclopentanone in the presence of NaH as the base and an alkylating agent.[87] The Pummerer rearrangement has been widely studied and has received considerable attention as a synthetically useful process.[88] α-Acylthionium ions, generated from



Scheme 37. Asymmetric domino olefination isomerisation Claisen rearrangement reaction.

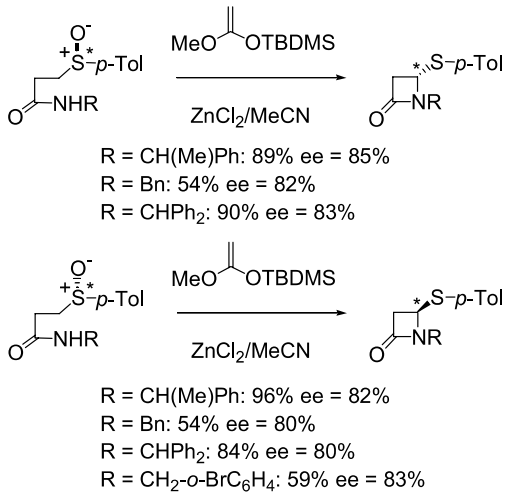
α-acylsulphoxides under Pummerer conditions, are powerful electrophiles, reacting efficiently with nucleophilic carbon species. There have been several reports in the literature dealing with the asymmetric conversion of chiral β-amidosulphoxides into β-lactams using an intramolecular Pummerer cyclisation process.[89] In a recent report, Kita et al. demonstrated that a highly asymmetric Pummerer reaction of acyclic sulphoxides could be induced to occur using an *O*-silylated ketene acetal.[89d,e] The reaction of a chiral sulphoxide with a silyloxy ketene acetal in the presence of a catalytic amount of ZnI_2 in MeCN provided the corresponding enantiomerically pure α-siloxy sulphide (Scheme 38).[89e] Although the exact mechanistic details of this process were unclear, the transformation appeared to involve silylation of the chiral sulphoxide, followed by proton removal at the α-carbon from the face opposite the sulphoxide group by the ester enolate, the siloxy group then migrating to the α-position.



Scheme 38. Asymmetric Pummerer-type rearrangement by *O*-silylated ketene acetal.

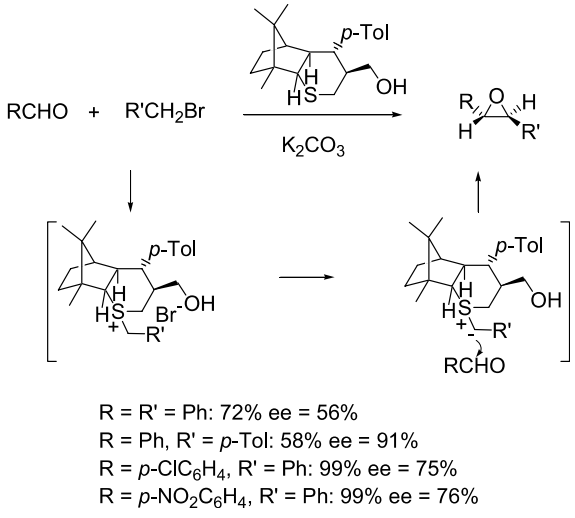
This methodology was also applied to the construction of enantiomerically enriched β-lactams, starting from chiral β-amido sulphoxides, by Kita et al. (Scheme 39).[90,89d] In addition, optically active carbapenem antibiotics have been synthesised by these authors using an amide to trap the thionium ion generated from a Pummerer reaction.[91]

The Corey-Chaykovsky reaction is the sulphonium ylide-mediated asymmetric one pot synthesis of optically active epoxides from aldehydes and bromides. This methodology involves the ylide formation via essentially two independent routes, either alkylation of a sulphide followed by deprotonation of the resulting sulfonium salt, or direct coupling of a sulphide and a carbene (or carbenoid) generated from a diazomethane. This latter procedure was developed by the groups of Durst,[92] Solladié-Cavallo,[93] and Dai.[94]



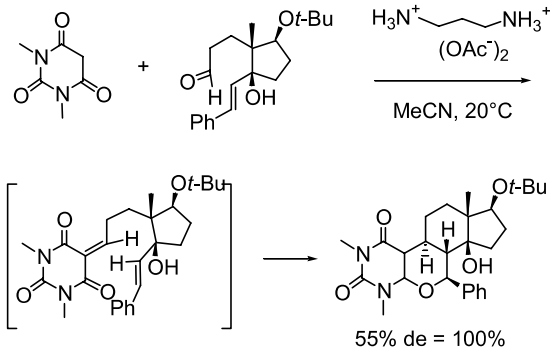
Scheme 39. Asymmetric Pummerer-type cyclisation of chiral β-amido sulphoxides.

Aggarwal et al. made advances in the sulphur ylide-catalysed, asymmetric epoxidation and reported excellent results when chiral 1,3-oxathianes (monothioacetals) derived from (+)-10-camphorsulphonic acid were employed as the catalyst.[95] Metzner et al. and then Goodman et al. showed that even a simple, C_2-symmetric, chiral sulphide, 2,3-dimethylthiolane, was an efficient mediator for the epoxidation reaction.[96,97] In more recent reports, efforts have also been made in the synthesis of new chiral sulphonium ylides for the epoxidation to give good to excellent enantioselectivity.[98] Thus, Saito et al. reported in 2001 the evaluation of a novel camphor-derived sulphide as a chiral mediator in asymmetric epoxidation via the Corey-Chaykovsky reaction (Scheme 40).[99]



Scheme 40. Asymmetric epoxidation via the Corey-Chaykovsky reaction.

2.2.2. Anionic–pericyclic reactions. Three well-investigated and versatile anionic–pericyclic domino reactions that have been developed by Tietze's group are the domino Knoevenagel hetero-Diels–Alder reactions,[100] domino Knoevenagel ene reactions[101] and domino Knoevenagel allylsilane cyclisations.[102] All three sequences are characterised by being simple to carry out and, when the second reaction step is intramolecular, by a very high stereoselectivity. In the domino Knoevenagel hetero-Diels–Alder reaction, a 1-oxa-1,3-butadiene is first formed[103] in situ by condensation of an aldehyde with a cyclic or highly reactive acyclic 1,3-dicarbonyl compound. This oxabutadiene then undergoes cycloaddition with a dienophile in the second step. In a similar fashion, 1,3-dicarbonyl compounds such as malonate or malonodinitrile, which cannot undergo hetero-Diels–Alder reactions, are used in the domino Knoevenagel ene reaction; for the domino Knoevenagel allylsilane cyclisation, aldehydes containing an allylsilane unit are used, which are easily available by photochemical Norrish type I cleavage of α-trimethylsilylmethylalkanones.[104] The range of applications of these reactions is very large since numerous aldehydes and 1,3-dicarbonyl compounds can be employed including enantiomerically pure compounds. Thus, in the case of the former domino reaction, various asymmetric versions have been developed, mostly by Tietze's group,[105] and applied to the synthesis of various biologically active natural products[106] such as indole alkaloids,[107] for example, hirsutine,[108] having a strong inhibitory effect on influenza A viruses, and dihydrocorynantheine,[109] as well as heterosteroids (Scheme 41).[110]

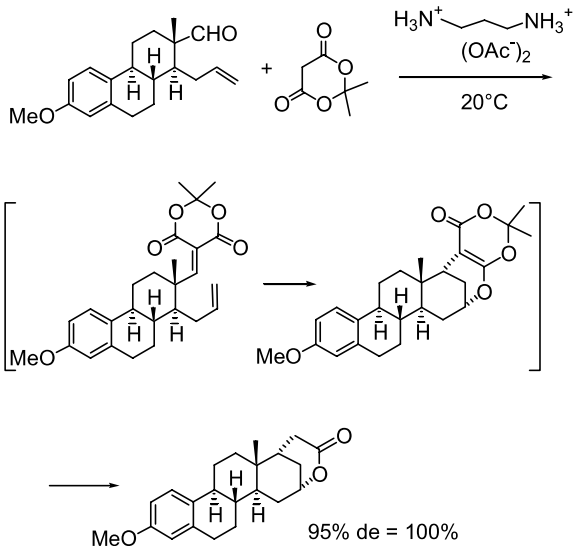


Scheme 41. Synthesis of heterosteroids by asymmetric domino Knoevenagel hetero-Diels–Alder reaction.

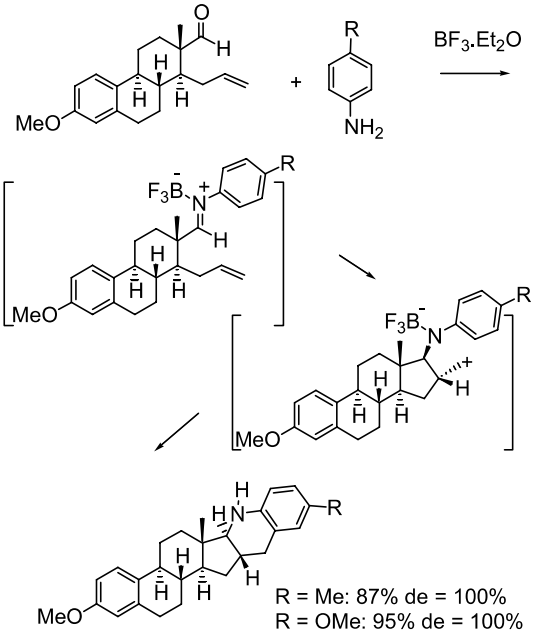
The asymmetric domino Knoevenagel hetero-Diels–Alder reaction of a D-secoestrone derivative with Meldrum's acid stereoselectively afforded the corresponding bridged D-homoestrone derivative (Scheme 42).[111] This reaction could be extended to other 1,3-dicarbonyl compounds such as dimethylbarbituric acid and various pyrazolones, thus providing the corresponding D-homosteroids.

In a similar manner to 1-oxa-1,3-butadienes, 2-aza-1,3-butadienes could be prepared by condensation of a secoestrone aldehyde with anilines to give the corresponding azasteroids in a following cycloaddition reaction. Thus, by condensation of this chiral aldehyde with anilines containing electron-donating substituents, an iminium ion was first formed, which was attacked by the alkene moiety to give a primary carbocation; electrophilic aromatic substitution then led to the final tetrahydroquinoline derivatives of estrone methyl ether (Scheme 43).[112]

A completely different pathway dominated, however, if the propenyl side chain in the starting material of Scheme 43 was first hydrogenated, thus providing the corresponding chiral aldehyde bearing a propyl group at C14 instead of



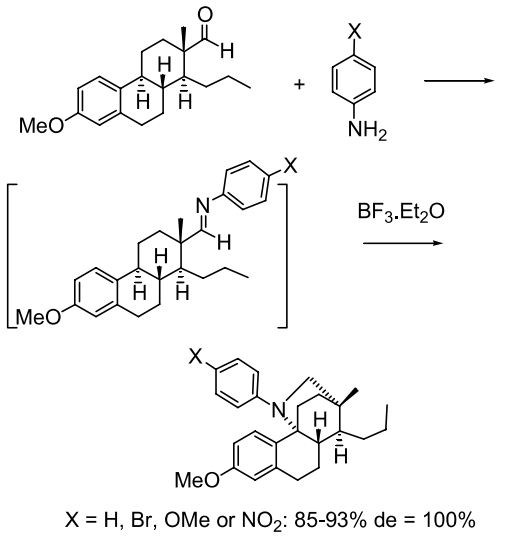
Scheme 42. Synthesis of D-homosteroids by asymmetric domino Knoevenagel hetero-Diels–Alder reaction.



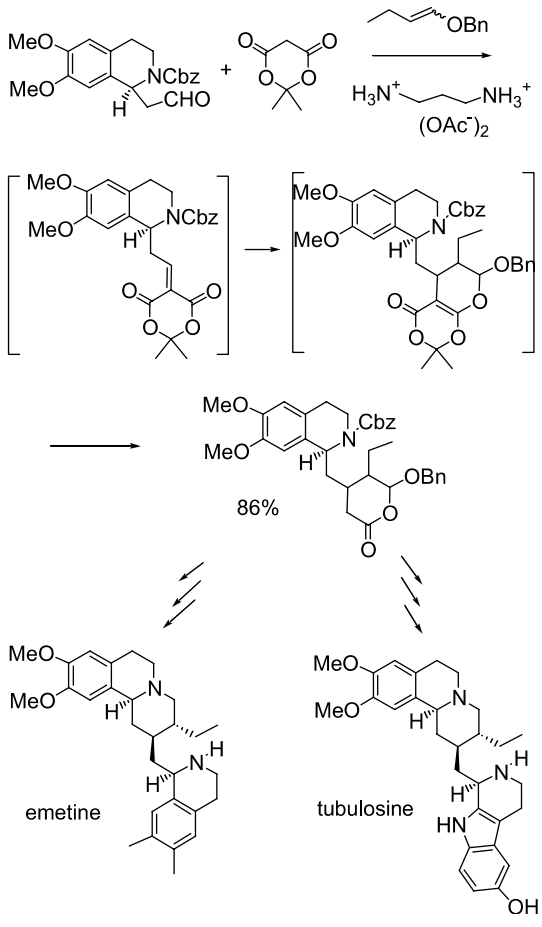
Scheme 43. Synthesis of azasteroids by asymmetric domino Knoevenagel hetero-Diels–Alder reaction.

a propenyl moiety. In this case, another domino process occurred, involving an iminium ion-induced 1,5-shift of a benzylic hydride, yielding an unusual bridged steroid alkaloid (Scheme 44).[113] Since this result was an extension of that previously described and, in spite of its very different mechanism, it was decided to maintain the reaction in this Section.

Tietze et al. also applied the domino Knoevenagel hetero-Diels–Alder reaction to the development of the first enantioselective total syntheses of alkaloids such as emetine and tubulosine (Scheme 45).[114] In addition, the so far unknown benzoquinolizidine alkaloids, which resemble the vallesiachotamine alkaloid, dihydroantirhin, and which probably also exist in nature, could be obtained using this



Scheme 44. Asymmetric domino reaction involving an iminium ion-induced 1,5-shift of a benzylic hydride.

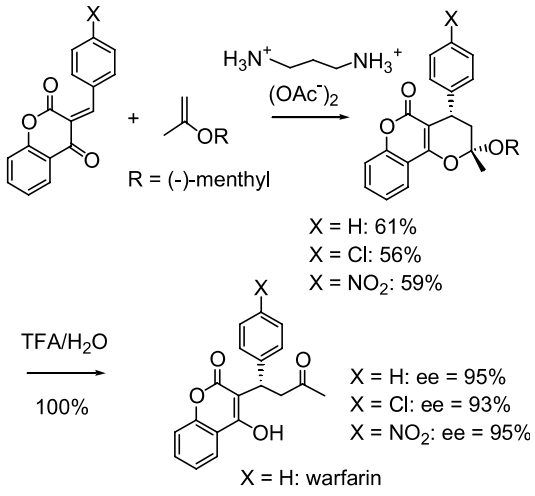


Scheme 45. Synthesis of emetine and tubulosine via asymmetric domino Knoevenagel hetero-Diels–Alder reaction.

approach.[114] This procedure invoving three components could also be included in Section 2.7.

This methodology has also been used by Cravotto et al. in order to prepare chiral coumarin anticoagulants such as

warfarin-like analogues from in situ-generated 3-arylidene-2,4-chromanediones and the *iso*-propenyl ether derived from (−)-menthol (Scheme 46).[115]



Scheme 46. Synthesis of chiral coumarin anticoagulants via asymmetric domino Knoevenagel hetero-Diels–Alder reaction.

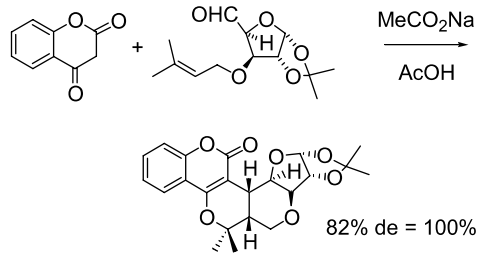
Similarly, the *O*-prenyl derivative of a sugar aldehyde derived from D-glucose underwent a smooth intramolecular domino Knoevenagel hetero-Diels–Alder reaction with 1,3-diones to afford a novel class of carbohydrate analogues, the *cis*-fused furopyranopyrans (Scheme 47).[116] An extension of this study to spirocyclic 1,3-dicarbonyl compounds (spiro 1,3-dihydropyranones) was performed with the same aldehyde, to furnish interesting chiral cis-annulated polycyclic heterocycles.[117]

The Diels–Alder reaction has also been coupled with other anionic processes such as the Michael reaction. In one example, Maruyama et al. involved an optically active 2-substituted 2,4-pentadienyltin as a chiral auxiliary and obtained in the presence of an acryloylquinone the corresponding optically active 11-deoxydaunomycinone precursor in 95% ee.[118] On the other hand, Bäckvall et al. reported that 2-nitro 1,3-dienes, generated in situ from the corresponding nitroseleno compounds, reacted with chiral enamines, affording the corresponding [4+2] heterocycloadducts (Scheme 48).[119]

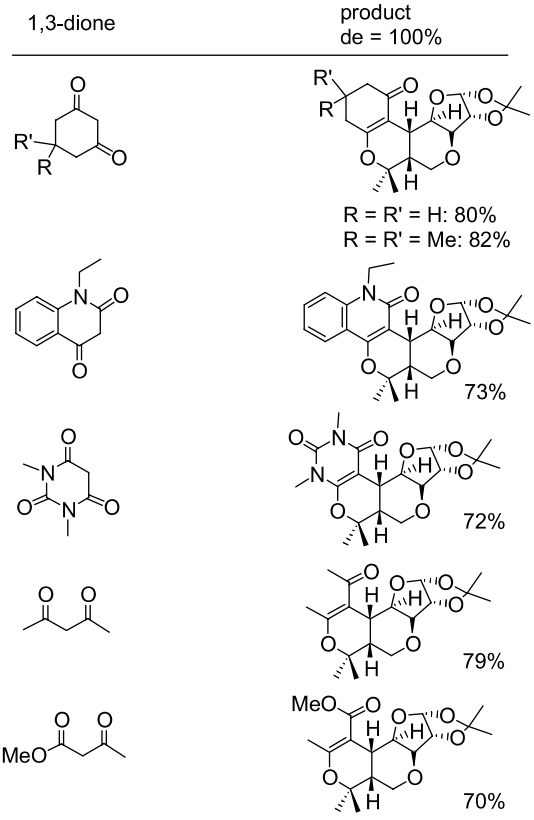
More recently, the Diels–Alder reaction was combined with an allenol transposition, providing a new domino process furnishing tricyclic structures found in many biologically active natural products such as β-lactams, cromenes, and pyrrolizidines. Thus, Alcaide et al. have noted the unexpected production of 2,3-difunctionalised dienes in total stereoselectivity by the addition of methanesulphonyl chloride and triethylamine to a dichloromethane solution of chiral α-allenyl alcohols (Scheme 49).[120]

An asymmetric domino Sakurai carbonyl-ene reaction was the key step of a stereoselective synthesis of the enantiomerically pure BCD part of steroid derivatives, starting from a chiral cyclopentanyl aldehyde (Scheme 50).[121]

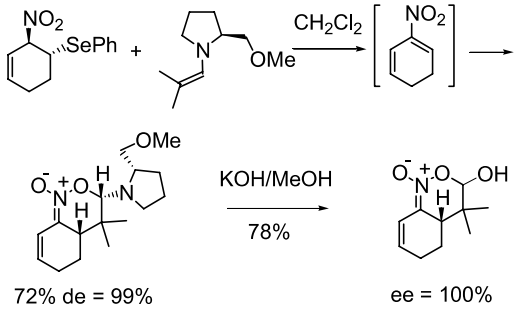
Asymmetric anionic amino-Cope rearrangements involving chiral 3-amino-1,5-dienes as chiral auxiliaries have been



Extension to other 1,3-diones:

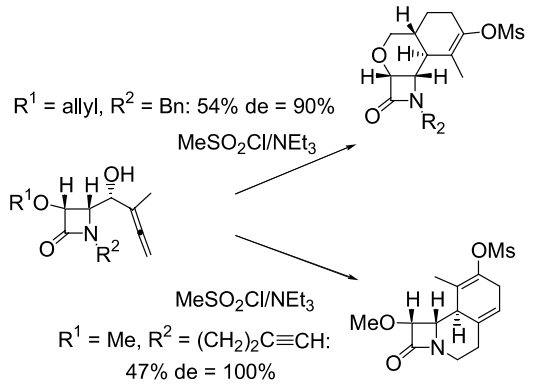


Scheme 47. Domino Knoevenagel hetero-Diels–Alder reactions with a D-glucose derivative.

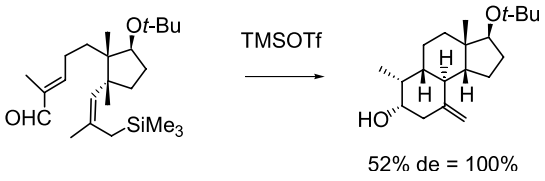


Scheme 48. Asymmetric domino base-catalysed elimination hetero-Diels–Alder reaction.

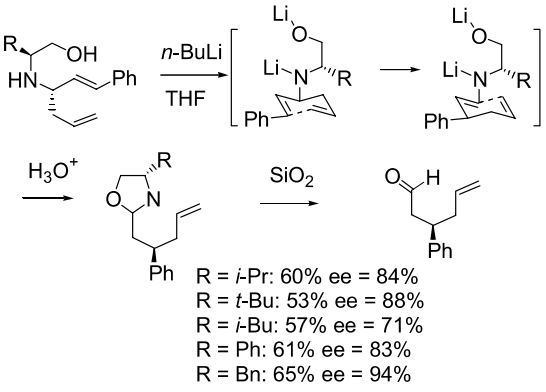
developed in order to prepare δ,ε-unsaturated aldehydes, which are precursors to synthesise optically active 2,5-disubstituted tetrahydropyrans (Scheme 51).[122] Paquette investigated dianionic oxy-Cope rearrangements when 2 equiv of vinyl anions were added to squarate esters, providing the corresponding enantio-enriched bicyclooctanone derivatives.[123]



Scheme 49. Asymmetric domino transposition intramolecular Diels–Alder reaction of α-allenyl alcohols.

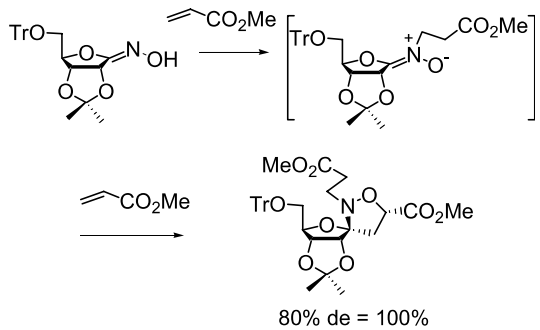


Scheme 50. Asymmetric domino Sakurai carbonyl-ene reaction with a chiral aldehyde.

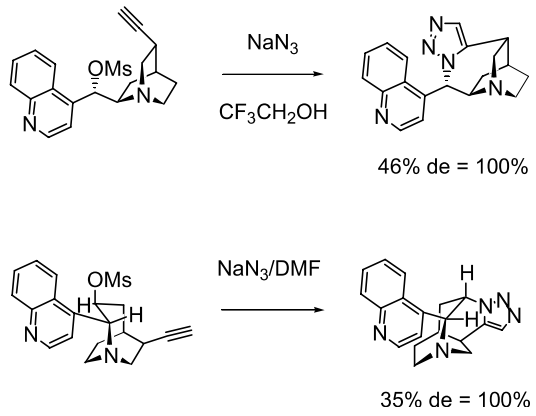


Scheme 51. Asymmetric anionic amino-Cope rearrangement with chiral 3-amino-1,5-dienes.

1,3-dipolar cycloadditions have also been incorporated into asymmetric domino schemes. As an example, Yokoyama et al. reported the Michael [3+2] cycloaddition of sugar hydroximolactones, giving the corresponding spiro sugar isoxazolidines (Scheme 52).[124] This reaction exploited the natural chirality of the sugar to induce asymmetry in the final heterocyclic products.



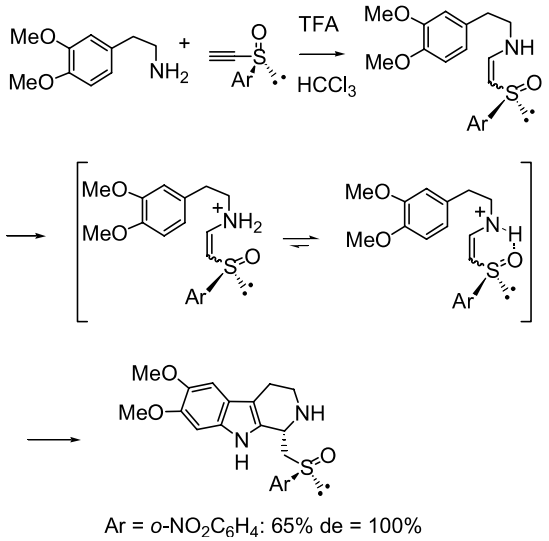
Scheme 52. Asymmetric domino Michael [3+2] cycloaddition reaction.



Scheme 53. Asymmetric domino reaction of activated cinchona alkaloids with azide ion.

In 1995, Grigg reported asymmetric cascade 1,3-dipolar cycloaddition reactions of imines successively converted into azomethine ylides and then chiral pyrrolidines.[125] On the other hand, intramolecular 1,3-dipolar cycloadditions of cinchona alkaloid azides to the C10–C11 alkyne and C10–C11 olefin unit of the alkaloid have been designed via a domino strategy, providing a new variety of fused triazoles and triazolines with a bis-azahomotwistane skeleton, both bearing a number of useful pharmacophoric groups (Scheme 53).[126]

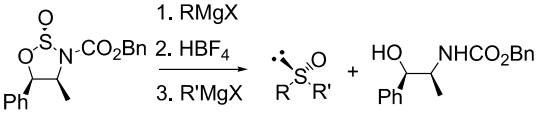
2.2.3. Anionic–miscellaneous reactions. This section describes a series of unrelated reactions for which the mechanistic pathway involved in the second step is other than anionic or pericyclic, the first step being anionic. As an example, Lee et al. reported the asymmetric domino Michael cyclisation reaction of amines with chiral acetylenic sulphoxides, affording the basic skeleton of tetrahydroisoquinoline and tetrahydro-β-carboline alkaloids (Scheme 54).[127]



Scheme 54. Asymmetric domino Michael cyclisation reaction of amines with chiral acetylenic sulphoxides.

A large number of structurally diverse enantiomerically pure sulphoxides could be prepared from norephedrine-derived sulphamidites through a simple one pot

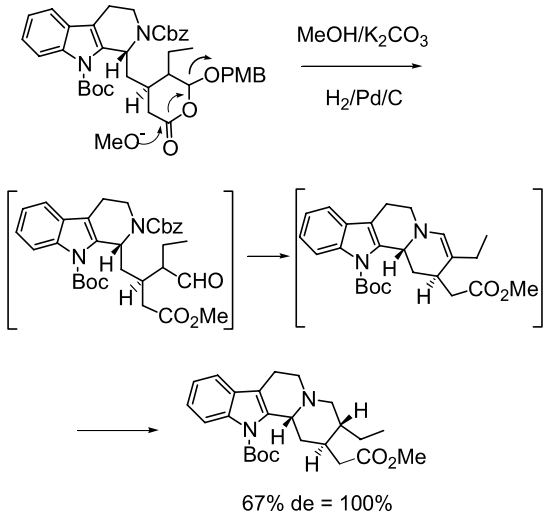
procedure.[128] In this methodology, *N*-benzyloxycarbonyl-sulphamidites derived from (1*R*,2*S*)-(−)-norephedrine were converted into the corresponding enantiomerically enriched sulphoxides by consecutive reactions with two different Grignard reagents, and addition of 1.2 equiv of HBF_4 after the first Grignard reagent and prior to the second (Scheme 55). This three-component reaction could also be included in Section 2.7.



R = Ph, R' = Me: 54% ee = 93% (*R*)
R = Ph, R' = *i*-Pr: 58% ee = 93% (*R*)
R = Ph, R' = vinyl: 53% ee = 95% (*R*)
R = *i*-Pr, R' = Ph: 75% ee = 95% (*S*)
R = mesityl, R' = *p*-Tol: 71% ee = 97% (*R*)
R = mesityl, R' = Me: 73% ee = 97% (*R*)
R = mesityl, R' = vinyl: 64% ee = 95% (*R*)
R = cyclohexyl, R' = *i*-Pr: 60% ee = 90% (*R*)

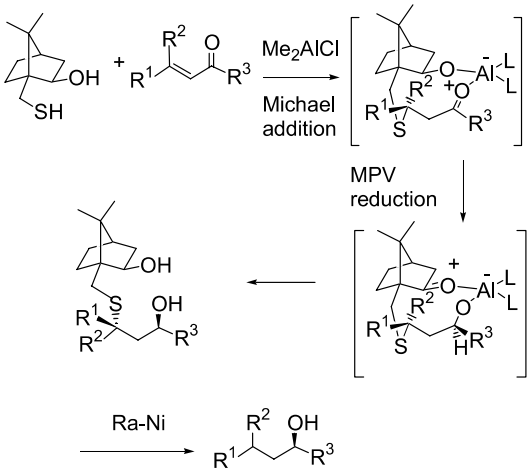
Scheme 55. One pot synthesis of chiral sulphoxides.

On the other hand, Tietze et al. have reported an asymmetric domino solvolysis hydrogenation process, which was involved in a total synthesis of (−)-hirsutine.[108] Treatment of the chiral precursor with methanol in the presence of K_2CO_3 led to an opening of the lactone, with the formation of a methyl ester and a hemiacetal, which lost the alcohol to give the corresponding aldehyde. Under hydrogenolytic conditions, the carbobenzoxy group from the nitrogen *N*-4 was then removed to form a secondary amine, which reacted with the aldehyde moiety to give the corresponding enamine, the hydrogenation of which produced the final enantiomerically pure hirsutine precursor (Scheme 56).



Scheme 56. Asymmetric domino solvolysis hydrogenation process.

Node et al. have developed a very efficient asymmetric domino Michael Meerwein-Ponndorf-Verley (MPV) reduction reaction of α,β-unsaturated ketones in the presence of 10-sulphanylisoborneol as the chiral auxiliary, which led to the corresponding chiral alcohols after subsequent reductive desulphurisation (Scheme 57).[129]



R^1 = Ph, R^2 = H, R^3 = Ph: 93% ee = 96%
R^1 = Ph, R^2 = H, R^3 = Me: 83% ee = 89%
R^1 = *p*-$MeOC_6H_5$, R^2 = H, R^3 = Ph: 73% ee = 96%
R^1 = *p*-MeC_6H_5, R^2 = H, R^3 = Ph: 66% ee = 98%
R^1 = R^2 = H, R^3 = Me: 60% ee = 98%

Scheme 57. Asymmetric domino Michael Meerwein-Ponndorf-Verley reduction reaction.

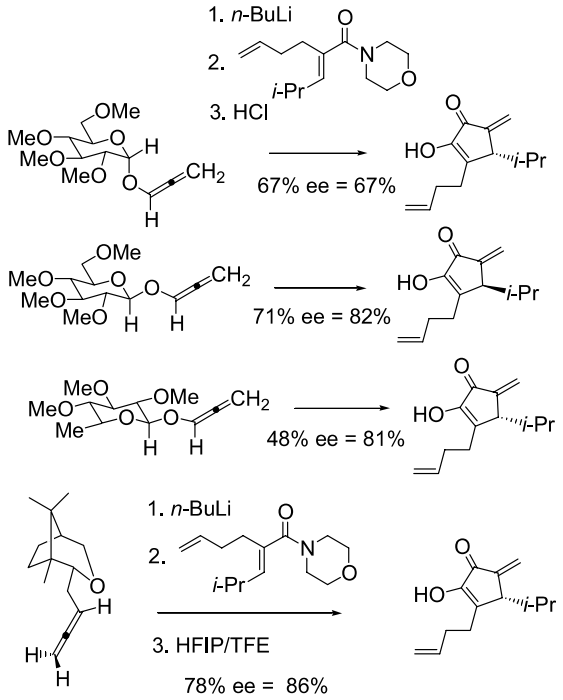
When the subsequent reductive desulphurisation was changed by a thiol-exchange reaction carried out in the presence of 1-dodecanethiol, the corresponding chiral 1,3-hydroxythiols were obtained.[129c]

The modified Nazarov cyclisation developed by Tius and Hoppe may be considered as a domino process involving the in situ preparation of a chiral lithium allenolate, and its subsequent conjugated addition onto an alkenoylmorpholinide, followed by a 4π-electrocyclisation process giving rise to enantio-enriched 5-alkylidene-2-cyclopentenones.[130] Various chiral auxiliaries were used such as D-glucose- or camphor-derived chiral allenes (Scheme 58).

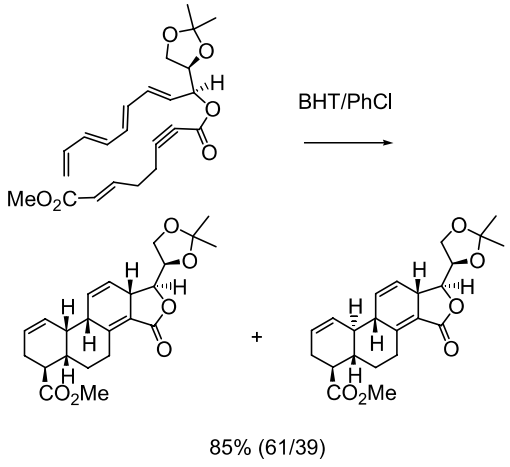
2.3. Pericyclic primary step

Pericyclic reactions such as the Diels–Alder, ene, Claisen, Cope, or electrocyclic reactions are by themselves extremely useful transformations. By combining two or more pericyclic reactions, however, the effect can be multiplied. There have been considerable advances in the use of pericyclic processes to initiate both inter- and intramolecular sequences. In particular, asymmetric domino sequences involving cycloaddition reactions are highly effective processes for the rapid elaboration of complex polycyclic systems, since each cycloaddition event generates a new ring and two new covalent bonds.

2.3.1. Pericyclic–pericyclic reactions. Most of the asymmetric pericyclic–pericyclic sequences include a Diels–Alder reaction most of the time in the first step. Asymmetric double Diels–Alder processes have been recently developed such as the domino intramolecular Diels–Alder approach to enantiomerically pure 16-oxasteroids, involving two successive intramolecular Diels–Alder reactions (Scheme 59).[131]



Scheme 58. Asymmetric domino cyclopentannelations of chiral allenes.

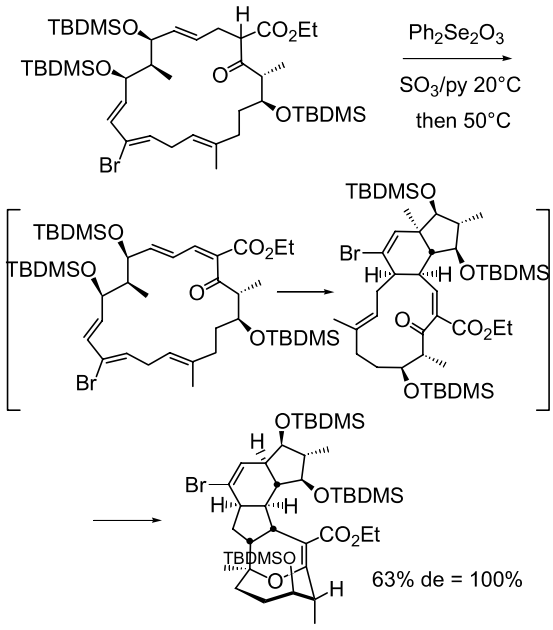


Scheme 59. Asymmetric domino intramolecular Diels–Alder reaction.

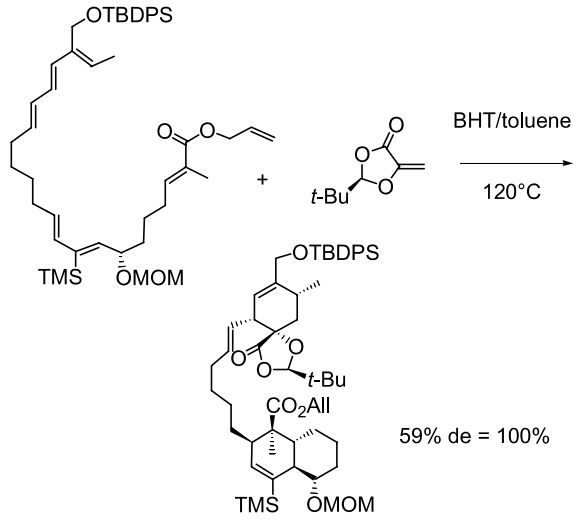
Although an in situ oxidation was required prior to the reaction cascade, the asymmetric domino transannular Diels–Alder hetero-Diels–Alder reaction, which constituted the key step of the total synthesis of antitumour agent, (−)-FR182877, was included in this section, since the major skeletal change involved two pericyclic processes (Scheme 60).[132]

An enantioselective total synthesis of (−)-chlorothricolide, the aglycon of the antibiotic, chlorothricin, was developed by Roush et al. via a route involving a domino inter- and intramolecular Diels–Alder reaction of a chiral dienophile (Scheme 61).[133]

Asymmetric domino reactions including an initial Diels–Alder cycloaddition have been developed such as the domino [4+2]/[3+2] cycloadditions reactions, which have been widely explored by Denmark et al.[134] In particular, the



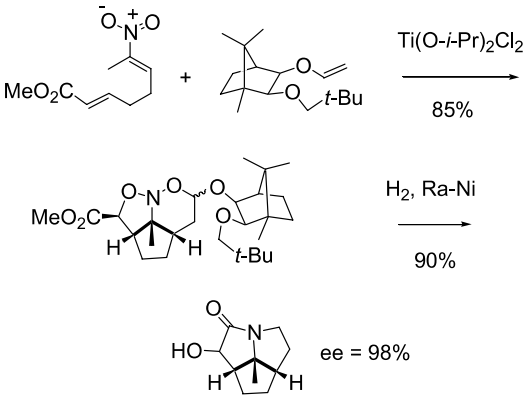
Scheme 60. Asymmetric domino intramolecular Diels–Alder hetero-Diels–Alder reaction.



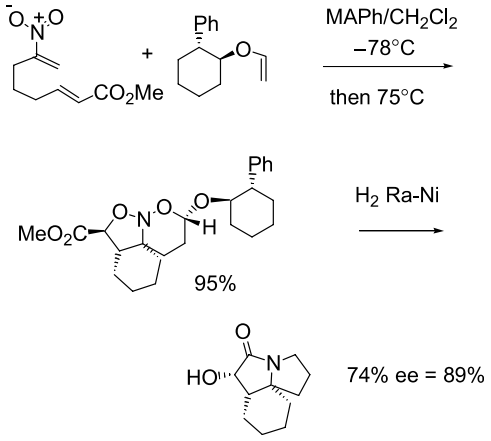
Scheme 61. Asymmetric domino intra-intermolecular Diels–Alder reaction.

sequential intermolecular [4+2] intramolecular [3+2] cycloaddition chemistry of nitroalkenes was used for the synthesis of various fused-ring systems such as fused-ring α-hydroxylactams[135] obtained by treatment of a nitroalkene with a chiral dienophile such as a camphor-derived enol ether (Scheme 62).[136] In addition, this methodology was applied to the synthesis of complex pyrrolizidine alkaloids such as (−)-rosmarinecine,[137] the potent glycosidase inhibitors, (+)-castanospermine, (+)-6-epicastanospermine, (+)-australine, or (+)-3-epiaustraline,[138] and (−)-hastanecine.[135c]

This author has extended the scope of this procedure to spiro mode cycloadditions by using nitroalkenes bearing the dipolarophile tether at the α-position [C(3) of the nitronate] instead of the β-position [C(4) of the nitronate], as in Scheme 62.[139] As an example, Scheme 63 illustrates the



Scheme 62. Asymmetric domino [4+2]/[3+2] nitroalkene cycloadditions reaction with chiral enol ethers.

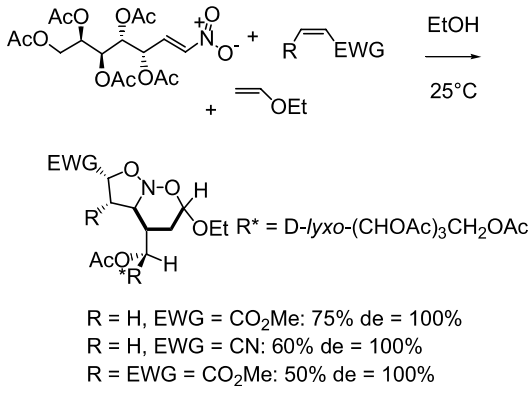


Scheme 63. Asymmetric spiro mode tandem [4+2]/[3+2] nitroalkene cycloaddition reaction.

asymmetric domino [4+2]/[3+2] cycloaddition reaction of a chiral vinyl ether with a nitroalkene of this nature, which provided, after subsequent hydrogenation, the corresponding enantiomerically enriched spirocyclic lactams.

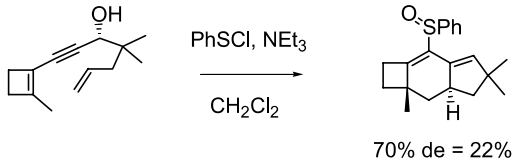
In 1996, Cintas et al. reported a highly stereoselective variation of the domino [4+2]/[3+2]-fused mode Denmark-type reaction, in which the chiral auxiliary was a galactose-based template.[140] The expected cycloadduct was obtained in ethanolic solution at room temperature without any catalyst. In order to extend the scope of this reaction, these authors performed a multicomponent reaction combining electron-rich and electron-withdrawing alkenes without mutual interference. Thus, in the presence of a nitroalkene, the initial inverse electronic demand [4+2] cycloaddition occurred with ethyl vinyl ether, whereas the resulting nitronate reacted exclusively in a [3+2] fashion with the electron-deficient alkene, providing the corresponding chiral nitrosoacetals (Scheme 64).[141] This three-component reaction could also be included in Section 2.7.

The molecular mechanism of the domino inter [4+2]/intra [3+2] cycloaddition reaction of nitroalkenes with chiral enol ethers to give nitrosoacetal adducts has been characterised by Domingo et al. using density functional theory methods with the B3LYP functional and the 6-31G* basis set.[142] On the other hand, an asymmetric domino



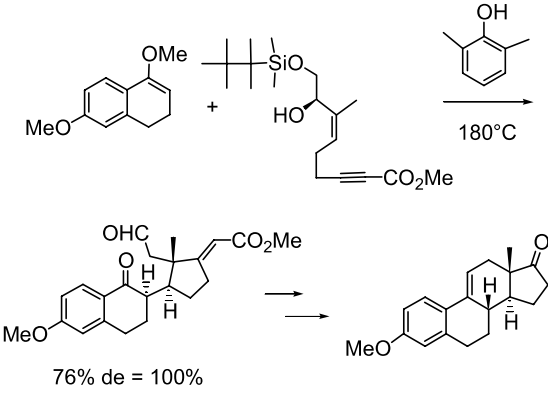
Scheme 64. Asymmetric domino three-component [4+2]/[3+2] nitroalkene cycloaddition reaction.

reaction of an initial Diels–Alder cycloaddition and a consecutive Cope rearrangement was published by Serrano et al. involving manno- and galacto-nitrocyclohexadienes as chiral auxiliaries.[143] To the best of the author's knowledge, asymmetric Diels–Alder cycloaddition-terminated processes are much less evident in the literature. As an example, Okamura et al. reported in 1988 a domino [2,3]-sigmatropic shift/[4+2] cycloaddition reaction, allowing the total enantioselective synthesis of (+)-sterpurene (Scheme 65).[144]



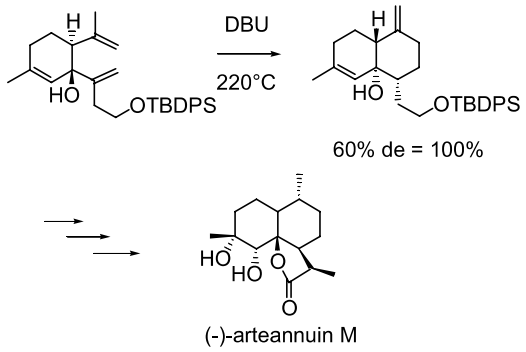
Scheme 65. Asymmetric domino [2,3]-sigmatropic shift/[4+2] cycloaddition reaction.

Several asymmetric domino processes have included the ene reaction. Mikami et al. reported in 1994 an asymmetric domino Claisen ene strategy for the total synthesis of (+)-9(11)-dehydroestrone methyl ether (Scheme 66).[145] Groen et al. have also documented a Claisen ene approach to the synthesis of the steroid nucleus in the course of their synthesis of (+)-13-ethyl-3-methoxygona-1,3,5,9(11)-tetraen-17-one, a potential precursor to the progestagens, desogestrel and 3-ketodesogestrel.[146]



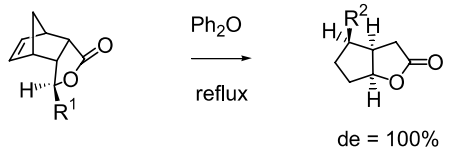
Scheme 66. Asymmetric domino Claisen ene reaction.

More recently, the first total synthesis of (+)-arteannuin M was accomplished using the domino oxy-Cope transannular ene reaction as the key step to construct the bicyclic core of the natural product (Scheme 67).[147] The chiral auxiliary was readily available from (+)-limonene.



Scheme 67. Asymmetric domino oxy-Cope ene reaction.

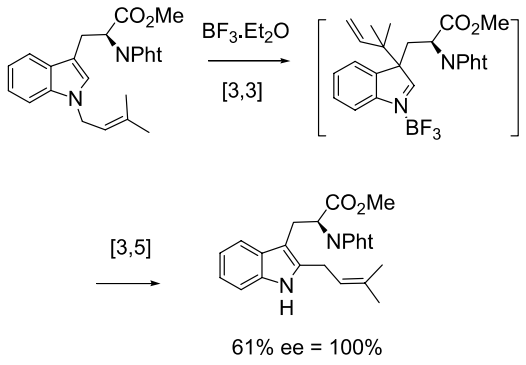
In addition, a new type of domino retro-Diels–Alder ene reaction activated by a trimethylsilyl substituent was reported in 2004, allowing an enantiocontrolled synthesis of jasmonates from a chiral tricyclic lactone (Scheme 68).[148]



R^1 = (*Z*)-$(CH_2)_2CH{=}CHMe$, R^2 = $CH{=}CH_2$: 50%
R^1 = (*E*)-$(CH_2)_2CH{=}CHMe$, R^2 = $CH{=}CH_2$: 19%
R^1 = (*Z*)-$(CH_2)_2CH{=}CHCH_2TMS$, R^2 = $CH{=}CH_2TMS$: 74%
R^1 = (*E*)-$(CH_2)_2CH{=}CHCH_2TMS$, R^2 = $CH{=}CH_2TMS$: 34%

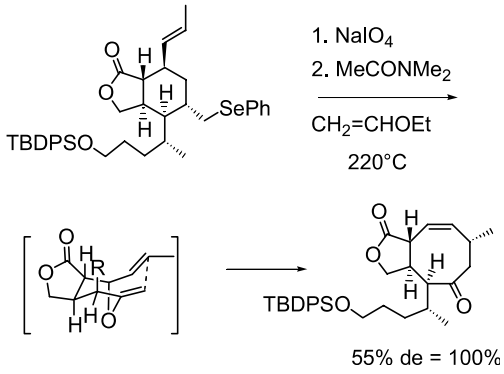
Scheme 68. Asymmetric domino retro-Diels–Alder ene reaction.

Two consecutive [3,3]- and [3,5]-rearrangement steps were involved in the total synthesis of tryprostatin B, starting from an L-tryptophan-derived chiral auxiliary upon treatment with $BF_3{\cdot}Et_2O$ (Scheme 69).[149]



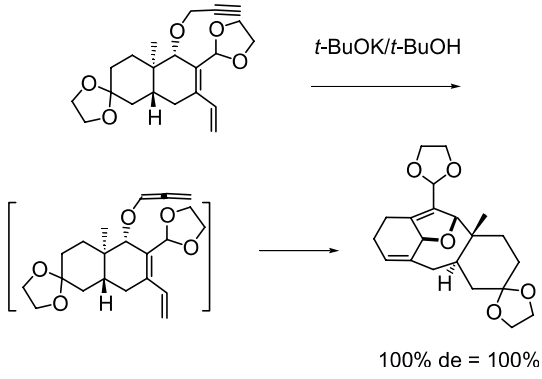
Scheme 69. Asymmetric domino [3,3]/[3,5]-sigmatropic rearrangement reaction.

In addition, a double [3,3]-sigmatropic rearrangement was the key step of the total synthesis of a geldanamycin oncogene inhibitor.[150] A chiral amino sugar was synthesised starting from an *N*-galactosyl derivative through an aza-Cope rearrangement occurring after an initial Lewis acid-mediated ring opening and an iminium salt formed.[151] Finally, selenoxide elimination has been linked with a Claisen rearrangement in a synthesis of (+)-acetoxy-crenulide starting from a chiral auxiliary derived from (*R*)-citronellol (Scheme 70).[152]



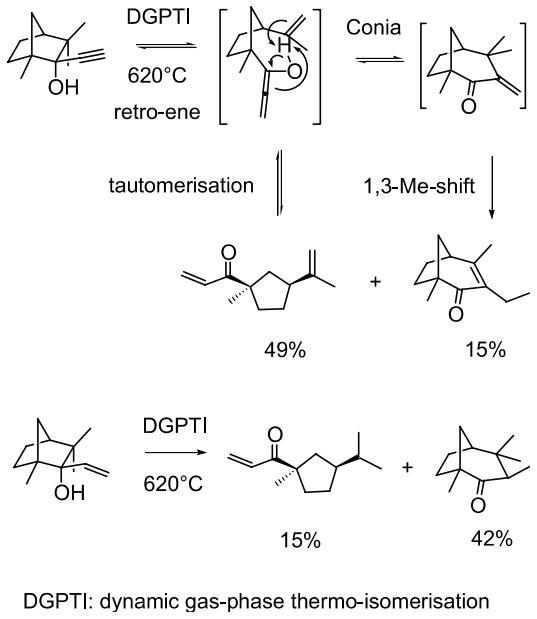
Scheme 70. Asymmetric domino elimination Claisen rearrangement reaction.

In 1986, a combination of a Cope with a Claisen rearrangement was successfully employed to accomplish the total synthesis of the germacrane sesquiterpene, (+)-dihydrocostunolide.[153] The Cope rearrangement was combined with a [2+2] cycloaddition in order to afford the oxa-taxane skeleton by the use of an optically pure Wieland–Miescher ketone derivative (Scheme 71).[154]



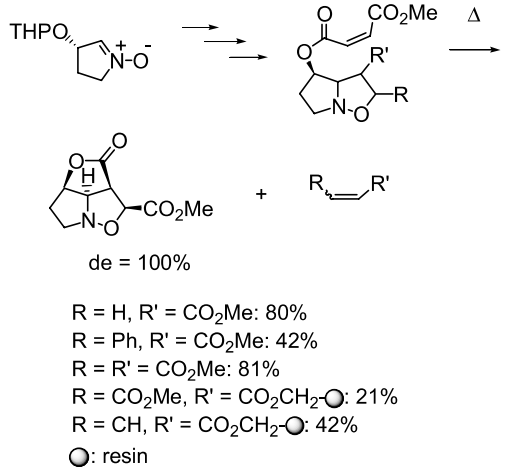
Scheme 71. Asymmetric domino [2+2] cycloaddition Cope rearrangement reaction.

In 2004, Rüedi et al. reported the first example of an asymmetric domino retro-ene Conia reaction that could be implemented to produce optically active bicyclo[3.2.1]-octan-2-ones from the easily available chiral bicyclo[2.2.1]-heptan-2-ols (Scheme 72).[155] Thus, at a temperature of 620 °C, the chiral substrates bearing a hydroxyallyl or a hydroxypropargyl moiety underwent an initial retro-ene reaction under cleavage of the C(2)–C(3) bond to form enol-ene intermediates, with no loss of optical activity. These intermediates then experienced either tautomerisation to the corresponding α,β-unsaturated ketones or subsequent Conia rearrangement under one-carbon ring expansion of the fenchone system to a bicyclo[3.2.1]octane framework.



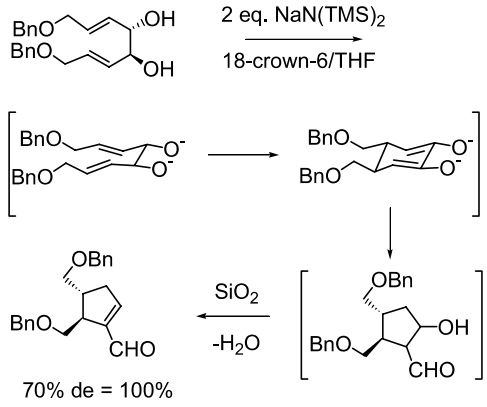
Scheme 72. Asymmetric domino retro-ene Conia reaction.

In 2003, Brandi et al. demonstrated that acrylate- and maleate-functionalised resins could be used to mask the nitrone moiety of a chiral pyrroline *N*-oxide to prevent racemisation at the C-3 stereogenic centre and to link them to a solid phase. After the elaboration of the linked cycloadducts, the product was disconnected from the resin through a 1,3-dipolar cycloreversion intramolecular cycloaddition domino process (Scheme 73).[156]



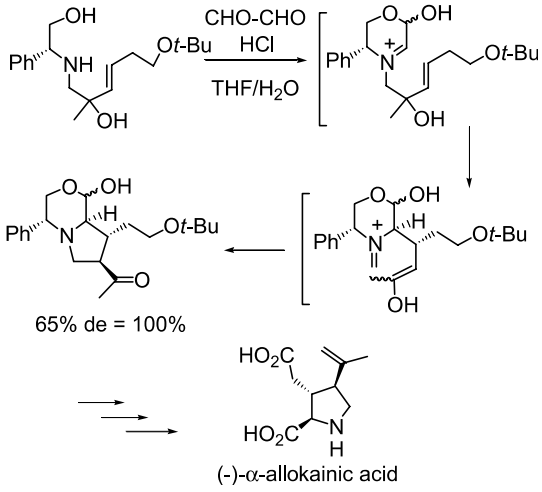
Scheme 73. 1,3-Dipolar cycloreversion intramolecular cycloaddition domino process.

2.3.2. Pericyclic–anionic reactions. Pericyclic processes are most easily coupled to anionic processes, since many rearrangements require deprotonation prior to reaction. The products of these sequences frequently incorporate enolates or other nucleophilic groups that can further react with electrophilic reagents. An interesting dianionic oxy-Cope aldol sequence has been advanced as an efficient route to chiral 1-cyclopentene-carboxaldehyde building blocks for natural product synthesis, starting from a chiral (*E*,*E*)-bis-allylic diol (Scheme 74).[157]



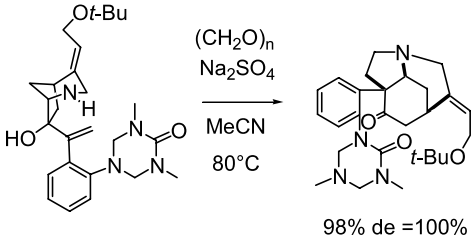
Scheme 74. Asymmetric domino dianionic oxy-Cope aldol reaction.

Several groups have developed asymmetric domino aza-Cope Mannich reactions such as Couty's group, who used this sequence as key step for the synthesis of several nitrogen-containing ring structures including a homochiral proline derivative and the non-proteinogenic amino acid, (−)-α-allokainic acid (Scheme 75).[158]



Scheme 75. Asymmetric domino aza-Cope Mannich reaction.

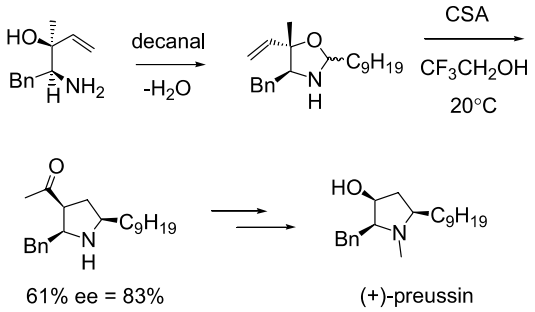
The strychnine synthesis strategy developed by Overman et al. provided an important benchmark of the power of the domino aza-Cope rearrangement Mannich cyclisation reaction to solve problems in alkaloid construction.[159] This central asymmetric domino reaction was accomplished in near-quantitative yield with complete stereoselection (Scheme 76).



Scheme 76. Asymmetric domino aza-Cope Mannich reaction.

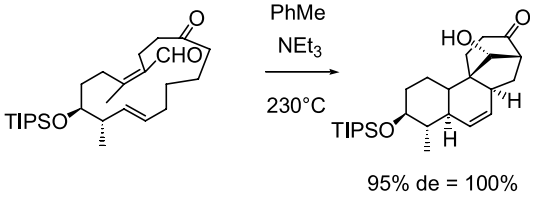
In addition, this latter domino reaction was applied by these authors to a chiral oxazolidine derived from L-phenylalanine

for the development of a total synthesis of the antifungal agent (+)-preussin (Scheme 77).[160] On the other hand, Florent et al. applied a similar methodology for a convenient construction of chiral 4-hydroxy-2-cyclopentenones from a dialdosugar.[161]



Scheme 77. Asymmetric domino aza-Cope Mannich reaction with chiral oxazolidine.

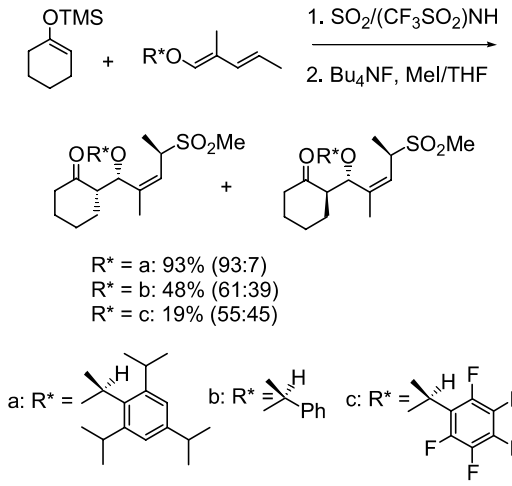
Another powerful asymmetric domino pericyclic–anionic reaction is the Diels–Alder aldol reaction, which has been widely studied by Deslongchamps et al.[162] This methodology was applied to the synthesis of anticancer aphidicolin derivatives, the skeleton of which was formed in one key reaction by this highly stereoselective domino reaction from a chiral macrocycle (Scheme 78).[163]



Scheme 78. Asymmetric domino Diels–Alder aldol reaction.

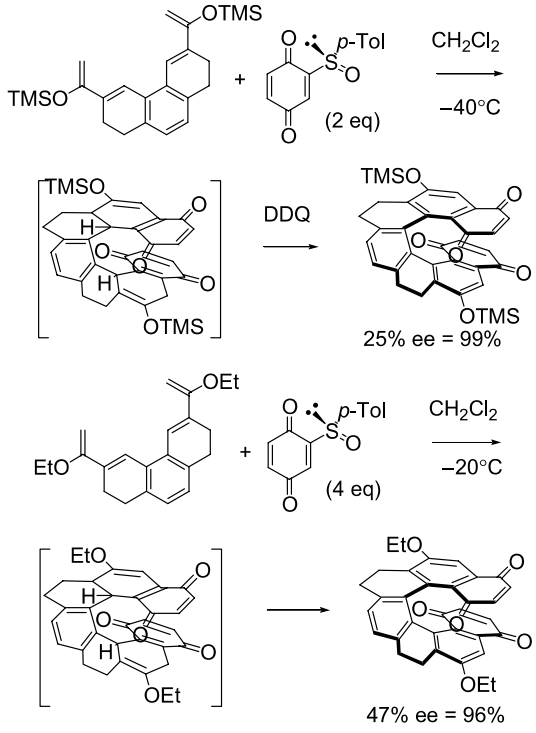
Asymmetric induction in a new domino reaction comprising a [3,3]-sigmatropic rearrangement of chiral allylic thiocyanates followed by intramolecular heterocyclisation was reported by Gonda et al. providing the corresponding 1,3-imidazolidin-2-thiones.[164] On the other hand, Vögel et al. have found a novel C–C bond-forming reaction that condensed enyl silyl ethers with chiral butadienyl-1-yl ethers, SO_2, and C-electrophiles (MeI) to generate polyfunctional sulphones in a one pot reaction. This process was believed to involve a cascade of reactions, starting with the hetero-Diels–Alder addition of SO_2 to the 1,3-dienyl ether, giving the corresponding 3,6-dihydro-1,2-oxathiin-2-oxides in a reversible fashion. The best results were obtained in the presence of 1-(trimethylsilyloxy)-cyclohexene and dienyl ethers bearing Greene's chiral auxiliary (Scheme 79).[165]

Carreno et al. have developed asymmetric domino Diels–Alder cycloaddition pyrolytic sulphoxide elimination reactions as key steps in the synthesis of several natural products such as angucyclinone-type antibiotics from chiral (2-*p*-tolylsulphinyl)-1,4-naphthoquinone,[166] and (+)-royleanone from chiral sulphinylquinones.[167] More recently, these authors involved the same domino reaction in order to achieve the first asymmetric synthesis of [5]helicenequinones and bisquinones from chiral (2-*p*-tolylsulphinyl)-1,4-benzoquinone.[168] In addition, in 2005,



Scheme 79. Asymmetric domino hetero-Diels–Alder Mukaiyama reaction.

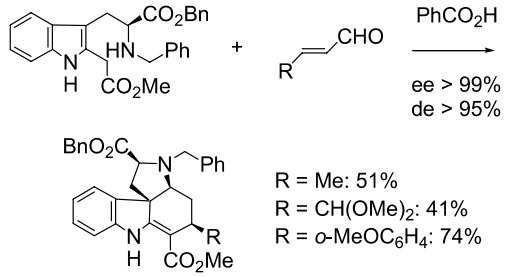
this methodology allowed the development of the first non-photochemical asymmetric access to helically chiral tetrahydro[7]helicene bisquinones from the reaction between several 3,6-divinyl-1,2,7,8-tetrahydrophenanthrenes and chiral (2-*p*-tolylsulphinyl)-1,4-benzoquinone, giving rise to the enantiopure heptacyclic system in an efficient one pot, six-step, double-domino process (Scheme 80).[169]



Scheme 80. Asymmetric domino Diels–Alder cycloaddition pyrolytic sulphoxide elimination reaction.

In 2003, Arseniyadis et al. developed several new asymmetric domino reactions, among which was a retro-Claisen intramolecular aldol reaction, allowing the synthesis of the bicyclo[3.2.2]ring system from the fused [6+7]-ring system via a mild base treatment.[170] Finally, an asymmetric domino condensation, [3,3]-sigmatropic rearrangement, and cyclisation sequence was elaborated by Kuehne et al. with the aim of generating tetracyclic

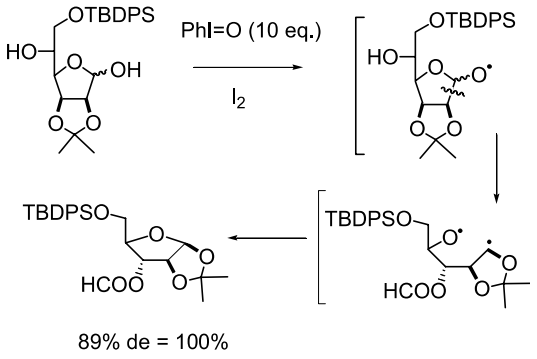
ABCE intermediates for the synthesis of strychnan- and aspidospermatan-type alkaloids (Scheme 81).[171] The chiral auxiliary was a tryptophan-derived diester, which reacted with an α,β-unsaturated aldehyde, providing a single stereoisomer of the corresponding tetracyclic product.



Scheme 81. Asymmetric domino [3,3]-sigmatropic rearrangement cyclisation reaction.

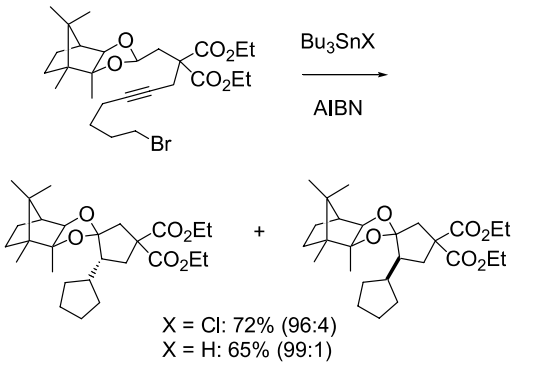
2.4. Radical sequences

The potential of these reactions is very high due to the mild conditions under which radicals are generated.[172] These mild reaction conditions tolerate a wide range of functionality in the substrates and complex synthetic targets can therefore be prepared with the minimum use of protecting groups. The majority of transformations in this category involve radical–radical tandem processes. As an example, carbohydrates have been converted into the next lower homologues by a domino β-fragmentation cyclisation sequence.[173] Thus, treatment of a mannofuranose with 10 equiv of iodosylbenzene and 3 equiv of iodine afforded the corresponding fully protected arabinofuranose. As the reaction proceeded, C(2) became C(1) and the anomeric carbon of the starting sugar became the formyl protecting group in the product via radicals (Scheme 82). The high selectivity of the reaction, together with the natural chirality of the sugars, made this procedure highly valuable as a source of chiral building blocks for organic synthesis.



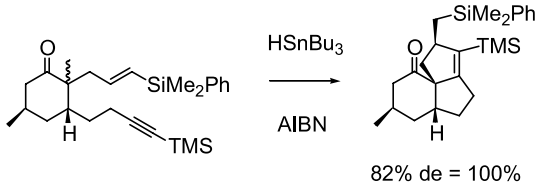
Scheme 82. Asymmetric domino β-fragmentation cyclisation reaction.

In 1998, Bertrand et al. reported that sterically constrained 1,3-dioxabicyclo[4.4.0]decan-2-yl radicals, readily available from 10-camphorsulphonic acid, underwent intramolecular hydrogen abstraction followed by 5-*exo*-dig cyclisation upon treatment with tributyltin hydride (or chloride) and AIBN, with nearly complete stereoinduction (Scheme 83).[174]



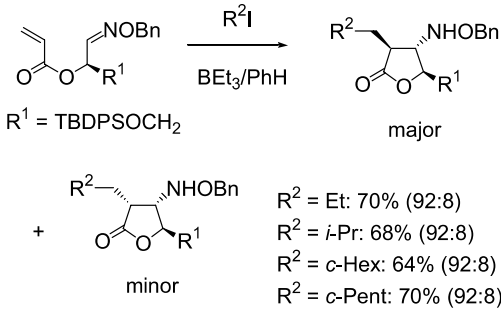
Scheme 83. Asymmetric domino radical reaction with sterically constrained camphor-derived 1,3-dioxolanyl radicals.

A very efficient α-carbonyl radical-initiated domino cyclisation reaction was developed by Sha et al. and applied as the key step of the first total synthesis of (+)-paniculatine.[175] In this process, the radical generated from a chiral iodoketone underwent a domino radical cyclisation reaction to produce the corresponding angularly fused tricyclic ketone (Scheme 84).



Scheme 84. Asymmetric domino radical cyclisation initiated with α-carbonyl radicals.

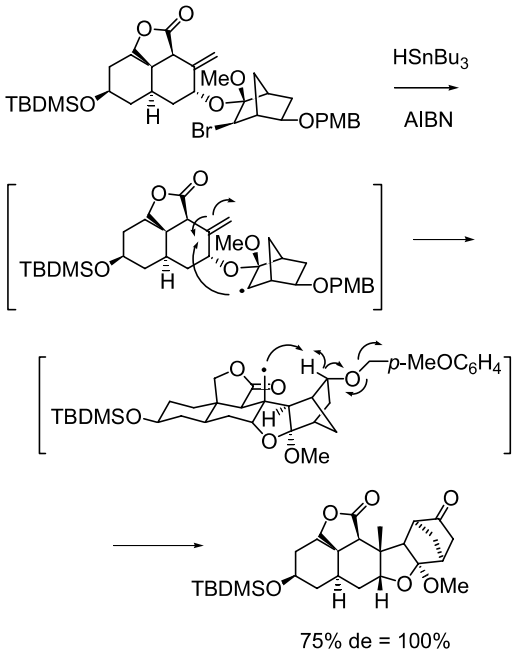
In 2000, Naito et al. reported a domino radical addition cyclisation reaction involving substrates having two different radical acceptors such as acrylate and aldoxime ether moieties. This new free radical-mediated Mannich-type reaction proceeded smoothly via a tandem C–C bond-forming process. Furthermore, the diastereoselective domino reaction provided a novel method for the asymmetric synthesis of γ-butyrolactones, easily convertible into the corresponding β-amino acid derivatives (Scheme 85).[176]



Scheme 85. Asymmetric Mannich-type domino radical addition cyclisation reaction.

With the aim of developing a total synthesis of azadirachtin, Nicolaou et al. studied a radical cascade reaction generated from a chiral bromoketal, which generated for the first time the corresponding secondary radical.[177] This latter radical underwent a 5-*exo-trig* cyclisation to forge the C(8)–C(14)

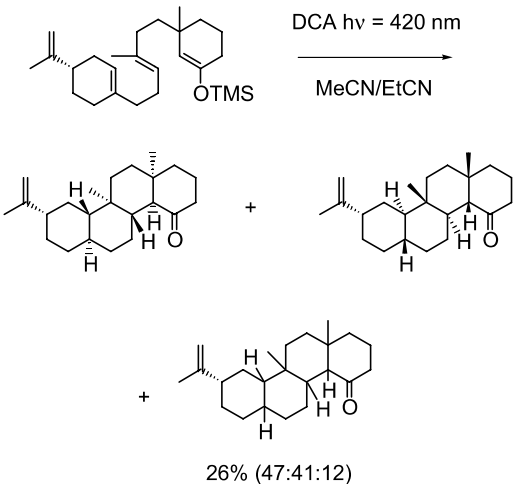
bond of azadirachtin, leading to a highly reactive primary radical. The proximity of the formed radical centre to the hydrogen atom on the carbon atom that bore the PMB ether, five bonds away, coupled with the overall rigidity and reactivity of the system, apparently allowed a subsequent 1,5-*H* shift, with concomitant oxidative rupture of the benzyl bond, leading to the final product (Scheme 86).



Scheme 86. Asymmetric radical domino 5-*exo-trig* cyclisation 1,5-H shift reaction.

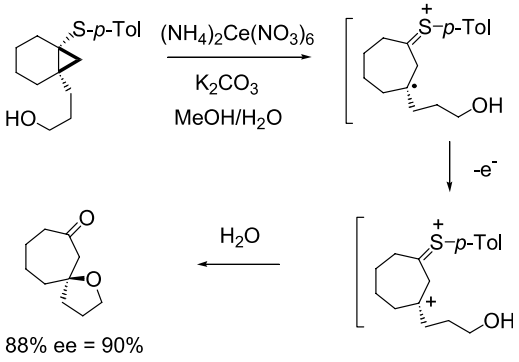
A major drawback in radical chemistry is a suitable and practical activation of the precursor molecule, for example, the commonly used tin hydrides as well as transition metals, in electron-transfer activation, counteract the efficiency and attractiveness of the domino synthesis, due to environmental problems.[178] Photoinduced electron-transfer (PET) activation offers an attractive alternative to these established methods since solely catalytic amounts of a sensitiser are required. Furthermore, PET allows the selective excitation of the sensitiser by light.[179] As an example, PET was used to activate chiral silyl enol ethers, generating the corresponding radical cations, which then underwent ring closure reactions to yield novel steroid backbones (Scheme 87).[180] These domino reactions proceeded with high stereoselectivity and used 9,10-dicyanoanthracene (DCA) as a sensitiser.

Several papers have described radical–cationic processes for the synthesis of ring compounds from sulphur- and selenium-containing substrates. As an example, Iwata et al. have detailed an oxidative ring expansion involving radical-cation intermediates that preserved the chirality built into the substrate.[181] In this work, an optically active 1-arylthiobicyclo[4.1.0]heptane, substituted at C(6) by a side chain bearing a nucleophilic functional group, was subjected to single electron transfer with ceric ammonium nitrate. The resulting radical cation underwent three-ring fission to afford a radical cation, loss of an electron to give the corresponding carbocation, and attack by the side-chain



Scheme 87. PET-initiated domino cyclisations of chiral silyl enol ethers.

nucleophile to produce the corresponding spiro ether, after aqueous workup (Scheme 88).

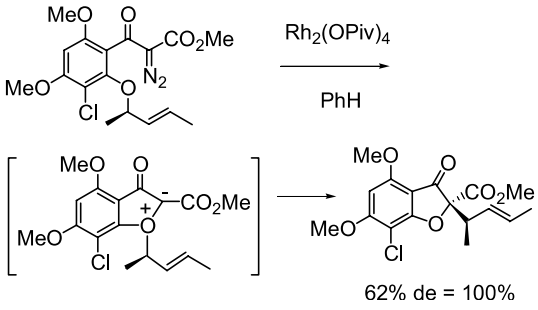


Scheme 88. Asymmetric domino radical–cationic process.

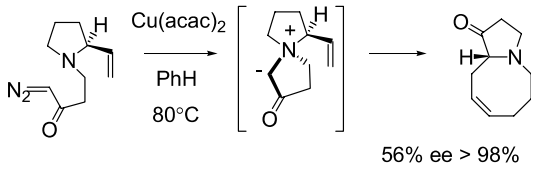
2.5. Carbene sequences

Cascade reactions initiated from carbene intermediates have been a productive area of discovery during the past 10 years. Carbenes and carbenoids can react with a series of functional groups, and a more reactive intermediate (ylide) is frequently formed that can undergo further subsequent reactions. Davies et al. have shown that oxygen-containing chiral auxiliaries induced modest enantioselectivity in cyclopropanation Cope reactions by blocking reaction at one face of a rhodium carbenoid through intramolecular coordination.[182] Pirrung et al. have used a carbene-based domino reaction in an enantioselective synthesis of the antifungal agent, (+)-griseofulvin.[183] In the presence of $Rh_2(OPiv)_4$, a chiral diazoketoester produced the corresponding oxonium ylide, which underwent [2,3]-sigmatropic rearrangement to afford the final product as a single stereoisomer (Scheme 89).

A related process was employed in an approach to the CE-ring system of the manzamine and ircinal alkaloids.[184] The key step was the thermolysis of an (*S*)-prolinol-derived diazoketone in the presence of $Cu(acac)_2$, which resulted in carbenoid formation, cyclisation to the corresponding ammonium ylide, and [2,3]-sigmatropic rearrangement to give the final azabicyclo[6.3.0]undecanone (Scheme 90).

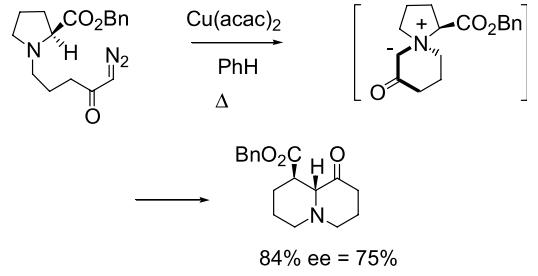


Scheme 89. Asymmetric carbene-based domino reaction with chiral diazoketoester.



Scheme 90. Asymmetric carbene-based domino reaction with chiral diazoketone.

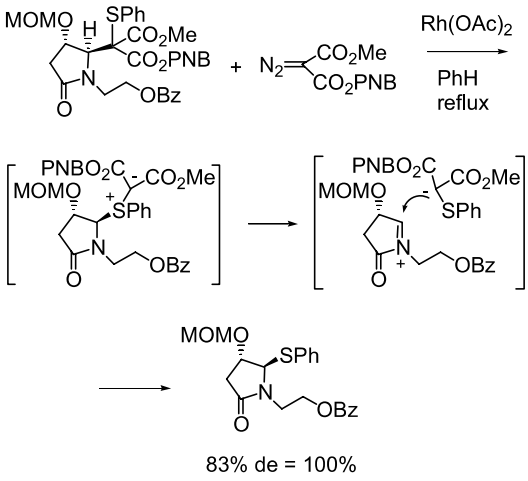
In a series of papers, West et al. have reported Stevens' [1,2]-alkyl shifts in oxonium and ammonium ylides, generated by carbene interaction with ether[185] and amine functional groups.[186] As an example, thermolysis of the chiral diazoketone depicted in Scheme 91 in the presence of $Cu(acac)_2$ afforded the corresponding quinolizidine, which was further converted into (−)-epilupinine.[187]



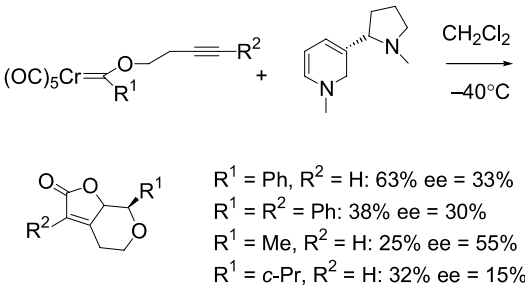
Scheme 91. Asymmetric carbene-based domino reaction involving Stevens' [1,2]-alkyl shifts.

In 1988, Kametani et al. investigated the intermolecular carbenoid displacement of an optically active sulphide derived from (*S*)-malic acid with α-diazomalonate in the presence of rhodium acetate to afford the carbon-introduced product (Scheme 92).[188] This original domino process was applied to the synthesis of biologically important pyrrolizidine alkaloids such as (+)-heliotridine and (+)-retronecine.

On the other hand, Hegedus et al. reported the synthesis of optically active β-lactams based on the photolytic reaction of in situ-generated chiral chromium aminocarbene complexes with imines.[189] This methodology was applied to the total synthesis of (+)-thienamycin. More recently, Rudler et al. have demonstrated that chromium alkoxy-carbene complexes tethered to a triple bond reacted with a series of chiral dihydropyridines, among which was *N*-methyl-1,2-dihydronicotine, to give, enantioselectively, upon cascade insertion reactions, polycyclic butenolides (Scheme 93).[190]

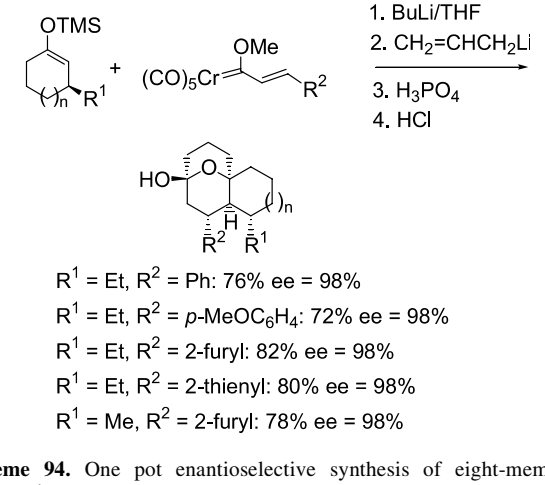


Scheme 92. Asymmetric domino intermolecular carbenoid displacement reaction.



Scheme 93. Asymmetric cascade insertion reactions with alkoxycarbene complexes.

In addition, Barluenga et al. developed, in 2002, a one pot enantioselective formation of eight-membered rings with up to five stereogenic centres from alkenyl Fisher carbene complexes and ketone enolates.[191] This sequence, which could also be included in Section 2.7, involves the coupling of three components in very high ees (Scheme 94).

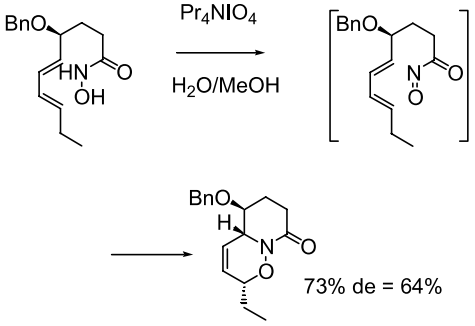


Scheme 94. One pot enantioselective synthesis of eight-membered carbocycles.

2.6. Miscellaneous sequences

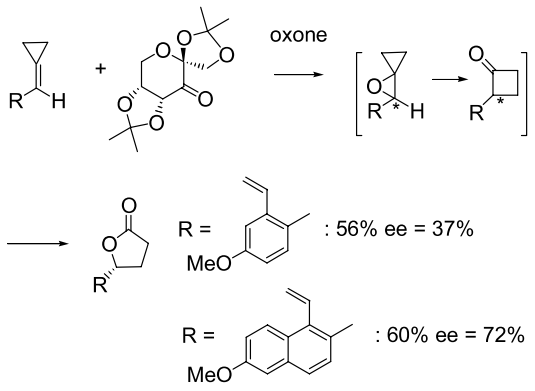
This section describes unrelated reactions, which cannot be included in the other sections, because of their different

mechanisms, among which are asymmetric domino reactions including an oxidation reaction as the first step. As a preliminary example, a domino oxidation Diels–Alder sequence was the key step of a total synthesis of (−)-pumiliotoxin C, starting from a chiral hydroxamic acid derived from L-malic acid (Scheme 95).[192]



Scheme 95. Asymmetric domino oxidation Diels–Alder reaction.

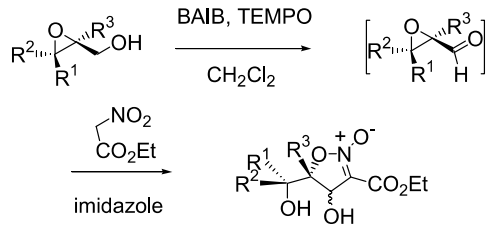
Another example was described by Ihara et al. as a novel method for the synthesis of chiral 4-aryl-γ-butyrolactones via asymmetric domino epoxidation ring expansion Baeyer–Villiger reaction of cyclopropylidene derivatives in the presence of a fructose-derived ketone and oxone (Scheme 96).[193]



Scheme 96. Asymmetric domino epoxidation ring expansion Baeyer–Villiger reaction.

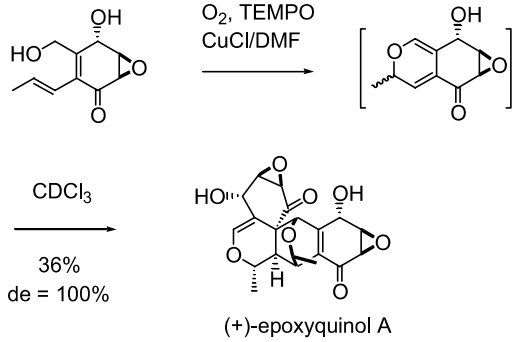
In 2001, Righi et al. reported the one pot direct conversion of chiral 2,3-epoxyalcohols into enantiomerically pure 4-hydroxy-4,5-dihydroisoxazole 2-oxides that required no isolation of the intermediate aldehyde.[194] This domino reaction was carried out under Piancatelli oxidation conditions,[195] followed by the addition of ethyl nitroacetate and imidazole (Scheme 97). In 2002, these authors reported the extension of this one pot multibond-forming process to chiral aziridine alcohols as the starting materials.[196]

A cascade oxidation electrocyclisation Diels–Alder dimerisation sequence of 2*H*-pyran monomers obtained by selective primary oxidation of a chiral epoxyquinol was observed during the NMR analysis of the crude product of the reaction, allowing the asymmetric synthesis of the natural product, (+)-epoxyquinol A (Scheme 98).[197]



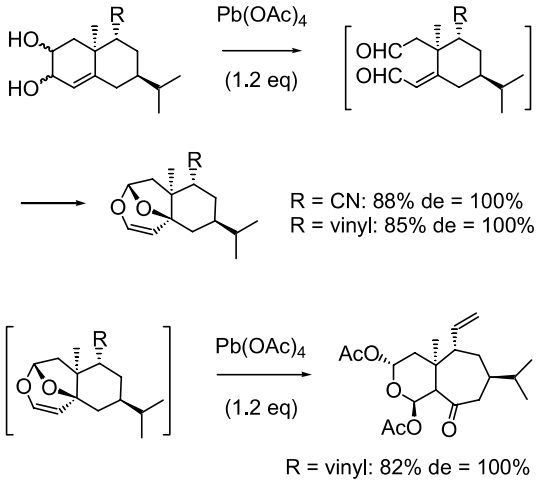
$R^1 = R^2 = R^3 = H$: 81% 4,5-*cis*:4,5-*trans* ratio = 60:40
$R^1 = R^2 = H$, $R^3 = Me$: 97% 4,5-*cis*:4,5-*trans* ratio = 72:28
$R^1 = R^3 = H$, $R^2 = Ph$: 71% 4,5-*cis*:4,5-*trans* ratio = 70:30

Scheme 97. Asymmetric domino oxidation nitroaldol reaction.



Scheme 98. Cascade oxidation electrocyclisation Diels–Alder dimerisation sequence.

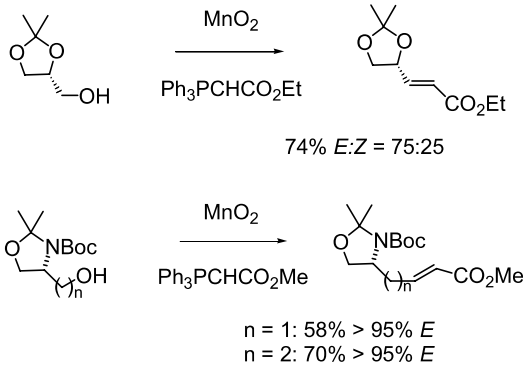
In 2003, Arseniyadis et al. developed lead tetraacetate-mediated domino reactions on (*R*)-(−)-carvone-derived bicyclic unsaturated 1,2-diols.[170] A first domino oxidation Diels–Alder reaction was observed when the chiral auxiliary was treated with 1.2 equiv of $Pb(OAc)_4$, providing the corresponding stable tricyclic enol ether, while subsequent treatment of the latter ether with an extra 1.2 equiv of $Pb(OAc)_4$ produced the corresponding ring-enlarged compound, through a second domino oxyplumbation ring expansion reaction (Scheme 99).



Scheme 99. Asymmetric domino oxidation Diels–Alder reaction and/or oxyplumbation ring-expansion reaction.

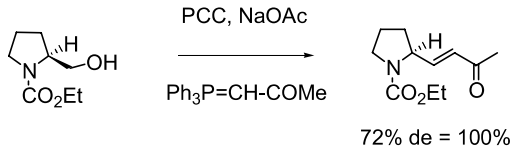
Recently, various other asymmetric domino reactions have been developed by Moeller et al. involving the domino

anodic coupling Friedel-Crafts alkylation strategy applied to the synthesis of (−)-alliacol A,[198] and by Nicolaou et al. using an oxidation polycyclisation reaction.[199] The sequence of oxidation of a primary alcohol and its condensation with a stable Wittig reagent is a routinely used step in organic synthesis. The most common problem associated with this sequence is the handling of the intermediate aldehydes. This problem has been overcome by the recent development of domino primary alcohol oxidation Wittig reactions such as those using a stabilised phosphorus ylide-$BaMnO_4$ system.[200] Manganese dioxide was used as the oxidant to in situ generate *N*-protected β-aminoaldehydes from enantiopure aminoalcohols in the presence of carbonyl-stabilised Wittig reagents, to produce, via a one pot procedure, the corresponding optically active α,β-unsaturated esters or ketones.[201] This oxidant was also employed by Taylor et al. for the domino reaction of several enantiomerically pure primary alcohols (Scheme 100).[202]



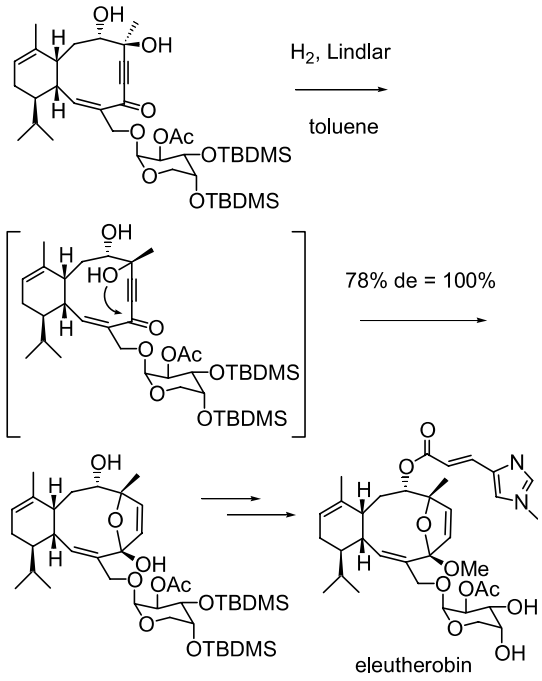
Scheme 100. Asymmetric domino primary alcohol oxidation Wittig reaction using MnO_2.

Crich et al. have used a hypervalent iodine reagent, *o*-iodoxybenzoic acid (IBX), for the selective oxidation of the 5′-OH in 2′-deoxynucleosides with in situ Wittig olefination, giving chiral 5′-homologated nucleosides.[203] In addition, Tilve et al. demonstrated in 2004 that the use of pyridinium chlorochromate (PCC) as an oxidant was also compatible with the domino process.[204] In particular, an asymmetric version was applied to *N*-ethoxycarbonyl-prolinol, providing a potential precursor for the synthesis of ABT-418, a potent cholinergic agent (Scheme 101).



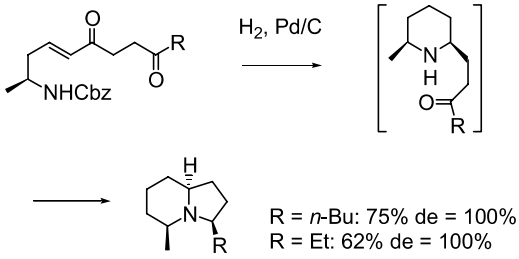
Scheme 101. Asymmetric domino primary alcohol oxidation Wittig reaction using PCC.

On the other hand, several asymmetric domino reactions including a reduction as the first step are also present in the literature. Thus, Nicolaou et al. have developed powerful asymmetric reduction cyclisation sequences in order to prepare important biological products such as eleutherobin (Scheme 102),[205] a potent antitumour agent, and diazonamide A.[206]



Scheme 102. Asymmetric domino reduction cyclisation reaction.

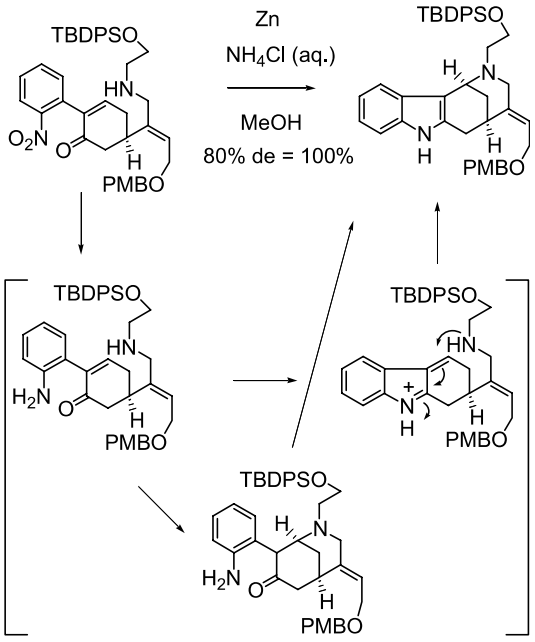
In 2003, Blechert et al. reported an efficient stereoselective synthesis of 3,5-dialkyl-substituted indolizidine alkaloids, based on a novel sequence of a cross-metathesis reaction of an α,β-unsaturated ketone and a chiral homoallylic amine, followed by a domino reaction involving hydrogenation, *N*-deprotection, and two diastereoselective reductive aminations (Scheme 103).[207]



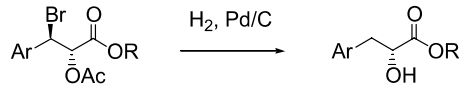
Scheme 103. Asymmetric domino double reductive amination reaction.

An enantioselective total synthesis of (−)-strychnine was accomplished in 2004, through the use of a domino cyclisation reaction, beginning by the reduction of a nitro group to an amine and allowing the simultaneous construction of the B- and D-rings of strychnine.[208] This domino cyclisation might proceed by the following sequence: either (1) reduction of the nitro group to the amine by Zn, (2) indole formation, and (3) 1,4-addition of the secondary amine, or (1) reduction of the nitro group to amine by Zn, (2) 1,4-addition of the secondary amine, and (3) irreversible indole formation of the aniline moiety with the resulting ketone (Scheme 104).

In the course of planning a novel route to chiral α-hydroxyesters from *syn*-1,2-diols, Lawrence et al. discovered a curious domino reaction, since the hydrogen bromide that was released in the hydrogenolysis reaction



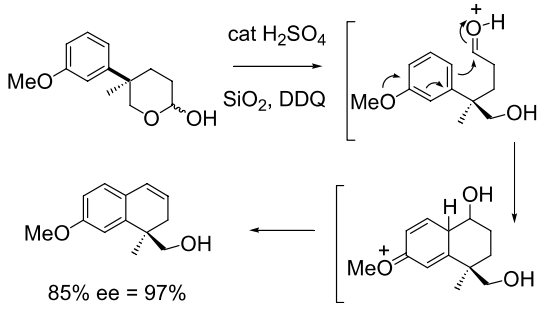
Scheme 104. Asymmetric domino cyclisation reaction promoted by Zn.



Scheme 105. Asymmetric domino hydrogenolysis methanolysis reaction.

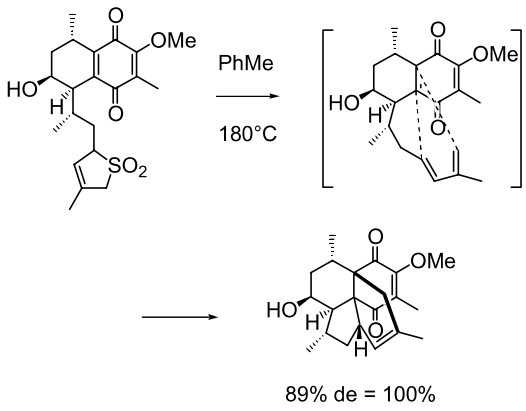
catalysed the subsequent methanolysis of the acetyl group (Scheme 105).[209]

A cationic cyclisation oxidation sequence has been employed in a formal synthesis of (−)-aphanorphine.[210] Exposure of a chiral lactol to catalytic sulphuric acid and 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) on silica gel resulted in cyclisation of the electron-rich aromatic ring on the protonated aldehyde, rearomatisation, and oxidation to the corresponding alcohol (Scheme 106).



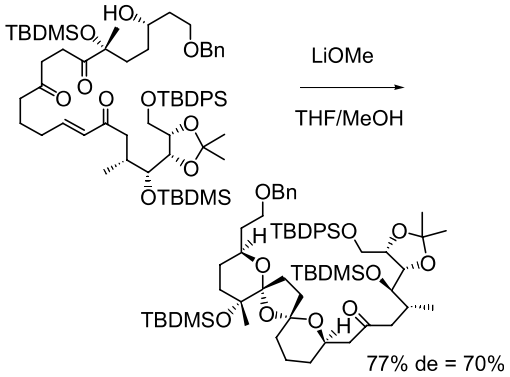
Scheme 106. Asymmetric domino cationic cyclisation oxidation reaction.

With a view to achieving a total synthesis of (−)-colombiasin, a potent antibiotic, Nicolaou et al. have developed a domino reaction involving a cheletropic elimination of SO_2 from a chiral sulphone, which was then coerced to participate in a Diels–Alder reaction, which furnished the complete tetracyclic skeleton of the natural product (Scheme 107).[211]



Scheme 107. Asymmetric domino cheletropic SO_2-elimination intramolecular Diels–Alder reaction.

In order to prepare the C10–C31 (BCDEF-ring) portion of pinnatoxin A, a domino double hemiketal formation intramolecular hetero-Michael addition reaction was performed by Hashimoto et al. allowing the construction of the 6,5,6-dispiroketal (BCD-ring) system (Scheme 108).[212]

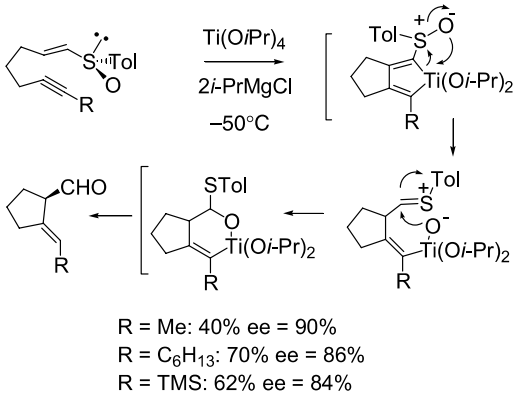


Scheme 108. Asymmetric domino double hemiketal formation intramolecular hetero-Michael addition reaction.

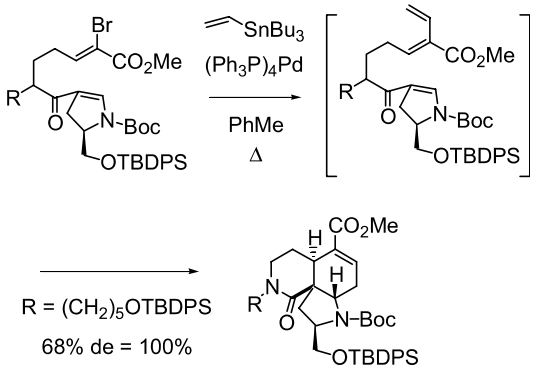
In 2002, Sato et al. reported an asymmetric domino cyclisation Pummerer reaction of chiral sulphoxides, which was promoted by a Ti(II) alkoxide reagent, [Ti(O*i*Pr)$_4$]/2*i*-PrMgCl.[213] The formation of the final chiral cyclic aldehyde could be rationalised by the titanium-mediated cyclisation of the chiral sulphoxide giving the corresponding titanacycle, followed by the subsequent Pummerer-type rearrangement to furnish the final product after aqueous workup (Scheme 109).

The enantioselective syntheses of the complex manzamine alkaloids were achieved by Martin et al. by employing a convergent strategy that featured a novel asymmetric domino Stille Diels–Alder reaction with a chiral dihydropyrrole to construct the tricyclic ABC-ring core embodied in these alkaloids (Scheme 110).[214]

More recently, Aubé et al. have reported an asymmetric synthesis of dendrobatid alkaloids using a domino ring-opening–ring-closing metathesis reaction as the key step,

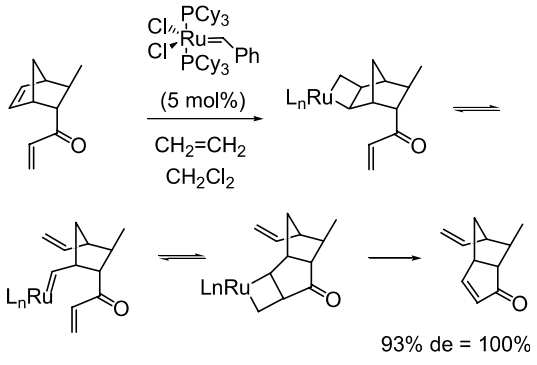


Scheme 109. Asymmetric domino cyclisation Pummerer reaction promoted by titanium(II).



Scheme 110. Asymmetric domino Stille Diels–Alder reaction.

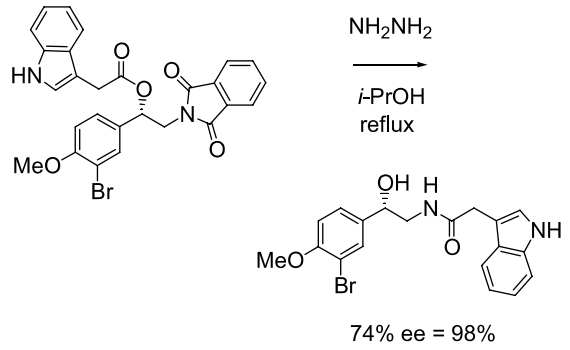
which effected an overall [2.2.1]→[3.3.0] skeletal rearrangement, to deliver a chiral diquinane derivative (Scheme 111).[215]



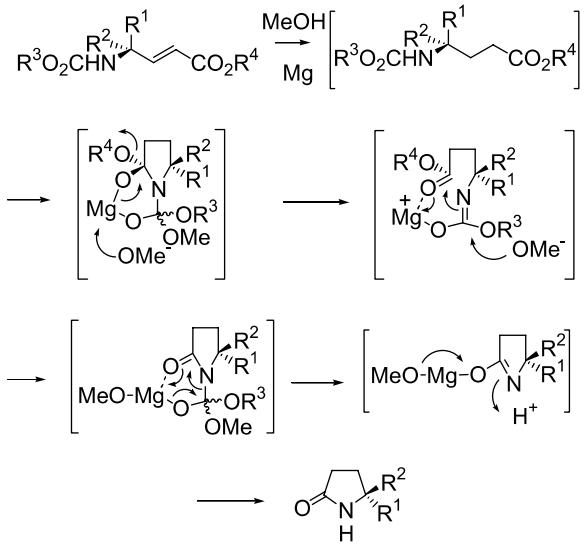
Scheme 111. Asymmetric domino ring-opening ring-closing metathesis reaction.

On the other hand, a domino deprotection rearrangement of a chiral phthalimido indole acetate was the key step of the first total synthesis of the marine natural product, (+)-chelonin B, reported by Lawrence et al. (Scheme 112).[216]

An unusual one pot reaction of chiral *N*-alkoxycarbonyl-γ-amino-α,β-unsaturated carboxylates with magnesium in methanol afforded chiral 5-substituted 2-pyrrolidinones through a mechanism involving the possible formation of the corresponding intermediate *N*-protected γ-aminocarboxylate (Scheme 113).[217]

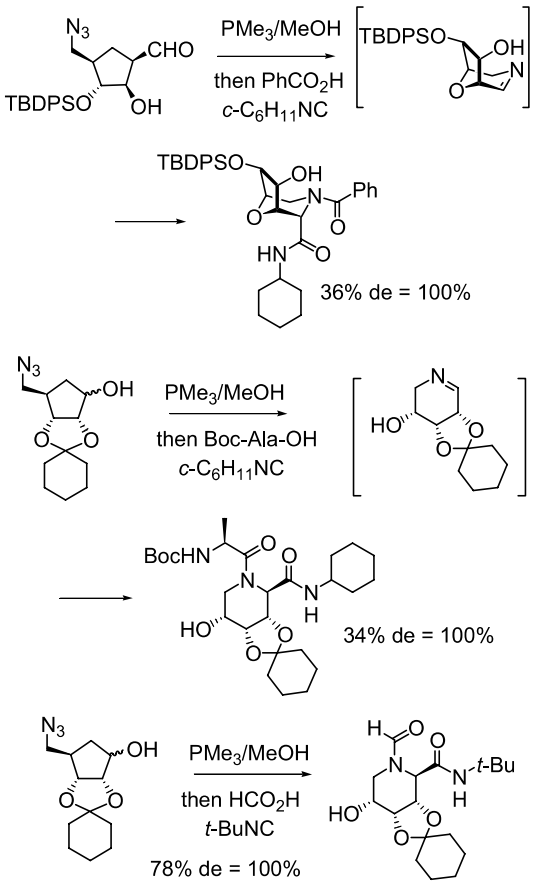


Scheme 112. Domino deprotection rearrangement of chiral phthalimido indole acetate reaction.



Scheme 113. Synthesis of chiral pyrrolidinones through domino reduction cyclisation reaction.

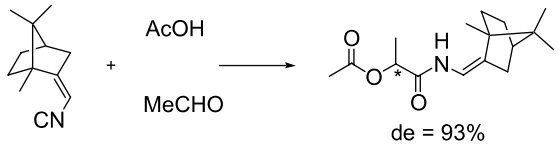
Pearson et al. have employed a beautiful asymmetric domino reaction involving a 1,3-dipolar azide cycloaddition followed by fragmentation of the thus-formed triazoline with concomitant hydride migration, and intramolecular *N*-alkylation in the course of preparation of (−)-slaframine.[218] Very recently, Overkleeft et al. reported the synthesis of various chiral functionalised heterocycles such as piperidines and morpholines, starting from orthogonally protected carbohydrate-derived azido-aldehydes, by combining a Staudinger, aza-Wittig and an Ugi three-component reaction in a one pot process. The application of this reaction on readily available azido-aldehydes gave easy access to highly functionalised, enantiomerically pure pipecolic acid amides and bridged morpholine amide derivatives (Scheme 114).[219]



Scheme 114. Asymmetric domino Staudinger, aza-Wittig, Ugi multicomponent reaction.

2.7. Domino multicomponent reactions

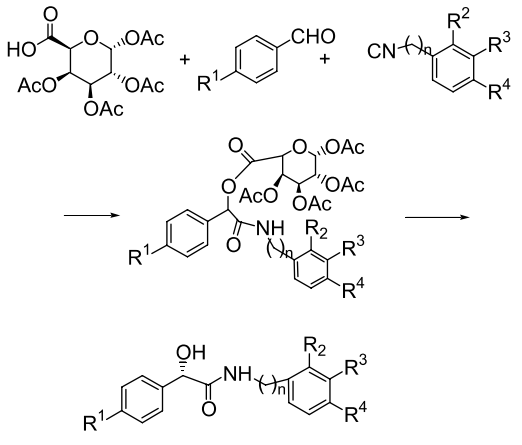
Multicomponent reactions (MCRs) are those in which three or more reactants come together (or nearly together) in a single reaction vessel to form a new product, which contains portions of all the components.[220] MCRs convert more than two educts directly into their product by one pot reactions. The starting materials for this kind of chemical transformation are rich in functional groups. Typically, MCRs lead to very complex products by reacting structurally simple starting materials. The MCR proceeds according to the domino principle, since subsequent transformations are a consequence of the functionalities produced in the previous transformation. These reactions are highly flexible, (chemo)-selective, convergent and atom efficient processes of high exploratory power. As such, they closely approach the concept of ideal synthesis. Increasingly severe economic and environmental constraints force the synthetic community to think about novel procedures and synthetic concepts to optimise efficiency. In an ideal synthetic route, the target molecule is prepared from readily available starting materials in one simple, safe, environmentally acceptable, and resource-effective operation that proceeds quickly and in quantitative yield.[221] Inspired by the mode of action of nature, numerous groups have reported the multistep, single-operation construction of complex molecules, in which several bonds are formed in one sequence without isolating the intermediate. Such processes, which are commonly referred to as tandem reactions, allow the ecologically and economically favourable production of a wide range of organic compounds and have brought the concept of ideal synthesis closer to reality.[222] A recent microreview describes multicomponent reactions in which the use of 1,3-dicarbonyl derivatives is necessary.[223] Despite intense interest, there are few reports of diastereo- or enantioselective MCRs for the synthesis of stereochemically complex polycyclic compounds. Asymmetric multicomponent reactions have been very recently reviewed by Yus et al.[4] Isocyanides have been widely involved in MCRs such as the Passerini and Ugi reactions.[224] Indeed, one of the most classical MCRs is the Passerini reaction occurring between carboxylic acids, oxo compounds and C-isocyanides opening the access to α-acyloxycarboxamides. Mostly, it was stated that chiral isocyanides have no influence on the diastereoselectivity of the Passerini reaction. The camphor-derived α,β-unsaturated isocyanide depicted in Scheme 115 was, however, an exception. Thus, the Passerini reaction of this chiral isocyanide with acetic acid and acetaldehyde yielded the corresponding product with 93% de.[225]



Scheme 115. Asymmetric Passerini reaction with a camphor-derived isocyanide.

In addition, Ziegler et al. have investigated the Passerini reaction in the presence of other chiral isocyanides such as benzyl- and acetyl-protected isocyanoglucose derivatives, but the stereoselectivity was, in most of these cases, relatively low.[226] The use of chiral benzaldehydes did not give better results.[227] A comprehensive study of the Passerini reaction has been performed with chiral α-aminoaldehydes derived from natural amino acids.[228] The results were very homogeneous, independent of the carboxylic acid or isocyanide reagents used, and the aldehyde side chain was found to have little influence on the diastereoselectivity. In contrast, the first examples of a highly stereoselective Passerini reaction were achieved in 2003 by involving chiral acids.[229] Thus, the use of 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid in the presence of benzaldehydes and isocyanides allowed the synthesis of enantiopure mandelamides (Scheme 116).

Combinations of two chiral reagents have also been studied such as chiral natural α-amino acids with chiral α-aminoaldehydes employed in the course of the synthesis of serine proteases,[230] or chiral aldehydes and isocyanides involved in the synthesis of eurystatin A.[231] These methodologies did not, however, allow good stereoselectivities. An enantioselective Passerini reaction performed in the presence of a chiral catalyst will be developed in Part B of this report. In addition, a diastereoselective Passerini reaction was performed with acyl cyanides, instead of classical aldehydes, to yield a 1:1 diastereoisomeric mixture of the expected α-alkanoyloxy-α-cyanoamides.[232]

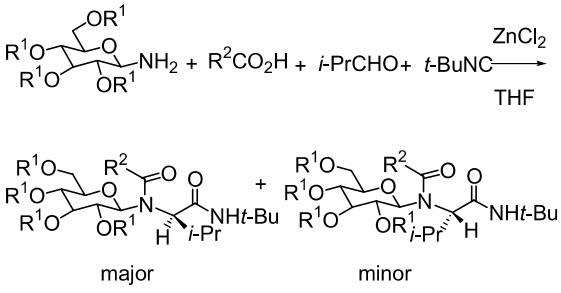


R^1 = R^2 = H, R^3 = R^4 = OMe, n = 2: 63% ee = 86%
R^1 = Br, R^2 = H, R^3 = OMe, R^4 = OCH_2CCH, n = 2: ee = 96%
R^1 = Cl, R^2 = H, R^3 = OMe, R^4 = OH, n = 2: ee = 42%
R^1 = Br, R^2 = Me, R^3 = R^4 = H, n = 0: ee = 12%
R^1 = *i*-Pr, R^2 = R^3 = R^4 = H, n = 1: ee = 80%

Scheme 116. Asymmetric Passerini reaction with 1,2,3,4-tetra-*O*-acetyl-α-D-galacturonic acid.

Ugi has widely studied, and given his name to, the reaction which is, typically, a four-component condensation between a carboxylic acid, an oxo compound, a C-isocyanide, and an amine component forming an α-aminoamide.[224] This reaction has been applied in the asymmetric synthesis of amino acids. In their early work, Ugi et al. determined that the use of a chiral acid or isonitrile in the reaction did not provide any degree of stereoselectivity.[233] In contrast, chiral ferrocenylamine inputs resulted in the synthesis of nonracemic amino acid derivatives with low to modest levels of diastereoselectivity.[234] Kunz et al. have developed more versatile chiral auxiliaries for the Ugi reaction using carbohydrate derivatives.[235] High enantiomeric ratios (>90%) of (*R*)-amino acids were obtained in reactions employing a galactosylamine derivative.[235a] A drawback of this asymmetric Ugi reaction was that high levels of stereoselectivity were only observed for reactions using *tert*-butyl isonitrile. The asymmetric synthesis of (*S*)-amino acids via the Ugi reaction was achieved using an arabinosylamine derivative, but the stereoselectivity was not as high as that observed in the synthesis of the corresponding (*R*)-enantiomer.[235b] A single variant on the chemistry developed by Kunz has been reported by Goebel et al.[236] In 1991, these authors showed that 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines used as chiral amine components were as favourable as the *O*-acyl-aldopyranosyl-amides of Kunz et al. (Scheme 117).[236a]

In addition, a 2-acetamido-glucosylamine derivative was shown to provide high levels of stereoselectivity (de>99%) for the (*R*)-amino acid derivative in the Ugi reaction, even if nonsterically demanding isonitriles were employed.[236b] No hydrolysis of the amide product was, however, reported, and a complementary method for the synthesis of the (*S*)-amino acid was not achieved. The chemical conversion of an Ugi product is restricted by the need to selectively hydrolyse a secondary amide functional group. Linderman et al. have

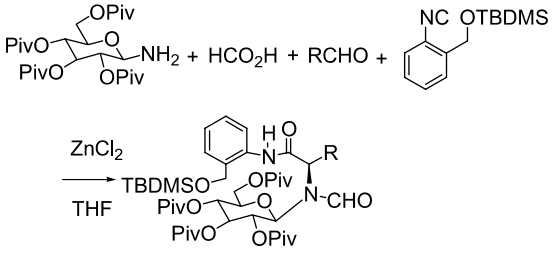


major minor

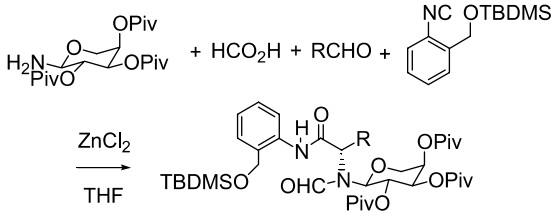
R^1 = Me, R^2 = $ClCH_2$: 78% de = 74%
R^1 = Me, R^2 = CF_3CO-Gly-OH: 70% de = 69%
R^1 = Me, R^2 = Ph: 70% de = 59%
R^1 = Et, R^2 = Ph: 77% de = 74%
R^1 = Et, R^2 = CF_3CO-Gly-OH: 87% de = 74%
R^1 = Et, R^2 = $PhSCH_2CO_2H$: 86% de = 72%
R^1 = *i*-Pent, R^2 = CF_3CO-Gly-OH: 80% de = 98%

Scheme 117. Asymmetric four-component Ugi reaction with 2,3,4,6-tetra-*O*-alkyl-β-D-glucopyranosylamines.

addressed this problem by the design of a convertible isonitrile, which was involved in an asymmetric Ugi reaction in the presence of an aldehyde, a galactosylamine or arabinosylamine auxiliary, and formic acid (Scheme 118).[237] The corresponding amides, obtained in excellent diastereoselectivities, could be easily converted into the corresponding enantiopure amino acids.



R = Ph: 61% de = 80%
R = *i*-Pr: 80% de = 94%
R = $(CH_2)_4CO_2Me$: 80% de = 96%
R = Bn: 85% de = 96%
R = $(CH_2)_2CF$=CHPh: 65% de = 96%

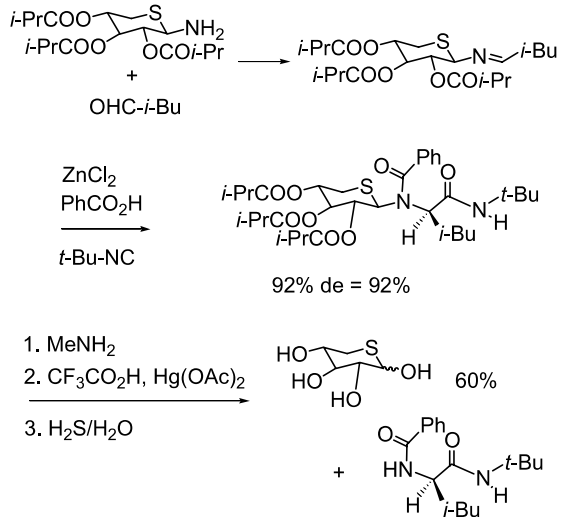


R = Ph: 48% de = 80%
R = *i*-Pr: 76% de = 80%
R = $(CH_2)_4CO_2Me$: 71% de = 92%
R = Bn: 66% de = 94%
R = $(CH_2)_2CF$=CHPh: 76% de = 90%

Scheme 118. Asymmetric Ugi reactions with a convertible isonitrile.

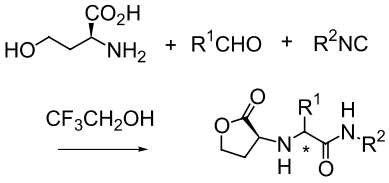
On the other hand, various combinations of two chiral reagents were studied with different levels of success. The

first example was the reaction between a chiral isocyanide (derived from phenylalanine), a chiral acid, isobutyraldehyde, and a cinnamylamine anchored to a resin yielding, without any diastereoselectivity, the expected tetrapeptide.[238] Combinations of chiral aldehydes and acids have also been used for the synthesis of demethyldysidenin,[239] polyoxin,[240] and nodularin-V,[241] but the stereoselectivity obtained was nearly zero in all cases. The combination of chiral amines and acids gave better results, since chiral protected α-amino acids or esters have been used in the synthesis of dipeptides containing iminocarboxylic derivatives.[242] In another example, a chiral peptide prepared from a chiral acid and a chiral arylamine was formed with a stereoselectivity of 95:5.[243] Combinations of chiral amines and aldehydes were also studied, but with modest stereoselectivities.[244] Ugi et al. have shown that, if a suitable ring-heteroanalogous pyranosylamine such as 1-amino-5-desoxy-5-thio-2,3,4-*O*-isobutanoyl-β-D-xylopyranose was used as the chiral amine component, the chiral auxiliary could be selectively cleaved under mild conditions.[245] In this case, a chiral imine was initially prepared by a reaction between the chiral amine with the aldehyde. This latter imine was then added with zinc chloride, *tert*-butyl isocyanide and benzoic acid, giving rise stereoselectively to the Ugi product, which was subsequently treated with a dilute methanolic solution of trifluoroacetic acid in the presence of mercury(II) acetate, in order to cleave the chiral auxiliary (Scheme 119).



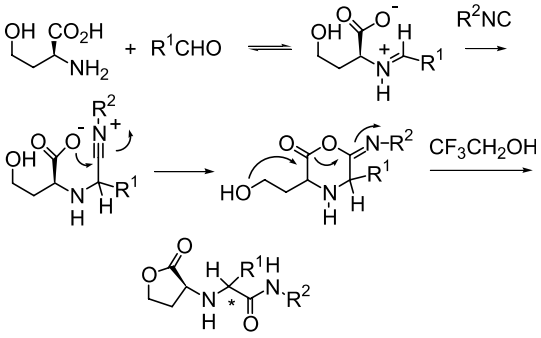
Scheme 119. Asymmetric Ugi reaction with 5-thio-β-D-xylopyranose, followed by cleavage of the chiral auxiliary.

Anomeric glycosyl isonitriles have been tested as chiral auxiliaries in the Ugi reaction by Ziegler et al.[226b] Low yields and no significant diastereoselectivity were, however, observed. In summary, an acceptable degree of diastereoselectivity is generally observed only when chiral amines are employed, the most efficient being glycosylamines. Although this type of derivatives represent, at the moment, the auxiliaries of choice in asymmetric Ugi reactions, their use still suffers from some drawbacks, such as the harsh conditions generally required to remove the auxiliary from the final product, the difficulties to prepare it in both enantiomeric forms, and the low temperatures necessary to achieve satisfactory control of the stereoselectivity. On the other hand, good stereoselectivities have also been observed when α-amino acids were employed as bifunctional reagents in an intramolecular version of the Ugi reaction to give α,α′-iminodicarboxylic acid derivatives.[246] Thus, Ugi et al. reported in 1995 an efficient synthesis of β-lactams based on an intramolecular Ugi reaction involving an aldehyde, an isocyanide and the inexpensive chiral-pool chemical, aspartic acid, the latter compound representing two components combined into one molecule.[247] A similar methodology was applied to L-homoserine, allowing, for the first time, a simple one pot synthesis of *N*-carbamoylmethyl-α-aminobutyrolactones,[248] the L-homoserine representing three functional groups combined into one molecule. As depicted in Scheme 120, the addition of the isocyanide to the prepared imine gave a first intermediate. Attack of the carboxylate on the nitrilium carbon of this intermediate, followed by the hydroxyl addition on the carboxylate carbon of the second intermediate, resulted in the formation of the final product by the double intramolecular attacks.



R^1 = *i*-Pr, R^2 = *t*-Bu: 71% de = 94%
R^1 = *t*-Bu, R^2 = *t*-Bu: 73% de = 98%
R^1 = *t*-Bu, R^2 = *c*-Hex: 78% de = 98%
R^1 = *p*-$MeCOC_6H_4$, R^2 = *c*-Hex: 69% de = 78%
R^1 = *i*-Pr, R^2 = $TsCH_2$: 97% de = 74%
R^1 = Ph, R^2 = $TsCH_2$: 71% de = 78%

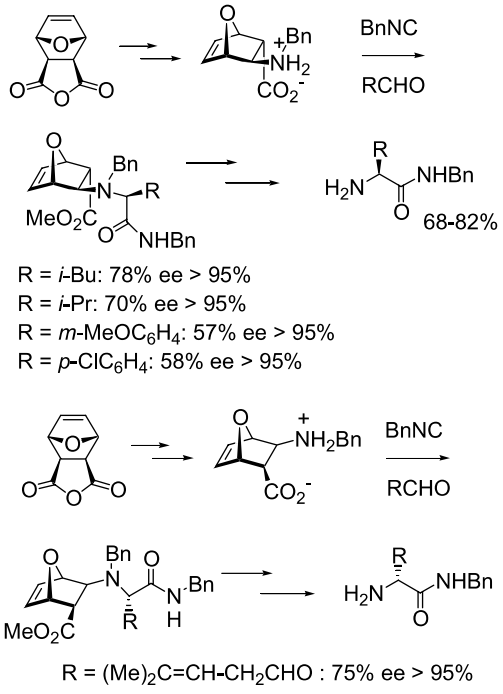
mechanism:



Scheme 120. Asymmetric intramolecular Ugi reaction with L-homoserine.

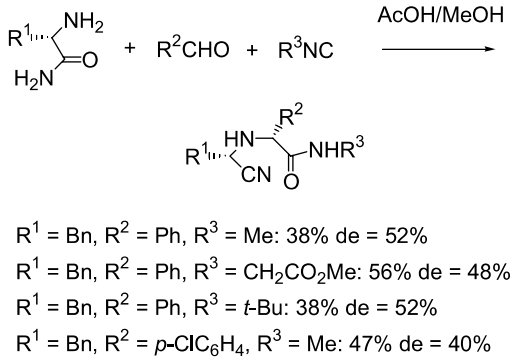
Similarly, Ugi et al. reported the synthesis of chiral 2,6-piperazinediones via a very effective variation of the Ugi reaction, performed in the presence of an α-amino acid, an aldehyde, and an isocyanide combined with an alcohol, which also served as the solvent.[249] This one pot multicomponent reaction combined very high yields (usually >95%) and excellent stereoselectivity with simple procedures. These intramolecular Ugi reactions gave des

>90%, but only when sterically hindered aldehydes and isocyanides were employed.[250] Additionally, in this variant of the Ugi reaction, a limitation on the use of α-amino acids as chiral auxiliaries was represented by their removal from the products and by the availability of both enantiomers. Very recently, Guanti et al. have described the synthesis of a bicyclic β-amino acid scaffold in both pure enantiomeric forms and its application as chiral auxiliary in an intramolecular version of the Ugi reaction to prepare α-amino acid derivatives of both D- and L-series in a straightforward and very stereoselective manner.[251] The mild conditions required for the Ugi condensation and for the removal of the chiral auxiliary made this method very attractive to prepare a wide range of differently structured *N*-alkylated and unalkylated amino acid derivatives (Scheme 121).



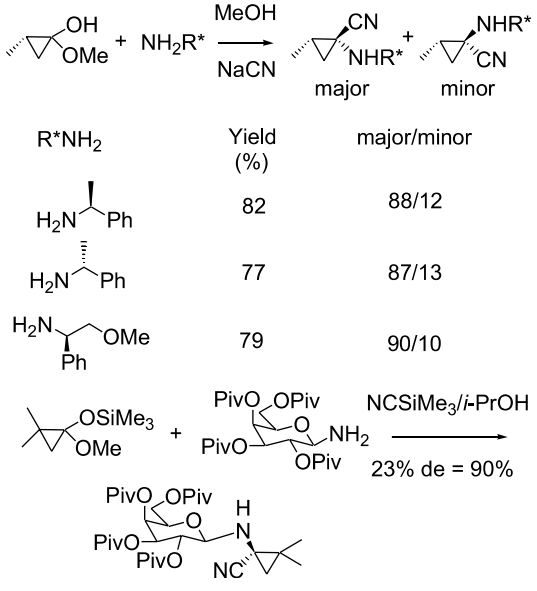
Scheme 121. Synthesis of both L- and D-α-amino acid derivatives via intramolecular Ugi reactions.

In addition, these authors reported, in 2004, another application of the Ugi reaction to the synthesis of 2,5-disubstituted pyrrolidines, starting from chiral cyclic imines.[252] The yields of the reaction ranged from moderate to excellent, whilst the diastereomeric ratio was, in all cases, only moderate. An example of the use of three chiral reagents during the three-component Ugi reaction (in which the condensation of the carbonyl compound with the amine takes place before the addition of the isocyanide and the acid derivatives) was reported in 1976, involving a chiral ferrocenylimine derivative, *N*-formylvaline and a chiral isocyanide.[253] The expected tetrapeptide was isolated in modest yield, but with excellent stereoselectivity. In 2004, Behnke et al. reported a new, special type of Ugi reaction occurring in the presence of a chiral amino acid amide as the amine, an aldehyde, an isocyanide, and acetic acid.[254] Surprisingly, this reaction did not lead to the expected Ugi reaction product, but to a chiral α-aminonitrile derivative (Scheme 122).



Scheme 122. Synthesis of chiral α-aminonitrile derivatives.

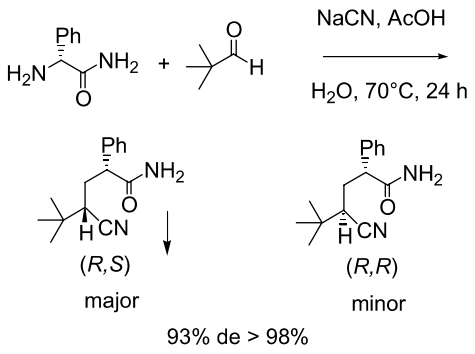
Some asymmetric versions of the one pot Strecker reaction have been recently developed, leading to *N*-protected aminonitriles from a ketone or a ketone derivative, a chiral amine and NaCN. As an example, Fadel showed, in 1993, that a mixture of a dimethylcyclopropanone acetal, NaCN and a chiral amine underwent a Strecker reaction to form, via the corresponding iminium intermediate, the corresponding aminocyclopropane (Scheme 123).[255] Similarly, this author applied the same methodology to chiral alkylcyclopropane hemiacetals, providing, in the presence of a chiral amine, the corresponding aminonitriles, which were subsequently converted into enantiomerically pure (1*R*,2*S*)-(+)-*allo*-norcoronamic acid (Scheme 123).[256]



Scheme 123. Asymmetric one pot Strecker reaction with alkylcyclopropane hemiacetals and acetals.

More recently, the same group extended the scope of this procedure to the preparation of chiral 1-amino-2-substituted cyclobutanecarboxylic acids starting from racemic cyclobutanones and chiral benzylic amines as the chiral auxiliaries, proceeding via the corresponding amino nitriles by an asymmetric one pot Strecker reaction.[257] On the other hand, de Lange et al. reported, in 2001, asymmetric Strecker

reactions based on (*R*)-phenylglycine amide as the chiral auxiliary with pivaldehyde or 3,4-dimethoxyphenylacetone.[258] Nearly diastereomerically pure amino nitriles could be obtained via a crystallisation-induced asymmetric transformation in water. This practical one pot asymmetric Strecker synthesis of a (*R*,*S*)-aminonitrile in water led to the straightforward synthesis of (*S*)-*tert*-leucine (Scheme 124).

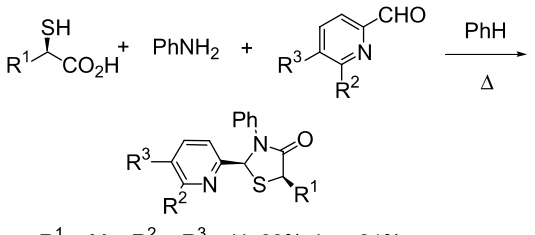


Scheme 124. Asymmetric Strecker reaction with (*R*)-phenylglycine amide.

Other chiral amines such as phenylglycinol,[259] or a morpholin-2-one derivative in combination with an aliphatic aldehyde and copper(I)[260] have been successfully used in the Strecker reaction. In addition, enantioselective Strecker reactions promoted by chiral catalysts are developed in Part B of this report.

The classic Mannich reaction involves an amine derivative, a non-enolisable aldehyde, and an enolisable carbonyl compound. All of the possibilities of using chiral starting materials for this asymmetric multicomponent reaction have been reported. Thus, the starting chiral compound could be the aldehyde which, when activated by, for instance, ytterbium triflate in water, provided the expected amino-ketone in excellent yield, albeit with a disappointing stereoselectivity.[261] The nucleophilic partner of the Mannich reaction could also be chiral,[262] but the best results were obtained using chiral amines such as valine methyl ester.[263]

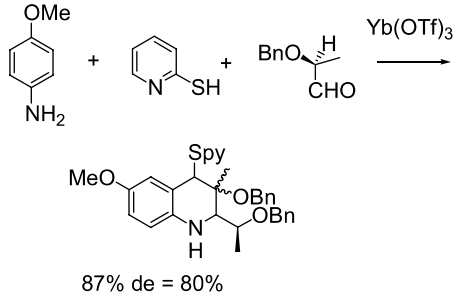
Various asymmetric multicomponent reactions have recently been developed such as the synthesis of chiral 2-pyridyl-thiazolidin-4-ones obtained in quantitative yield by mixing a chiral α-mercapto acid, aniline, and the 2-pyridinecarboxaldehyde (Scheme 125).[264]



R^1 = Me, R^2 = R^3 = H: 68% de = 91%
R^1 = R^2 = Me, R^3 = H: 51% de = 54%
R^1 = Me, R^2-R^3 = $(CH=CH)_2$: 22% de = 24%
R^1 = *i*-Pr, R^2 = R^3 = H: 39% de = 85%

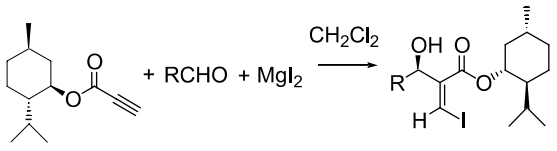
Scheme 125. Synthesis of chiral thiazolidin-4-ones via three-component reaction.

In 1997, Cozzi et al. reported a new and efficient asymmetric three-component reaction of 4-methoxyaniline, 2-pyridylthiol, and chiral 2-benzyloxypropanal as the chiral auxiliary under $Yb(OTf)_3$ catalysis, providing a new access to enantiomerically pure 1,2,3,4-tetrahydroquinolines (Scheme 126).[265]



Scheme 126. Synthesis of chiral 1,2,3,4-tetrahydroquinolines via three-component reaction.

An asymmetric synthesis of chiral β-iodo Baylis–Hillman esters using MgI_2 as promoter via a one pot, three-component reaction was developed by Paré et al. in 2003.[266] This procedure involved the conjugate addition of I^- to menthyl propiolates to give β-iodo allenolate intermediates, which then underwent 1,2-addition to form the β-iodo Baylis–Hillman products (Scheme 127).

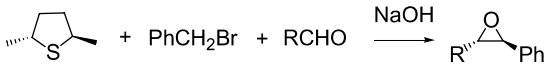


R = Ph: 86% de = 44%
R = *p*-MeC_6H_4: 85% de = 40%
R = *p*-FC_6H_4: 87% de = 46%
R = *p*-ClC_6H_4: 86% de = 44%
R = *p*-BrC_6H_4: 86% de = 47%
R = *p*-$BnOC_6H_4$: 80% de = 58%
R = $Me(CH_2)_3CHO$: 82% de = 40%
R = $MeCH_2CHO$: 83% de = 38%

Scheme 127. Synthesis of chiral β-iodo Baylis–Hillman esters via three-component reaction.

A very simple procedure for the asymmetric synthesis of 1,2-dialkyloxiranes was achieved by Metzner et al. using the very simple enantiopure *trans*-2,5-dimethylthiolane as the chiral auxiliary for the asymmetric benzylidene transfer on aldehydes (Scheme 128).[96b] In the category of one pot procedures using simple reagents, this methodology was excellent, since, for stilbene oxide, the yield was 92% and the ee 88% with a chiral sulphide prepared in two steps and 95% yield.

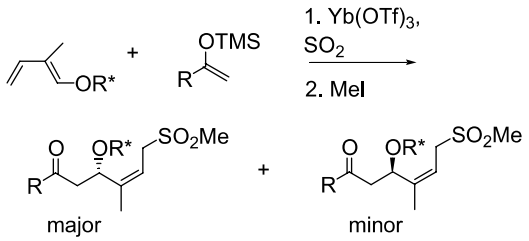
The first example of a multicomponent coupling of aldehydes, amides, and dienophiles was described by Beller et al. as the most simple and direct high-yield approach to a variety of amino functionalised cyclohexene and cyclohexadiene derivatives.[267] When the in situ-generated 1-acylamino-1,3-butadiene resulting from the condensation of octanal and benzamide was trapped by a chiral dienophile



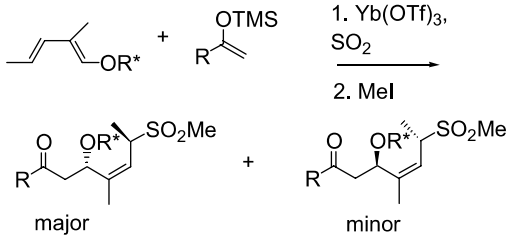
R = Ph: 92% de (*trans*) = 86% ee = 88%
R = *p*-ClC$_6$H$_4$: 89% de (*trans*) = 84% ee = 86%
R = *p*-MeC$_6$H$_4$: 88% de (*trans*) = 84% ee = 88%
R = *c*-C$_6$H$_{10}$: 87% de (*trans*) = 30% ee = 94%

Scheme 128. Asymmetric synthesis of 1,2-dialkyloxiranes via three-component reaction.

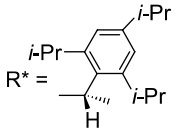
such as (4*S*)-5-(2-propenoyl)-4-(phenylmethyl)-2-oxazolidinone, the corresponding cyclohexene derivative was formed with stereoselectivities (des) of >90%. On the other hand, Vogel et al. reported in 2001 an asymmetric four-component synthesis of polyfunctional sulphones.[268] Thus, chiral (*E*)-1-alkoxy-2-methylbutadienes, or (*E*,*E*)-1-alkoxy-2-methylpenta-1,3-dienes added to sulphur dioxide activated by a Lewis acid and generated zwitterionic intermediates that could be quenched by enoxysilanes. The resulting β,γ-unsaturated silyl sulphinates could be desilylated and reacted with methyl iodide to provide chiral polyfunctional sulphones (Scheme 129). It should be noted that the evaporation of SO_2 was required before the addition of the fourth component, methyl iodide. The reaction occurring before this evaporation was, however, still a three-component reaction and, consequently, it could be maintained in the context of the report.



R = Me: 80% de = 76%
R = Ph: 99% de = 92%
R = H: 48% de = 90%
R = *c*-C$_3$H$_5$: 79% de = 82%

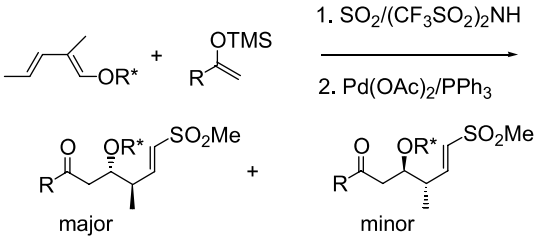


R = *t*-Bu: 85% de = 88%

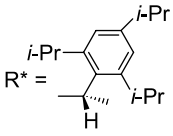


Scheme 129. Asymmetric synthesis of polyfunctional sulphones via four-component reaction.

This asymmetric three-component reaction was very recently incorporated by the same author into a cascade reaction in which a subsequent retro-ene reaction elimination of SO_2 occurred under $Pd(OAc)_2/PPh_3$ catalysis (Scheme 130).[269] This new reaction has opened up a novel approach to the asymmetric synthesis of polypropionate fragments.

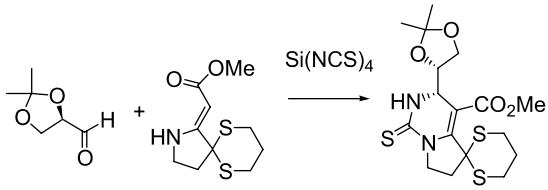


R = Ph: 70% de = 66% ee = 94%
R = *t*-Bu: 71% de = 90% ee = 92%



Scheme 130. Asymmetric domino oxyallylation desilylation retro-ene reaction.

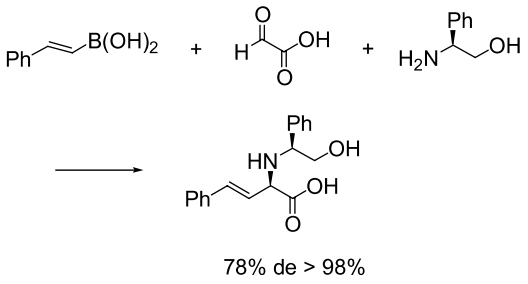
The Biginelli dihydropyrimidine synthesis consists of the condensation of urea, an aldehyde, and a 1,3-ketoester. The first asymmetric versions of this reaction were developed by Dondoni et al. who used chiral aldehydes derived from galactose as the chiral auxiliaries.[270] A high level of stereoselectivity was obtained when the chiral acetonide derived from glyceraldehyde was reacted with an enamine, and silicon tetraisothiocyanate (Scheme 131).[271] In addition, Elliot et al. reported, in 2004, an asymmetric Biginelli reaction involving a chiral 1,3-ketoester derivative, which was the key step of the synthesis of the bicyclic core of batzelladine alkaloids.[272]



80% de = 90%

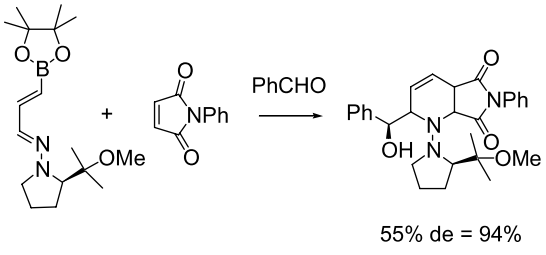
Scheme 131. Asymmetric Biginelli reaction with chiral glyceraldehyde acetonide.

The Petasis reaction is the condensation between carbonyl compounds, amines, and aryl- or vinylboronic derivatives. This reaction has been performed with the three possible chiral reactants. Thus, various chiral amines have been implicated such as phenylglycinol (Scheme 132),[273] phenylethylamine,[274] a 1,2-diamino-cyclohexyl derivative,[275] a morpholin-2-one derivative,[276] and an amino-diol.[277] Petasis and Kobayashi have demonstrated the possibility of using chiral aldehydes as chiral auxiliaries, which gave excellent results in terms of yield and stereoselectivity.[278] In addition, the use of chiral boronic acids derived from chiral diols such as dialkyl tartrate has been less successful.[279]



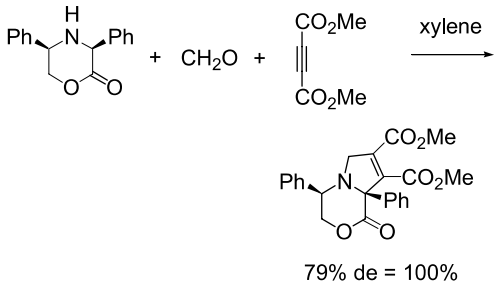
Scheme 132. Asymmetric Petasis reaction with chiral phenylglycinol.

In 2002, Carreira et al. reported the oxidation of alkylsulphanylarenes by a chiral nitridomanganese(V) complex, which provided the corresponding chiral acylsulphinimine derivatives.[280] It has been demonstrated that, in the presence of a carbonyl compound, a chiral vinylcopper reagent could react with the carbenoid, bis(iodomethyl)zinc, to give new chiral allylzinc intermediates, which, in turn, reacted with the carbonyl compound to yield, after hydrolysis, the corresponding chiral sulphoxides in high yields and stereoselectivities.[281] In 1993, an asymmetric multicomponent reaction based on a Diels–Alder reaction, was performed in the presence of a chiral 3,4-dihydroisoquinoline derivative, a 2,4-pentadienyltin reagent and acryloyl chloride, furnishing the corresponding chiral bicycloannulated products.[282] Recently, Hall et al. have reported an asymmetric multicomponent reaction based on an aza-Diels–Alder reaction performed in the presence of a chiral imine, *N*-phenylmaleimide and benzaldehyde (Scheme 133).[283] An asymmetric multicomponent Knoevenagel nMichael reaction was recently reported by Laronze et al. using different chiral hydroxyl- or amino-functionalised aldehydes as the chiral auxiliaries in the presence of indole and Meldrum acid, providing stereoselectively the corresponding tetracyclic products.[284] A synthesis of chiral oxazole derivatives was recently developed on the basis of a new multicomponent reaction involving a chiral isocyanide, an amine, and an aldehyde, but only moderate diastereoselectivity was observed.[285] Asymmetric aziridination-based multicomponent reactions of chiral electron-rich olefins have been developed using a nitridomanganese(IV) complex as the source of nitrogen in the presence of trifluoroacetic anhydride.[286]



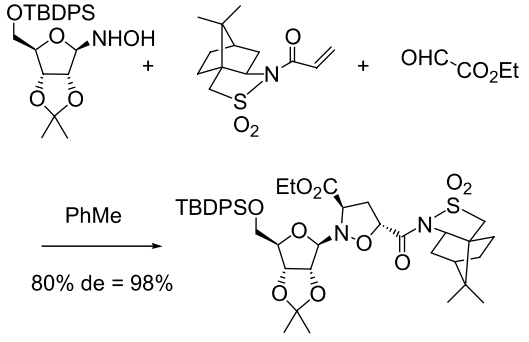
Scheme 133. Asymmetric multicomponent reaction based on aza-Diels–Alder reaction.

Several asymmetric multicomponent reactions based on a 1,3-dipolar cycloaddition have recently been developed using chiral amines as the chiral auxiliaries.[287] A typical procedure is the reaction of a chiral amine with an aldehyde to form a chiral intermediary azomethine ylide, which is then trapped in situ by reaction with an alkene or an alkyne dipolarophile (Scheme 134).[288]



Scheme 134. Diastereoselective 1,3-dipolar multicomponent reaction with chiral amine.

Not only chiral amines, but also chiral hydroxyamines,[289] have been involved in this type of reaction. As an example, a hydroxylamine derived from D-ribofuranose was used as a template in the 1,3-cycloaddition reaction with glyoxylate derivatives and various dipolarophiles, such as camphor derivatives, to provide the corresponding *N*,*O*-nucleoside precursors (Scheme 135).[290] Excellent results have also been obtained with other chiral dipolarophiles such as a cinnamyl derivative in the presence of *N*-phenyl isatin and proline, which yielded the corresponding spirooxindole derivative.[291]

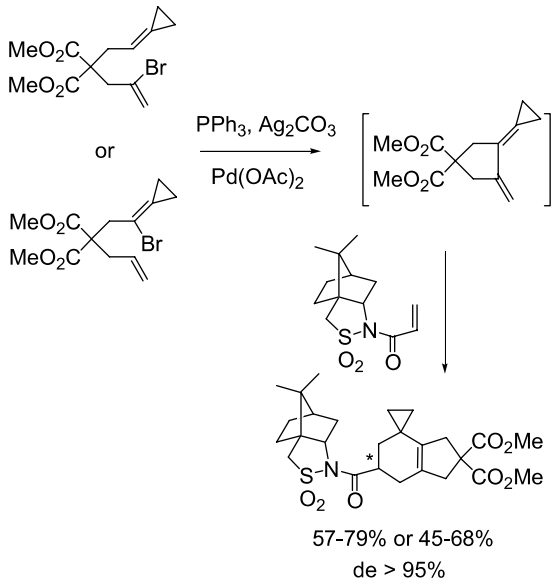


Scheme 135. Diastereoselective 1,3-dipolar multicomponent reaction with chiral hydroxylamine.

2.8. Transition-metal-catalysed sequences

2.8.1. Palladium-catalysed domino reactions. Transition-metal-catalysed transformations are of increasing importance in synthetic organic chemistry. One of the most extensively studied families of transition-metal catalysts are those based on palladium.[292] Although palladium-catalysed domino processes have only recently been extensively reported in the literature,[293] the concept of sequential palladium-mediated transformations was actually pioneered some time before the word 'domino' was coined. The discovery of the ability of this transition metal to interact with organic moieties, to connect inter- or intra-molecularly alkenes, alkynes, carbon monoxide, etc. in cascading processes is certainly a breakthrough in organometallic synthesis. It must be remembered that the astonishing simplicity of realising many complex polycyclisations is sometimes directly proportional to the labour required for the synthesis of the cyclisation precursor. The possible modes by which a living organopalladium complex can be

engaged in consecutive bond formations, or the manner in which two sequential palladium-catalysed processes can be coupled by using a single catalytic system, is only limited by a chemist's imagination. The Heck reaction is an important method to couple aryl and vinyl systems in the presence of palladium, and it forms the cornerstone of many domino reaction processes.[294] As an example, de Meijere et al. reported, in 1996, a domino Heck Diels–Alder reaction of a terminally unsubstituted 2-bromo-1,6-diene and a chiral dienophile such as (*R*)-myrtenyl acrylate or an acryloyl-camphorsultam, providing the corresponding chiral bicyclic products with diastereomeric excesses of 82 and >95%, respectively.[295] This methodology was, remarkably, applied to 2-bromo-1,6-dienes bearing a methylenecyclopropane terminator or starter moiety, both of which reacted in the presence of a chiral acryloylcamphorsultam, giving the corresponding cycloadduct as a single diastereo- and enantiomer (Scheme 136).[293]

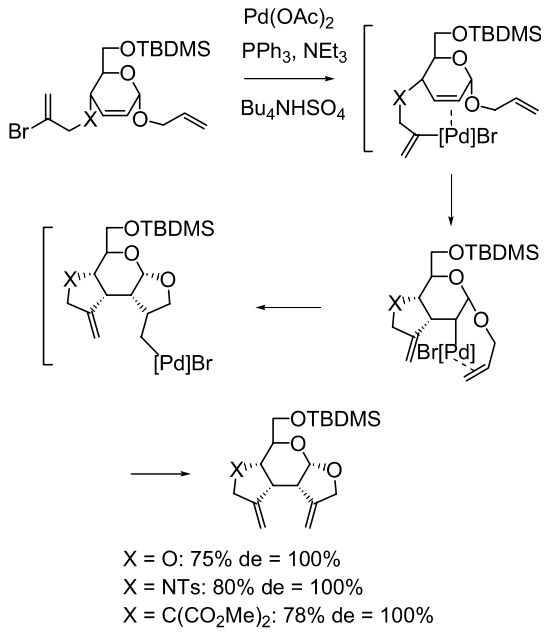


Scheme 136. Asymmetric domino Heck Diels–Alder reaction.

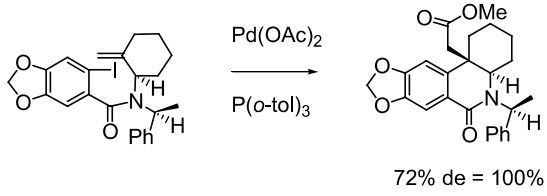
Sinou et al. have developed a palladium-catalysed Heck-type cyclisation of glucal-derived templates, leading to enantiopure triquinane-type products.[296] The process started with the formation of a σ-vinylpalladium intermediate, which was followed by two consecutive intramolecular carbopalladations and by a final dehydropalladation (Scheme 137).

In 1999, Grigg et al. elaborated an asymmetric domino reaction involving an intramolecular Heck reaction, followed by an anion capture, which was the key step of the synthesis of the natural product, (*R*,*R*)-crinan (Scheme 138).[297,298]

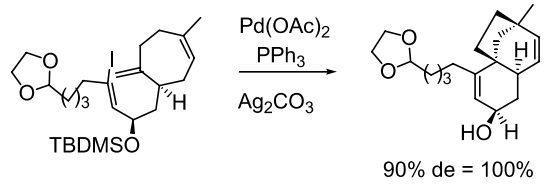
The first enantioselective total synthesis of scopadulcic acid A was achieved by Overman in 1999.[299] The central transformation was a palladium-catalysed bis-Heck cyclisation of a 5-methylenecycloheptenyl iodide, which occurred with complete stereo- and regioselectivity, to construct the B-, C-, and D-rings of the scopadulan skeleton (Scheme 139).



Scheme 137. Asymmetric palladium-catalysed Heck-type cyclisation of glucal derivatives.



Scheme 138. Asymmetric domino Heck-cyclisation anion-capture reaction.

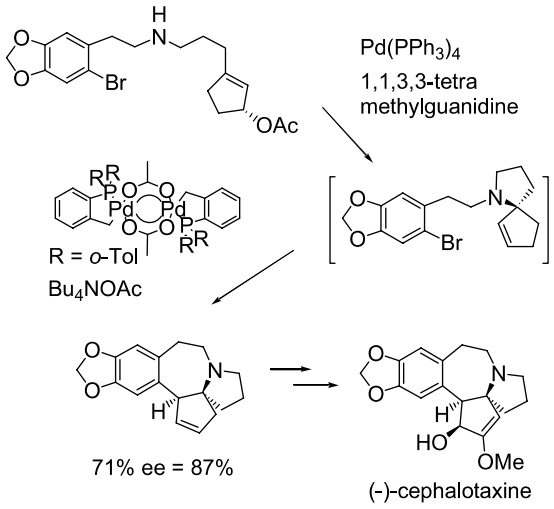


Scheme 139. Asymmetric bis-Heck reaction.

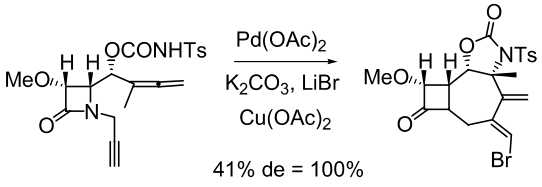
The first synthesis of the enantiopure pentacyclic alkaloid, (−)-cephalotaxine, was achieved by Tietze et al. on the basis of two successive palladium-catalysed reactions, namely a palladium-catalysed nucleophilic N-alkylation (Tsuji–Trost allylation) followed by a Heck reaction (Scheme 140).[300]

Remarkably, an unprecedented asymmetric domino allene cyclisation intramolecular Heck reaction occurred when a chiral 2-azetidinone-tethered allenyne carbamate was submitted to palladium catalysis, providing the corresponding enantiopure fused tricyclic β-lactam (Scheme 141).[301]

In addition, Shibasaki et al. have reported an asymmetric synthesis of halenaquinone and halenaquinol incorporating the first example of a cascade Suzuki cross-coupling asymmetric Heck reaction (see Part B of this report), as well as a single-step process promoted by Pd(0) for



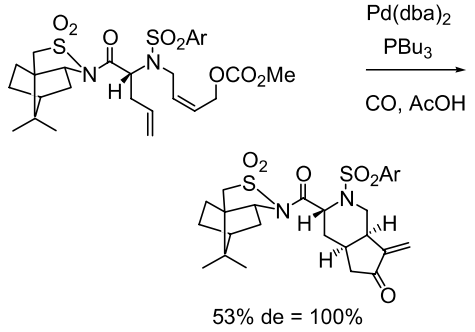
Scheme 140. Asymmetric domino Tsuji–Trost allylation Heck reaction.



Scheme 141. Asymmetric domino allene cyclisation intramolecular Heck reaction.

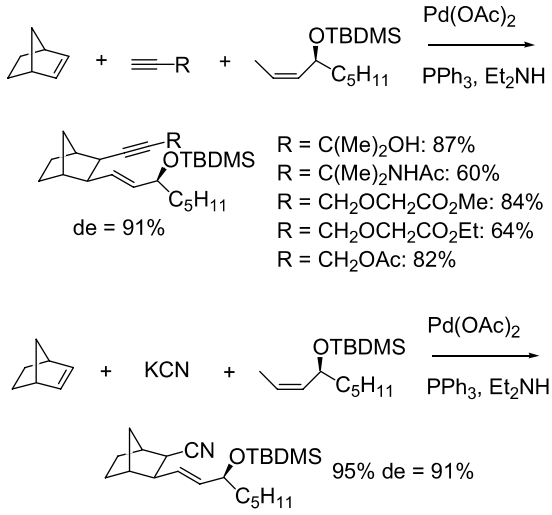
constructing a chiral pentacyclic from a chiral tricyclic ring system.[302]

Various asymmetric domino palladium-catalysed reactions, other than those incorporating a Heck reaction, are also present in the literature. As an early example, a domino palladium-promoted alkene insertion was developed, starting from a chiral γ-stannylallylic alcohol, in order to give access to benzoprostacyclins.[303] Unfortunately, a separable 1:1 mixture of diastereomers was obtained in only 30% yield. On the other hand, an asymmetric domino palladium-ene carbonylation reaction involving a chiral sultam has been successfully developed by Oppolzer et al. in order to prepare the heteroyohimbine alkaloid, (+)-isorauniticine (Scheme 142).[304]



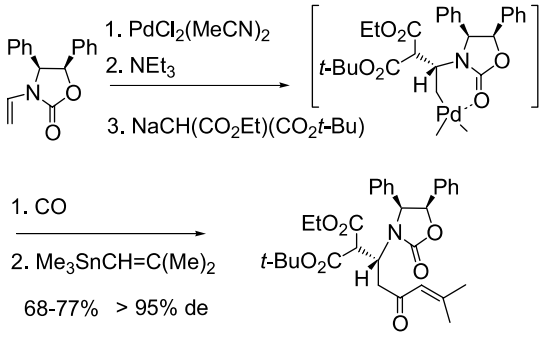
Scheme 142. Asymmetric domino ene cyclisation carbonylation reaction.

In 1992, Torii et al. executed a palladium-catalysed diastereo-differentiative tandem connection of a chiral *cis*-alkene, norbornene, and a terminal acetylene or cyano nucleophile, with the accompanying isomerisation of the cis- to trans-geometry of the olefin (Scheme 143).[305]



Scheme 143. Asymmetric Pd-catalysed three-component reactions.

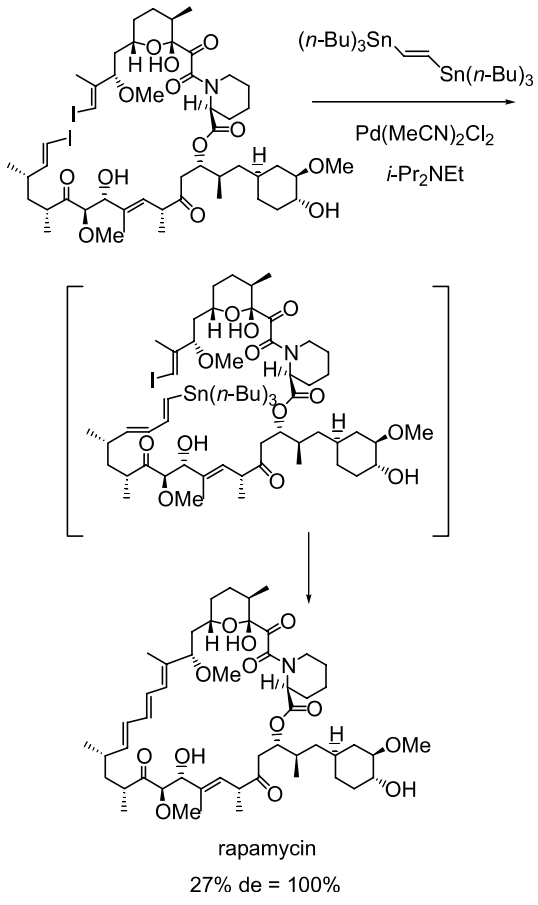
An efficient palladium(II)-assisted domino alkylation carbonylative coupling procedure for optically active ene carbamates was achieved by Hegedus et al. and applied to the synthesis of the antibiotics, (+)-negamycin and (−)-5-*epi*-negamycin (Scheme 144).[306] The reactions depicted in Schemes 143 and 144 involve three components and, consequently, they could also be included in Section 2.7.



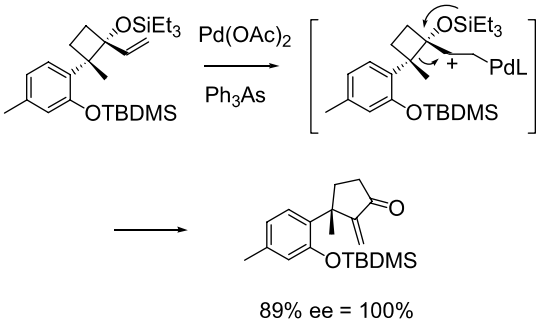
Scheme 144. Asymmetric Pd-catalysed domino alkylation carbonylation reaction.

The first total synthesis of rapamycin, reported by Nicolaou et al. was based on a unique stitching macrocyclisation using a double inter-intramolecular Stille coupling. This elegant domino reaction comprised an initial intermolecular palladium-catalysed reaction with *trans*-1,2-bis-(tri-*n*-butylstannyl)ethylene, followed by a second, intramolecular, Stille reaction that secured the requisite all-trans geometry for the triene and furnished the expected rapamycin (Scheme 145).[307]

Fukumoto et al. have devised a general approach to *cis*-hydrindanes employing novel palladium-mediated processes such as the ring expansion of a chiral vinylcyclobutanol into the corresponding 2-methylenecyclopentanone upon exposure to $Pd(OAc)_2$ and Ph_3As (Scheme 146).[308]

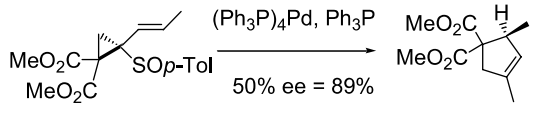


Scheme 145. Asymmetric domino inter-intramolecular Stille reaction.



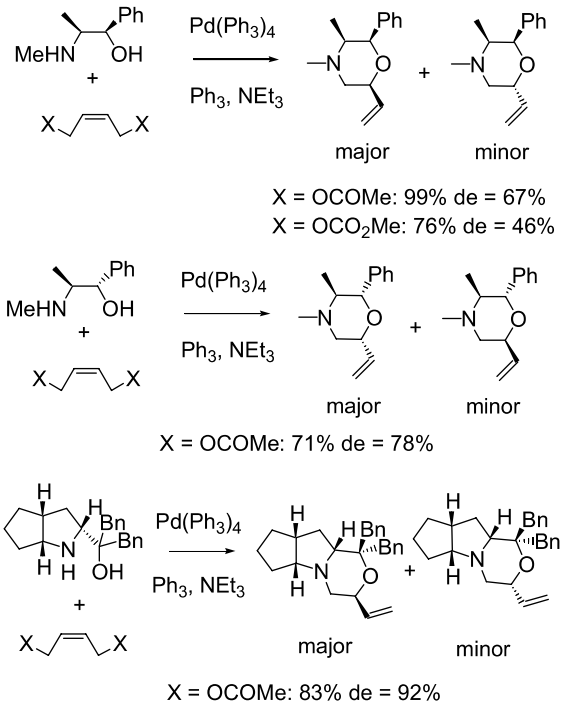
Scheme 146. Asymmetric domino ring expansion of vinylcyclobutanol.

Studies have demonstrated that a high stereoselectivity in vinylcyclopropane rearrangements could be achieved in the presence of palladium catalysts, for example, treatment of a chiral cyclopropane sulphoxide with Pd(0) gave the corresponding enantiopure cyclopentene (Scheme 147).[309]



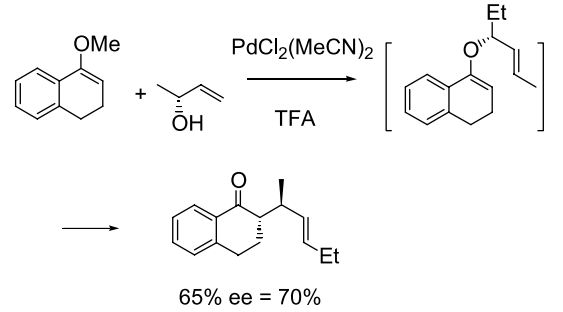
Scheme 147. Asymmetric domino ring expansion of vinylcyclopropane sulphoxide.

Palladium-catalysed domino allylic substitutions using chiral aminoalcohols as bifunctional nucleophiles have allowed the diastereoselective synthesis of various enantiopure vinylmorpholines (Scheme 148).[310]



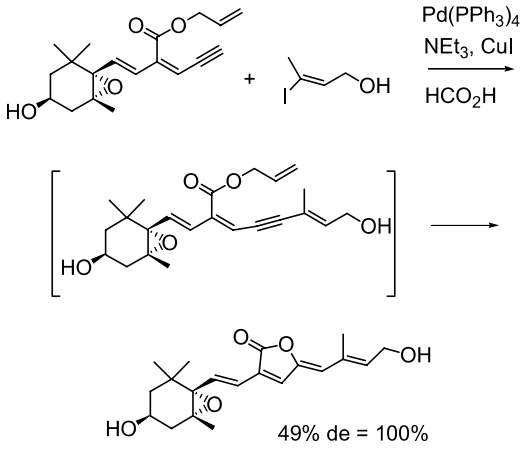
Scheme 148. Asymmetric domino allylic disubstitution reactions.

Nakai et al. were among the first authors to report domino palladium-catalysed reactions including a Claisen rearrangement. An initial enantioselectively catalysed step generated the allyl vinyl backbone for the consecutive [3,3]-sigmatropic rearrangement, providing the corresponding enantiomerically enriched γ,δ-unsaturated ketone (Scheme 149).[311]



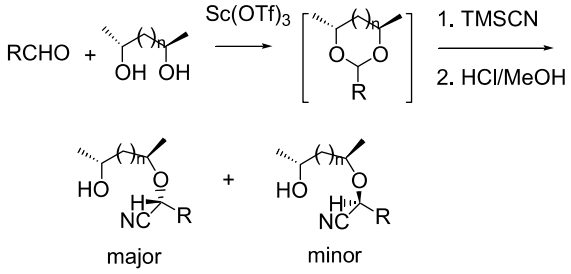
Scheme 149. Asymmetric domino allylation Claisen rearrangement reaction.

A very efficient and novel palladium-catalysed domino ylidenebutenolide formation reaction was developed by Katsumura et al. in 2002 and was applied to the stereocontrolled synthesis of the polyfunctional carotenoid, peridinin.[312] Sonogashira coupling of a chiral allyl ester with a vinyl iodide, reductive de-allylation, and highly stereoselective intramolecular lactonisation proceeded successfully, in one pot, by the successive action of Pd^0 and Pd^{II} catalysts (Scheme 150).



Scheme 150. Asymmetric domino ylidenebutenolide formation reaction.

2.8.2. Domino reactions catalysed by metals other than palladium. In 1995, Fukuzawa et al. reported a facile and direct preparation of chiral acetals from carbonyl compounds and chiral diols catalysed by scandium(III) triflate. Successive addition of Me_3SiCN to the reaction system led to the one pot stereoselective ring scission of acetals to produce optically active cyanohydrin ethers without isolation of acetals (Scheme 151).[313]



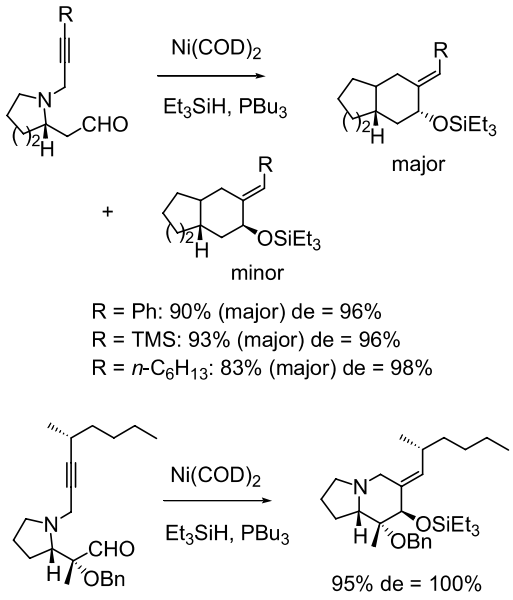
R = C_4H_9, n = 0: 99% de = 54%
R = *c*-C_6H_{11}, n = 0: 99% de = 50%
R = $Ph(CH_2)_2$, n = 0: 99% de = 56%
R = Ph, n = 0: 66% de = 90%
R = Ph, n = 1: 83% de = 76%

Scheme 151. Asymmetric domino acetalisation silylcyanation reaction.

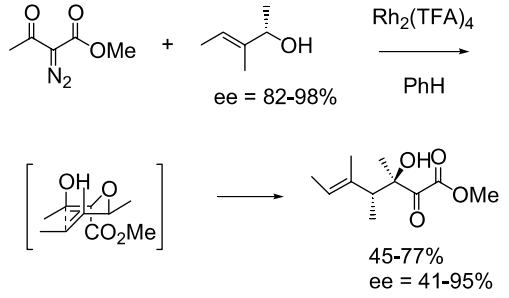
In 1999, Montgomery et al. reported that $Ni(COD)_2/PBu_3$ was a highly effective catalyst system for the triethylsilane-mediated reductive cyclisation of ynals that allowed the preparation of functionally rich pyrrolizidine, indolizidine, and quinolizidine alkaloid frameworks (Scheme 152).[314]

A rhodium(II) catalyst has been employed to induce the reaction between a diazoketone with a chiral allylalcohol. This latter reaction could be described as an addition of an alcohol to a carbenoid, generating an intermediate *Z*-enol. The resulting allyl vinyl system underwent a final Claisen rearrangement to give a chiral α-alkoxy ketone (Scheme 153).[315]

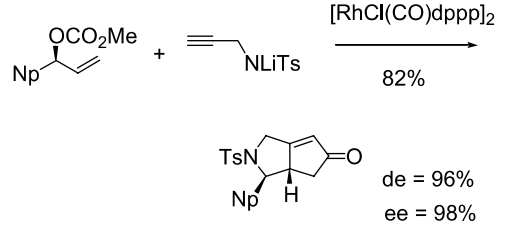
In 2001, Evans et al. developed a domino rhodium-catalysed allylic alkylation Pauson–Khand annulation using a chiral allylic carbonate, which furnished the corresponding azabicycle (Scheme 154).[316]



Scheme 152. Asymmetric domino triethylsilane-mediated reductive cyclisation of ynals.



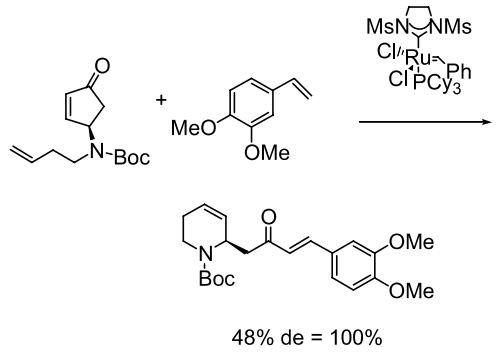
Scheme 153. Rhodium(II)-catalysed asymmetric domino reaction.



Scheme 154. Asymmetric domino rhodium-catalysed allylic alkylation Pauson–Khand annulation reaction.

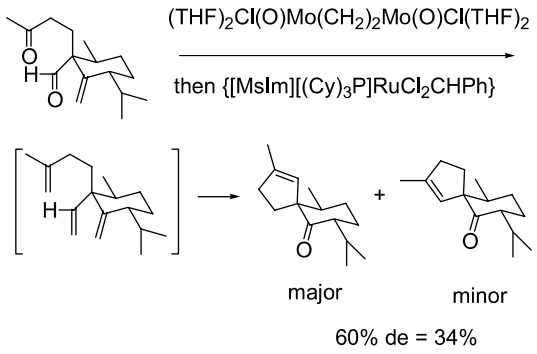
A ruthenium-catalysed domino ring-closing metathesis hydrogenation reaction was developed by Nielsen et al. in the course of preparing cyclic dinucleotides containing a butylene nucleobase-phosphotriester connection.[317] On the other hand, a domino ring-opening–ring-closing-cross metathesis reaction was reported by Blechert et al. in 2004 and successfully applied to a concise enantioselective synthesis of the quinolizidine alkaloid, (−)-labusine II (Scheme 155).[318]

Hanna et al. have prepared various polyoxygenated bicyclic systems containing medium-sized rings from carbohydrates via domino ring-closing metathesis reactions of dienynes.[319] In addition, Spitzner et al. have combined



Scheme 155. Ruthenium-catalysed asymmetric domino ring-opening–ring-closing-cross metathesis reaction.

another ring-closing metathesis with an olefination in order to elaborate a total synthesis of the spirocyclic marine sesquiterpene, (+)-axenol.[320] Thus, this new organometallic domino reaction applied to a (+)-menthone derivative involved a methylenation reaction followed by a ring-closing olefin metathesis, respectively, induced by Mo- and Ru-complexes (Scheme 156).



Scheme 156. Organometallic asymmetric domino olefination ring-closing metathesis reaction.

Finally, in 2004, Saniere et al. reported the one pot copper-catalysed iminodane-mediated aziridination of an α-allylglycine derivative, allowing the preparation of novel rigid analogues of arginine.[321]

3. Conclusions

The first part of this review clearly demonstrates the diversity and power of asymmetric domino reactions based on the use of chiral auxiliaries in the field of synthetic organic chemistry. The design and development of new asymmetric domino reactions is regarded as a great intellectual challenge for organic chemists. The rational design of an asymmetric domino reaction is a complex action, requiring imagination, knowledge and creativity. The increasing number of publications regarding the applications of this type of reactions paints a comprehensive picture for their real possibilities in organic synthesis, offering the advantages of atom economy, simple procedures, and savings in cost and time.

References and notes

1. Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136.
2. Tietze, L. F.; Lieb, M. E. *Curr. Opin. Chem. Biol.* **1998**, *2*, 363–371.
3. (a) Ho, T.-L. *Tandem Organic Reactions*; Wiley: New York, 1992. (b) Waldmann, H. *Nachr. Chem. Tech. Lab.* **1992**, *40*, 1133–1140. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 131–163. (d) Posner, G. H. *Chem. Rev.* **1986**, *86*, 831–844. (e) Fukumoto, K. *J. Synth. Org. Chem. Jpn.* **1994**, *52*, 2–18. (f) Bunce, R. A. *Tetrahedron* **1995**, *51*, 13103–13159. (g) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195–206. (h) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967–1983. (i) Capdevila, E.; Rayo, J.; Carrion, F.; Jové, I.; Borrell, J. I.; Teixido, J. *Afinidad* **2003**, *506*, 317–337.
4. Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602–1634.
5. Johnson, W. S.; Fletcher, V. R.; Chenera, B.; Bartlett, W. R.; Tham, F. S.; Kullnig, R. K. *J. Am. Chem. Soc.* **1993**, *115*, 497–504.
6. Burke, S. D.; Takeuchi, K.; Murtiashaw, C. W.; Liang, D. W. M. *Tetrahedron Lett.* **1989**, *30*, 6299–6302.
7. Jiricek, J.; Blechert, S. *J. Am. Chem. Soc.* **2004**, *126*, 3534–3538.
8. Booma, C.; Balasubramanian, K. K. *Tetrahedron Lett.* **1993**, *34*, 6757–6760.
9. Nicolaou, K. C.; Nadin, A.; Leresche, J. E.; Yue, E. W.; La Greca, S.; Tsuri, T.; Yang, Z. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2187–2191.
10. Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 9229–9235.
11. Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909–2913.
12. Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, *5*, 901–903.
13. De la Moya Cerero, S.; Garcia Martinez, A.; Teso Vilar, E.; Garcia Fraile, A.; Lora Maroto, B. *J. Org. Chem.* **2003**, *68*, 1451–1458.
14. McDonald, F. E.; Bravo, F.; Wang, X.; Wei, X.; Toganoh, M.; Rodriguez, J. R.; Do, B.; Neiwert, W. A.; Hardcastle, K. I. *J. Org. Chem.* **2002**, *67*, 2515–2523.
15. Nakamura, M.; Suzuki, A.; Nakatani, M.; Fuchikami, T.; Inoue, M.; Katoh, T. *Tetrahedron Lett.* **2002**, *43*, 6929–6932.
16. Nakatani, M.; Nakamura, M.; Suzuki, A.; Inoue, M.; Katoh, T. *Org. Lett.* **2002**, *4*, 4483–4486.
17. Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310–1312.
18. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1993**, *115*, 9293–9294.
19. (a) Hopkins, M. H.; Overman, L. E. *J. Am. Chem. Soc.* **1987**, *109*, 4748–4749. (b) Gasparski, C. M.; Herrinton, P. M.; Overman, L. E.; Wolfe, J. P. *Tetrahedron Lett.* **2000**, *41*, 9431–9435. (c) Overman, L. E.; Pennington, L. D. *J. Org. Chem.* **2003**, *68*, 7143–7157.
20. Hanaki, N.; Link, J. T.; MacMillan, D. W. C.; Overman, L. E.; Trankle, W. G.; Wurster, J. A. *Org. Lett.* **2000**, *2*, 223–226.
21. (a) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2003**, *125*, 6650–6652. (b) MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391–10392. (c) MacMillan, D. W. C.; Overman, L. E.; Pennington, L. D. *J. Am. Chem. Soc.* **2001**, *123*, 9033–9044. (d) Overman, L. E.; Pennington, L. D. *Org. Lett.* **2000**, *2*, 2683–2686.

(e) Corminboeuf, O.; Overman, L. E.; Pennington, L. D. *Org. Lett.* **2003**, *5*, 1543–1546.
22. Hirst, G. C.; Johnson, T. O.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992–2993.
23. Lebsack, A. D.; Overman, L. E.; Valentekovich, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 4851–4852.
24. Tesson, N.; Dorigneux, B.; Fadel, A. *Tetrahedron: Asymmetry* **2002**, *13*, 2267–2276.
25. Hashihayata, T.; Ikegai, K.; Jona, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829–1848.
26. Mukaiyama, T.; Ikegai, K.; Hashihayata, T.; Kiyota, K.; Jona, H. *Chem. Lett.* **2002**, 730–731.
27. Tanaka, H.; Adachi, M.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1433–1436.
28. (a) Ihara, M.; Hirabayashi, A.; Taniguchi, N.; Fukumoto, K. *Tetrahedron* **1992**, *33*, 81–82. (b) Ihara, M.; Suzuki, M.; Fukumoto, K.; Kabuto, C. *J. Am. Chem. Soc.* **1990**, *112*, 1164–1171. (c) Ihara, M.; Toyota, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2151–2161. (d) Ihara, M.; Hirabayashi, A.; Taniguchi, N.; Fukumoto, K. *Tetrahedron* **1992**, *48*, 5089–5098.
29. Ihara, M.; Takino, Y.; Tomotake, M.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2287–2292.
30. (a) Saito, S.; Hirohara, Y.; Narahara, O.; Moriwake, T. *J. Am. Chem. Soc.* **1989**, *111*, 4533–4535. (b) Shida, N.; Uyehara, T.; Yamamoto, Y. *J. Org. Chem.* **1992**, *57*, 5049–5051. (c) Hanessian, S.; Gomtsyan, A. *Tetrahedron Lett.* **1994**, *35*, 7509–7512.
31. (a) Iwashima, M.; Nagaoka, H.; Kobayashi, K.; Yamada, Y. *Tetrahedron Lett.* **1992**, *33*, 81–82. (b) Nagaoka, H.; Kobayashi, K.; Okamura, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 6641–6644.
32. (a) Barco, A.; Benetti, S.; Casolari, A.; Pollini, G. P.; Spalluto, G. *Tetrahedron Lett.* **1990**, *31*, 4917–4920. (b) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *Chem. Commun.* **1991**, 390–391. (c) Barco, A.; Benetti, S.; Spalluto, G. *J. Org. Chem.* **1992**, *57*, 6279–6286.
33. Barco, A.; Benetti, S.; De Risi, C.; Pollini, G. P.; Romagnoli, R.; Spalluto, G.; Zanirato, V. *Tetrahedron* **1994**, *50*, 2583–2590.
34. Hagiwara, H.; Akama, T.; Okano, A.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2173–2184.
35. Hagiwara, H.; Nakano, T.; Kon-no, M.; Uda, H. *J. Chem. Soc., Perkin Trans. 1* **1995**, 777–783.
36. (a) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M. *Org. Lett.* **2001**, *3*, 251–254. (b) Hagiwara, H.; Kobayashi, K.; Miya, S.; Hoshi, T.; Suzuki, T.; Ando, M.; Okamoto, T.; Kobayashi, M.; Yamamoto, I.; Ohtsubo, S.; Kato, M.; Uda, H. *J. Org. Chem.* **2002**, *67*, 5969–5976.
37. Chetia, A.; Saikia, C. J.; Lekhok, K. C.; Boruah, R. C. *Tetrahedron Lett.* **2004**, *45*, 2649–2651.
38. Carreno, M. C.; Garcia Luzon, C.; Ribagorda, M. *Chem. Eur. J.* **2002**, *8*, 208–216.
39. (a) Urones, J. G.; Garrido, N. M.; Diez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1997**, *8*, 2683–2685. (b) Garrido, N. M.; Hammoumi, M. M. E.; Diez, D.; Garcia, M.; Urones, J. G. *Molecules* **2004**, *9*, 373–382.
40. (a) Davies, S. G.; Diez, D.; Dominguez, S. H.; Garrido, N. M.; Kruchinin, D.; Price, P. D.; Smith, A. D. *Org. Biomol. Chem.* **2005**, *3*, 1284–1301. (b) Urones, J. G.; Garrido, N. M.; Diez, D.; Dominguez, S. H.; Davies, S. G. *Tetrahedron: Asymmetry* **1999**, *1637*, 1641.
41. (a) Chan, W.; Lee, A. W. M.; Jiang, L. *Tetrahedron Lett.* **1995**, *36*, 715–718. (b) Lee, A. W. M.; Chan, W. H.; Mo, T. *Tetrahedron Lett.* **1997**, *38*, 3001–3004.
42. (a) Enders, D.; Scherer, H. J.; Raabe, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1664–1666. (b) Enders, D.; Scherer, H. J.; Runsink, J. *Chem. Ber.* **1993**, *126*, 1929–1944.
43. Amputch, M. A.; Matamoros, R.; Little, R. D. *Tetrahedron* **1994**, *50*, 5591–5614.
44. Le Gac, S.; Monnier-Benoit, N.; Doumampouom Metoul, L.; Petit, S.; Jabin, I. *Tetrahedron: Asymmetry* **2004**, *15*, 139–145.
45. Kato, K.; Suemune, H.; Sakai, K. *Tetrahedron Lett.* **1993**, *34*, 4979–4980.
46. Chen, Q.; Geng, Z.; Huang, B. *Tetrahedron: Asymmetry* **1995**, *6*, 401–404.
47. Li, G.; Jarosinski, M. A.; Hruby, V. J. *Tetrahedron Lett.* **1993**, *34*, 2561–2564.
48. Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, *10*, 1511–1516.
49. White, J. D.; Xu, Q.; Lee, C.-S.; Valeriote, F. A. *Org. Biomol. Chem.* **2004**, *2*, 2092–2102.
50. Sani, M.; Bruché, L.; Chiva, G.; Fustero, S.; Piera, J.; Volonterio, A.; Zanda, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2060–2063.
51. Krohn, K.; Riaz, M. *Tetrahedron Lett.* **2004**, *45*, 293–294.
52. Cramer, N.; Laschat, S.; Baro, A.; Schwalbe, H.; Richter, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 820–822.
53. Palomo, C.; Aizpurua, J. M.; Gracenea, J. J.; Garcia-Granda, S.; Pertierra, P. *Eur. J. Org. Chem.* **1998**, 2201–2207.
54. Takasu, K.; Ueno, M.; Ihara, M. *Tetrahedron Lett.* **2000**, *41*, 2145–2148.
55. (a) Schneider, C.; Reese, O. *Angew. Chem., Int. Ed.* **2000**, *39*, 2948–2950. (b) Schneider, C.; Reese, O. *Chem. Eur. J.* **2002**, *8*, 2585–2594.
56. Kataoka, T.; Kinoshita, H.; Kinoshita, S.; Osamura, T.; Watanabe, S.; Iwamura, T.; Muraoka, O.; Tanabe, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 2889–2891.
57. Nishimura, K.; Tsubouchi, H.; Ono, M.; Hayama, T.; Nagaoka, Y.; Tomioka, K. *Tetrahedron Lett.* **2003**, *44*, 2323–2326.
58. Li, G.; Xu, X.; Chen, D.; Timmons, C.; Carducci, M. D.; Headley, A. D. *Org. Lett.* **2003**, *5*, 329–331.
59. Brzezinski, L. J.; Rafel, S.; Leahy, J. W. *Tetrahedron* **1997**, *53*, 16423–16434.
60. Jauch, J. *J. Org. Chem.* **2001**, *66*, 609–611.
61. Ihara, M.; Taniguchi, N.; Suzuki, S.; Fukumoto, K. *Chem. Commun.* **1992**, 976–977.
62. Collado, I.; Ezquerra, J.; Vaquero, J. J.; Pedregal, C. *Tetrahedron Lett.* **1994**, *35*, 8037–8040.
63. Waldmann, H.; Braun, M. *J. Org. Chem.* **1992**, *57*, 4444–4451.
64. Lock, R.; Waldmann, H. *Tetrahedron Lett.* **1996**, *37*, 2753–2756.
65. Guarna, A.; Occhiato, E. G.; Machetti, F.; Scarpi, D. *J. Org. Chem.* **1998**, *63*, 4111–4115.
66. Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151–1160.
67. Zech, G.; Kunz, H. *Angew. Chem., Int. Ed.* **2003**, *42*, 787–790.
68. Reetz, M. T.; Schmitz, A.; Holdgrün, X. *Tetrahedron Lett.* **1989**, *30*, 5421–5424.
69. Wedler, C.; Costisella, B.; Schick, H. *J. Org. Chem.* **1999**, *64*, 5301–5303.
70. Marotta, E.; Baravelli, M.; Maini, L.; Righi, P.; Rosini, G. *J. Org. Chem.* **1998**, *63*, 8235–8246.

71. Sielecki, T. M.; Meyers, A. I. *J. Org. Chem.* **1992**, *57*, 3673–3676.
72. Tietze, L. F.; Geissler, H.; Gewert, J. A.; Jakobi, U. *Synlett* **1994**, 511–512.
73. Loh, T.-P.; Ho, D. S.-C.; Xu, K.-C.; Sim, K.-Y. *Tetrahedron Lett.* **1997**, *38*, 865–868.
74. Warrener, R. N.; Liu, L.; Russell, R. A. *Chem. Commun.* **1997**, 2173–2174.
75. Drew, M. D.; Jackson, D. A.; Lawrence, N. J.; Liddle, J.; Pritchard, R. G. *Chem. Commun.* **1997**, 189–190.
76. Kitaori, K.; Mikami, M.; Furukawa, Y.; Yoshimoto, H.; Otera, J. *Synlett* **1998**, 499–500.
77. Flamme, E. M.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 13644–13645.
78. Suzuki, K.; Inomata, K. *Tetrahedron Lett.* **2003**, *44*, 745–749.
79. Dolle, R. E.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1985**, *107*, 1691–1694.
80. (a) Nicolaou, K. C.; Baran, P. S.; Zhong, Y.-L.; Choi, H.-S.; Yoon, W. H.; He, Y.; Fong, K. C. *Angew. Chem., Int. Ed.* **1999**, *38*, 1669–1675. (b) Nicolaou, K. C.; Zhong, Y. L.; Baran, P. S.; Jung, J.; Choi, H. S.; Yoon, W. H. *J. Am. Chem. Soc.* **2002**, *124*, 2190–2201.
81. Bhaskar, G.; Satish Kumar, V.; Venkateswara Rao, B. *Tetrahedron: Asymmetry* **2004**, *15*, 1279–1283.
82. (a) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851–5852. (b) Tietze, L. F.; Hölskeen, S.; Adrio, J.; Kinzel, T.; Wegner, C. *Synthesis* **2004**, 2236–2239.
83. (a) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164–1172. (b) Tietze, L. F.; Wulff, C.; Wegner, A.; Schuffenhauer, A.; Schiemann, K. *J. Am. Chem. Soc.* **1998**, *120*, 4276–4280. (c) Mekhalfia, A.; Marko, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779–4782. (d) Manju, K.; Trehan, S. *Chem. Commun.* **1999**, 1929–1930. (e) Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147–150. (f) Huckins, J. R.; Rychnovsky, S. D. *J. Org. Chem.* **2003**, *68*, 10135–10145.
84. Kleinfeld, S. H.; Wegelius, E.; Hoppe, D. *Helv. Chim. Acta* **1999**, *82*, 2413–2424.
85. Gurjar, M. K.; Murugaiah, A. M. S.; Radhakrishna, P.; Ramana, C. V.; Chorghade, M. S. *Tetrahedron: Asymmetry* **2003**, *14*, 1363–1370.
86. Kawasaki, T.; Ogawa, A.; Takashima, Y.; Sakamoto, M. *Tetrahedron Lett.* **2003**, *44*, 1591–1593.
87. Csàkÿ, A. G.; Mba, M.; Plumet, J. *Tetrahedron: Asymmetry* **2004**, *15*, 647–652.
88. Padwa, A.; Waterson, A. G. *Curr. Org. Chem.* **2000**, *4*, 175–203.
89. (a) Kita, Y.; Tamura, O.; Miki, T.; Tono, H.; Shibata, N.; Tamura, Y. *Tetrahedron Lett.* **1989**, *30*, 729–730. (b) Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimor, C.; Ohishi, H. *J. Am. Chem. Soc.* **1994**, *116*, 5116–5121. (c) Carreno, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760. (d) Kita, Y.; Shibata, N.; Yoshida, N.; Fujita, S. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2405–2410. (e) Kita, Y.; Shibata, N. *Synlett* **1996**, 289–296.
90. Kita, Y.; Shibata, N.; Kawano, N.; Tohjo, T.; Fujimori, C.; Matsumoto, K. *Tetrahedron Lett.* **1995**, *36*, 115–118.
91. Kita, Y.; Shibata, N.; Miki, T.; Takemura, Y.; Tamura, O. *Chem. Pharm. Bull.* **1992**, *40*, 12–20.
92. Durst, T.; Breau, L.; Ben, R. N. *Phosphorus Sulfur Silicon Relat. Elem.* **1993**, *74*, 215–232.
93. Solladié-Cavallo, A.; Diep-Vohuule, A.; Sunjic, A.; Vinkovic, V. *Tetrahedron: Asymmetry* **1996**, *7*, 1783–1788.
94. Li, A.-H.; Dai, L.-X.; Hou, L.-X.; Huang, Y.-Z.; Li, F.-W. *J. Org. Chem.* **1996**, *61*, 489–493.
95. (a) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004–7005. (b) Aggarwal, V. K.; Ford, J. G.; Fonquerna, S.; Adams, H.; Jones, R. V. H.; Fieldhouse, R. *J. Am. Chem. Soc.* **1998**, *120*, 8328–8339. (c) Aggarwal, V. K.; Thompson, A. *Tetrahedron: Asymmetry* **1995**, *6*, 2557–2564. (d) Aggarwal, V. K.; Ford, J. G.; Jones, R. V. H.; Fieldhouse, R. *Tetrahedron: Asymmetry* **1998**, *9*, 1801–1807. (e) Aggarwal, V. K.; Bell, L.; Coogan, M. P.; Jubault, P. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2037–2042.
96. (a) Julienne, K.; Metzner, P.; Henryon, V. *J. Chem. Soc., Perkin Trans. 1* **1999**, 731–735. (b) Julienne, K.; Metzner, P. *J. Org. Chem.* **1998**, *63*, 4532–4534. (c) Zanardi, J.; Leriverend, C.; Aubert, D.; Julienne, K.; Metzner, P. *J. Org. Chem.* **2001**, *66*, 5620–5623.
97. Winn, C. L.; Bellenie, B. R.; Goodman, J. M. *Tetrahedron Lett.* **2002**, *43*, 5427–5430.
98. (a) Hayakawa, R.; Shimizu, M. *Synlett* **1999**, 1328–1330. (b) Imashiro, R.; Yamanaka, T.; Seki, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2845–2851. (c) Zhou, Y.-G.; Hou, X.-L.; Dai, L.-X.; Xia, L.-J.; Tang, M.-H. *J. Chem. Soc., Perkin Trans. 1* **1999**, 77–80. (d) Baird, C. P.; Taylor, P. C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3399–3403.
99. Saito, T.; Akiba, D.; Sakairi, M.; Kanazawa, S. *Tetrahedron Lett.* **2001**, *42*, 57–59.
100. Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47–69.
101. (a) Tietze, L. F.; Beifuss, U.; Ruther, M. *J. Org. Chem.* **1989**, *54*, 3120–3129. (b) Tietze, L. F.; Beifuss, U.; Ruther, M.; Rühlmann, A.; Antel, J.; Sheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1186–1187. (c) Tietze, L. F.; Beifuss, U. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1042–1043.
102. Tietze, L. F.; Ruther, M. *Chem. Ber.* **1990**, *123*, 1387–1395.
103. Tietze, L. F,; Beifuss, U. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed. Permagon: Oxford, 1991; Vol. 2, p 341.
104. Tietze, L. F.; Wünsch, J. R. *Synthesis* **1990**, 985–990.
105. (a) Tietze, L. F.; von Kiedrowski, G. *Tetrahedron Lett.* **1981**, *22*, 219–222. (b) Tietze, L. F.; von Kiedrowski, G.; Berger, B. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 221–222. (c) Tietze, L. F.; Denzer, H.; Holdgrün, X.; Neumann, M. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1295–1297.
106. Tietze, L. F.; Modi, A. *Med. Res. Rev.* **2000**, *20*, 304–322.
107. Tietze, L. F.; Bachmann, J.; Wichmann, J.; Burkhardt, O. *Synthesis* **1994**, 1185–1194.
108. Tietze, L. F.; Zhou, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 2045–2047.
109. Tietze, L. F.; Bachmann, J.; Wichmann, J.; Zhou, Y.; Raschke, T. *Liebigs Ann. Recl.* **1997**, 881–886.
110. Tietze, L. F.; Beifuss, U.; Lökös, M.; Rischer, M.; Göhrt, A.; Scheldrick, G. M. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 527–529.
111. (a) Tietze, L. F.; Wölfling, J.; Schneider, G. *Chem. Ber.* **1991**, *124*, 591–594. (b) Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013–3020.
112. Wölfling, J.; Frank, E.; Schneider, G.; Bes, M. T.; Tietze, L. F. *Synlett* **1998**, 1205–1206.
113. Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Angew. Chem., Int. Ed.* **1999**, *38*, 200–201.
114. Tietze, L. F.; Rackelmann, N.; Müller, I. *Chem. Eur. J.* **2004**, *10*, 2722–2731.
115. Cravotto, G.; Nano, G. M.; Palmisano, G.; Tagliapietra, S. *Tetrahedron: Asymmetry* **2001**, *12*, 707–709.

116. Yadav, J. S.; Reddy, B. V. S.; Narsimhaswamy, D.; Naga Lakshmi, P.; Narsimulu, K.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3493–3497.
117. Sabitha, G.; Reddy, E. V.; Fatima, N.; Yadav, J. S.; Rama Krishna, K. V. S.; Kunwar, A. C. *Synthesis* **2004**, *8*, 1150–1154.
118. Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Chem. Commun.* **1989**, 1203–1205.
119. Chinchilla, R.; Bäckvall, J.-E. *Tetrahedron Lett.* **1992**, *33*, 5641–5644.
120. Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *Chem. Commun.* **2002**, 1472–1473.
121. Tietze, L. F.; Rischer, M. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1221–1222.
122. Nubbemeyer, U. *Synthesis* **2003**, *7*, 961–1008.
123. Paquette, L. A.; Tae, J. *J. Org. Chem.* **1998**, *63*, 2022–2030.
124. Yokoyama, M.; Sujino, K.; Irie, M.; Yamazaki, N.; Hiyama, T.; Yamada, N.; Togo, H. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2801–2809.
125. Grigg, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2475–2486.
126. Röper, S.; Franz, M. H.; Wartchow, R.; Hoffmann, H. M. R. *Org. Lett.* **2003**, *5*, 2773–2776.
127. Lee, A. W. M.; Chan, W. H.; Tao, Y.; Lee, Y. K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 477–481.
128. Garcia Ruano, J. L.; Alemparte, C.; Aranda, M. T.; Zarzuelo, M. M. *Org. Lett.* **2003**, *5*, 75–78.
129. (a) Nishide, K.; Shigeta, Y.; Obata, K.; Node, M. *J. Am. Chem. Soc.* **1996**, *118*, 13103–13104. (b) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927–1936. (c) Nishide, K.; Ozeki, M.; Kunishige, H.; Shigeta, Y.; Patra, P. K.; Hagimoto, Y.; Node, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 4515–4517.
130. (a) Schultz-Fademrecht, C.; Tius, M. A.; Grimme, S.; Wibbeling, B.; Hoppe, D. *Angew. Chem., Int. Ed.* **2002**, *41*, 1532–1534. (b) Harrington, P. E.; Murai, T.; Chu, C.; Tius, M. A. *J. Am. Chem. Soc.* **2002**, *124*, 10091–10100. (c) Harrington, P. E.; Tius, M. A. *Org. Lett.* **2000**, *2*, 2447–2450. (d) Harrington, P. E.; Tius, M. A. *J. Am. Chem. Soc.* **2001**, *123*, 8509–8514. (e) Zimmermann, M.; Wibbeling, B.; Hoppe, D. *Synthesis* **2004**, *5*, 765–774.
131. Turner, C. I.; Williamson, R. M.; Turner, P.; Sherburn, M. S. *Chem. Commun.* **2003**, 1610–1611.
132. Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787–1790.
133. (a) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1994**, *116*, 6457–6458. (b) Roush, W. R.; Sciotti, R. J. *J. Am. Chem. Soc.* **1998**, *120*, 7411–7419.
134. Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137–165.
135. (a) Denmark, S. E.; Senanayake, C. B. W.; Ho, G.-D. *Tetrahedron* **1990**, *46*, 4857–4876. (b) Denmark, S. E.; Schnute, M. E.; Marcin, L. R.; Thorarensen, A. *J. Org. Chem.* **1995**, *60*, 3205–3220. (c) Denmark, S. E.; Thorarensen, A. *J. Org. Chem.* **1994**, *59*, 5672–5680.
136. Denmark, S. E.; Schnute, M. E.; Senanayake, C. B. W. *J. Org. Chem.* **1993**, *58*, 1859–1874.
137. Denmark, S. E.; Thorarensen, A.; Middleton, D. S. *J. Org. Chem.* **1995**, *60*, 3574–3575.
138. Denmark, S. E.; Martinborough, E. A. *J. Am. Chem. Soc.* **1999**, *121*, 3046–3056.
139. Denmark, S. E.; Schnute, M. E.; Thorarensen, A.; Middleton, D. S.; Stolle, A. *Pure Appl. Chem.* **1994**, *66*, 2041–2044.
140. Avalos, M.; Babiano, R.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *J. Org. Chem.* **1996**, *61*, 1880–1882.
141. Avalos, M.; Babiano, R.; Cintas, P.; Jiménez, J. L.; Palacios, J. C.; Silva, M. A. *Chem. Commun.* **1998**, 459–460.
142. Domingo, L. R.; Asensio, A. *J. Org. Chem.* **2000**, *65*, 1076–1083.
143. Roman, E.; Banos, M.; Higes, F. J.; Serrano, J. A. *Tetrahedron: Asymmetry* **1998**, *9*, 449–458.
144. Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062–4063.
145. Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948–10954.
146. Groen-Piotrowska, E. M.; Groen, M. B. *Rec. Trav. Chim. Pays-Bas* **1993**, *112*, 627–634.
147. Barriault, L.; Deon, D. H. *Org. Lett.* **2001**, *3*, 1925–1927.
148. Suzuki, K.; Inomata, K.; Endo, Y. *Org. Lett.* **2004**, *6*, 409–411.
149. (a) Cardoso, A. S.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* **2000**, *41*, 3611–3613. (b) Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463–12464.
150. Schnur, R. C.; Corman, M. L. *J. Org. Chem.* **1994**, *59*, 2581–2584.
151. Deloisy, S.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 791–794.
152. Paquette, L. A.; Wang, T.-Z.; Pinard, E. *J. Am. Chem. Soc.* **1995**, *117*, 1455–1456.
153. Raucher, S.; Chi, K.-W.; Hwang, K.-J.; Burks, J. E. *J. Org. Chem.* **1986**, *51*, 5503–5505.
154. Yeo, S.-K.; Hatae, N.; Seki, M.; Kanematsu, K. *Tetrahedron* **1995**, *51*, 3499–3506.
155. Rüedi, G.; Laikov, D. N.; Hansen, H.-J. *Helv. Chim. Acta* **2004**, *87*, 1990–2015.
156. Pisaneschi, F.; Cordero, F. M.; Brandi, A. *Synlett* **2003**, *12*, 1889–1891.
157. Saito, S.; Yamamoto, T.; Matsuoka, M.; Moriwake, T. *Synlett* **1992**, 239–240.
158. (a) Agami, C.; Cases, M.; Couty, F. *J. Org. Chem.* **1994**, *59*, 7937–7940. (b) Agami, C.; Couty, F.; Poursoulis, M. *Synlett* **1993**, 847–848. (c) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A. *Synlett* **1993**, 349–350. (d) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239–7250.
159. Knight, S. D.; Overman, L. E.; Pairaudeau, G. *J. Am. Chem. Soc.* **1995**, *117*, 5776–5788.
160. Deng, W.; Overman, L. E. *J. Am. Chem. Soc.* **1994**, *116*, 11241–11250.
161. Kuhn, C.; Le Gouadec, G.; Skaltsounis, A. L.; Florent, J.-C. *Tetrahedron Lett.* **1995**, *36*, 3137–3140.
162. Hall, D. G.; Deslongchamps, P. *J. Org. Chem.* **1995**, *60*, 7796–7814.
163. (a) Bélanger, G.; Deslongchamps, P. *J. Org. Chem.* **2000**, *65*, 7070–7074. (b) Bélanger, G.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 285–287.
164. (a) Martinkovà, M.; Gonda, J. *Tetrahedron Lett.* **1997**, *38*, 875–878. (b) Gonda, J.; Martinkovà, M.; Imrich, J. *Tetrahedron* **2002**, *58*, 1611–1616.
165. Narkevitch, V.; Vogel, P.; Schenk, K. *Helv. Chim. Acta* **2002**, *85*, 1674–1684.
166. (a) Carreno, M. C.; Urbano, A.; Di Vitta, C. *Chem. Commun.* **1999**, 817–818. (b) Carreno, M. C.; Urbano, A.; Di Vitta, C. *Chem. Eur. J.* **2000**, *6*, 906–913.
167. Carreno, M. C.; Garcia Ruano, J. L.; Toledo, M. A. *Chem. Eur. J.* **2000**, *6*, 288–291.

168. (a) Carreno, M. C.; Garcia-Cerrada, S.; Sanz-Cuesta, M. J.; Urbano, A. *Chem. Commun.* **2001**, 1452–1453. (b) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *J. Am. Chem. Soc.* **2001**, *123*, 7929–7930. (c) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem. Commun.* **2002**, 1412–1413. (d) Carreno, M. C.; Garcia-Cerrada, S.; Urbano, A. *Chem. Eur. J.* **2003**, *9*, 4118–4131.
169. Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. *Chem. Commun.* **2005**, 611–613.
170. Sanchez Fernandez, E. M.; Candela Lena, J. I.; Altinel, E.; Birlirakis, N.; Barrero, A. F.; Arseniyadis, S. *Tetrahedron: Asymmetry* **2003**, *14*, 2277–2290.
171. Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1997**, *62*, 7950–7960.
172. (a) Malacria, M. *Chem. Rev.* **1996**, *96*, 289–306. (b) McCarroll, A. J.; Walton, J. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 2224–2248.
173. (a) de Armas, P.; Francisco, C. G.; Suarez, E. *J. Am. Chem. Soc.* **1993**, *115*, 8865–8866. (b) de Armas, P.; Francisco, C. G.; Suarez, E. *Tetrahedron Lett.* **1993**, *34*, 7331–7334.
174. Stien, D.; Crich, D.; Bertrand, M. P. *Tetrahedron* **1998**, *54*, 10779–10788.
175. Sha, C.-K.; Lee, F.-K.; Chang, C.-J. *J. Am. Chem. Soc.* **1999**, *121*, 9875–9876.
176. Miyabe, H.; Fujii, K.; Goto, T.; Naito, T. *Org. Lett.* **2000**, *2*, 4071–4074.
177. Nicolaou, K. C.; Roecker, A. J.; Monenschein, H.; Guntupalli, P.; Follmann, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 3637–3642.
178. Baguley, P. A.; Walton, J. C. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3072–3082.
179. Balzani, V., Ed.; Electron Transfer in Chemistry; Wiley-VCH: Weinheim, 2001; Vols. 1 and 2.
180. Bunte, J. O.; Rinne, S.; Mattay, J. *Synthesis* **2004**, *4*, 619–633.
181. Takemoto, Y.; Ohra, T.; Koike, H.; Furuse, S.; Iwata, C. *J. Org. Chem.* **1994**, *59*, 4727–4729.
182. Davies, H. M. L.; Huby, N. J. S. *Tetrahedron Lett.* **1992**, *33*, 6935–6938.
183. Pirrung, M. C.; Brown, W. L.; Rege, S.; Laughton, P. *J. Am. Chem. Soc.* **1991**, *113*, 8561–8562.
184. (a) Clark, J. S.; Hodgson, P. B. *Chem. Commun.* **1994**, 2701–2702. (b) Clark, J. S.; Hodgson, P. B. *Tetrahedron Lett.* **1995**, *36*, 2519–2522.
185. Eberlein, T. H.; West, F. G.; Tester, R. W. *J. Org. Chem.* **1992**, *57*, 3479–3482.
186. West, F. G.; Naidu, B. N.; Tester, R. W. *J. Org. Chem.* **1994**, *59*, 6892–6894.
187. West, F. G.; Naidu, B. N. *J. Am. Chem. Soc.* **1994**, *116*, 8420–8421.
188. Kametani, T.; Yukawa, H.; Honda, T. *Chem. Commun.* **1988**, 685–687.
189. Montgomery, J.; Wieber, G. M.; Hegedus, L. S. *J. Am. Chem. Soc.* **1990**, *112*, 6255–6263.
190. Rudler, H.; Parlier, A.; Certal, V.; Frison, J.-C. *Tetrahedron Lett.* **2001**, *42*, 5235–5237.
191. Barluenga, J.; Diéguez, A.; Rodriguez, F.; Florez, J.; Fananas, F. J. *J. Am. Chem. Soc.* **2002**, *124*, 9056–9057.
192. Naruse, M.; Aoyagi, S.; Kibayashi, C. *Tetrahedron Lett.* **1994**, *35*, 9213–9216.
193. Yoshida, M.; Ismail, M. A.-H.; Nemoto, H.; Ihara, M. *Heterocycles* **1999**, *50*, 673–675.
194. Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727–729.
195. Piancatelli, G.; Margherita, R.; De Mico, A.; Parlanti, L.; Vescovi, A. *J. Org. Chem.* **1997**, *62*, 6974–6977.
196. Righi, P.; Scardovi, N.; Marotta, E.; ten Holte, P.; Zwanenburg, B. *Org. Lett.* **2002**, *4*, 497–500.
197. Li, C.; Bardhan, S.; Pace, E. A.; Liang, M.-C.; Gilmore, T. D.; Porco, J. A. *Org. Lett.* **2002**, *4*, 3267–3270.
198. Mihelcic, J.; Moeller, K. D. *J. Am. Chem. Soc.* **2004**, *126*, 9106–9111.
199. Nicolaou, K. C.; Sugita, K.; Baran, P. S.; Zhong, Y.-L. *J. Am. Chem. Soc.* **2002**, *124*, 2221–2232.
200. Shuto, S.; Niizuma, S.; Matsuda, A. *J. Org. Chem.* **1998**, *63*, 4489–4493.
201. Davies, S. B.; McKervey, M. A. *Tetrahedron Lett.* **1999**, *40*, 1229–1232.
202. Blackburn, L.; Wei, X.; Taylor, J. K. *Chem. Commun.* **1999**, 1337–1338.
203. Crich, D.; Mo, X.-S. *Synlett* **1999**, *1*, 67–68.
204. Shet, J.; Desai, V.; Tilve, S. *Synthesis* **2004**, *11*, 1859–1863.
205. (a) Nicolaou, K. C.; Xu, J.; Kim, S.; Ohshima, T.; Hosokawa, S.; Pfefferkorn, J. *J. Am. Chem. Soc.* **1997**, *119*, 11353–11354. (b) Nicolaou, K. C.; van Delft, F.; Ohshima, T.; Vourloumis, D.; Xu, J.; Hosokawa, S.; Pfefferkorn, J.; Kim, S.; Li, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2520–2524.
206. Nicolaou, K. C.; Bella, M.; Chen, D. Y.-K.; Huang, X.; Ling, T.; Snyder, S. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3495–3499.
207. Randl, S.; Blechert, S. *J. Org. Chem.* **2003**, *68*, 8879–8882.
208. Ohshima, T.; Xu, Y.; Takita, R.; Shibasaki, M. *Tetrahedron* **2004**, *60*, 9569–9588.
209. Lawrence, N. J.; Brown, S. *Tetrahedron* **2002**, *58*, 613–619.
210. Fadel, A.; Arzel, P. *Tetrahedron: Asymmetry* **1995**, *6*, 893–900.
211. (a) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2482–2486. (b) Nicolaou, K. C.; Vassilikogiannakis, G.; Mägerlein, W.; Kranich, R. *Chem. Eur. J.* **2001**, *7*, 5359–5371.
212. Nakamura, S.; Inagaki, J.; Sugimoto, T.; Ura, Y.; Hashimoto, S. *Tetrahedron* **2002**, *58*, 10375–10386.
213. Narita, M.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3671–3674.
214. Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584–8592.
215. Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475–5481.
216. Lawrence, N. J.; Bushell, S. M. *Tetrahedron Lett.* **2001**, *42*, 7671–7674.
217. Wei, Z.-Y.; Knaus, E. E. *Tetrahedron Lett.* **1993**, *34*, 4439–4442.
218. Pearson, W. H.; Bergmeier, S.; Williams, J. P. *J. Org. Chem.* **1992**, *57*, 3977–3987.
219. Timmer, M. S. M.; Risseeuw, M. D. P.; Verdoes, M.; Filippov, D. V.; Plaisier, J. R.; van der Marel, G. A.; Overkleeft, H. S.; van Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *16*, 177–185.
220. *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Weinheim, 2005.
221. Wender, P. A.; Handy, S. T.; Wright, D. L. *Chem. Ind. (London)* **1997**, 765–769.
222. Hall, N. *Science* **1994**, *266*, 32–34.
223. Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980.

224. Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169–3210.
225. Bock, H.; Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 385–389.
226. (a) Ziegler, T.; Kaisers, H.-J.; Schlömer, R.; Koch, C. *Tetrahedron* **1999**, *55*, 8397–8408. (b) Ziegler, T.; Kaisers, H.-J.; Schlömer, R.; Koch, C. *Tetrahedron Lett.* **1998**, *39*, 5957–5960.
227. Moran, E. J.; Amstrong, R. W. *Tetrahedron Lett.* **1991**, *32*, 3807–3810.
228. Banfi, L.; Guanti, G.; Riva, R. *Chem. Commun.* **2000**, 985–986.
229. Frey, R.; Galbraith, S. G.; Guelfi, S.; Lamberth, C.; Zeller, M. *Synlett* **2003**, *10*, 1536–1538.
230. Banfi, L.; Guanti, G.; Riva, R.; Basso, A.; Calcagno, E. *Tetrahedron Lett.* **2002**, *43*, 4067–4069.
231. Schmidt, U.; Weinbrenner, S. *Chem. Commun.* **1994**, 1003–1004.
232. Oaksmith, J. M.; Peters, U.; Ganem, B. *J. Am. Chem. Soc.* **2004**, *126*, 13606–13607.
233. (a) Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 810–819. (b) Ugi, I. *J. Prakt. Chem.* **1997**, *339*, 499–516.
234. Sigmuller, F.; Herrmann, R.; Ugi, I. *Tetrahedron* **1986**, *42*, 5931–5940.
235. (a) Kunz, H.; Pfrengle, W. *Tetrahedron* **1988**, *44*, 5487–5494. (b) Kunz, H.; Pfrengle, W.; Sager, W. *Tetrahedron Lett.* **1989**, *30*, 4109–4110. (c) Kunz, H.; Pfrengle, W. *J. Am. Chem. Soc.* **1988**, *110*, 651–652. (d) Kunz, H.; Pfrengle, W.; Rück, K.; Sager, W. *Synthesis* **1991**, 1039–1042.
236. (a) Goebel, M.; Ugi, I. *Synthesis* **1991**, 1095–1098. (b) Lehnhoff, S.; Goebel, M.; Karl, R. M.; Klösel, R.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1104–1107.
237. Linderman, R. J.; Binet, S.; Petrich, S. R. *J. Org. Chem.* **1999**, *64*, 336–337.
238. Piscopio, A. D.; Miller, J. F.; Koch, K. *Tetrahedron* **1999**, *55*, 8189–8198.
239. De Laszlo, S. E.; Williard, P. G. *J. Am. Chem. Soc.* **1985**, *107*, 199–203.
240. Boehm, J. C.; Kingsbury, W. D. *J. Org. Chem.* **1986**, *51*, 2307–2314.
241. Bauer, S. M.; Armstrong, R. W. *J. Am. Chem. Soc.* **1999**, *121*, 6355–6366.
242. Yamada, T.; Motoyama, N.; Taniguchi, T.; Kazuta, Y.; Miyazawa, T.; Kuwata, S.; Matsumoto, K.; Sugiura, M. *Chem. Lett.* **1987**, 723–726.
243. Hebach, C.; Kazmaier, U. *Chem. Commun.* **2003**, 596–597.
244. Kelly, C. L.; Lawrie, K. W. M.; Morgan, P.; Willis, C. L. *Tetrahedron Lett.* **2000**, *41*, 8001–8005.
245. Ross, G. F.; Herdtweck, E.; Ugi, I. *Tetrahedron* **2002**, *58*, 6127–6133.
246. Demharter, A.; Horl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 173–175.
247. Kehagia, K.; Ugi, I. K. *Tetrahedron* **1995**, *51*, 9523–9530.
248. Park, S. J.; Keum, G.; Kang, S. B.; Koh, H. Y.; Kim, Y. *Tetrahedron Lett.* **1998**, *39*, 7109–7112.
249. Ugi, I.; Hörl, W.; Hanusch-Kompa, C.; Schmid, T.; Hrdtweck, E. *Heterocycles* **1998**, *47*, 965–975.
250. Sung, K.; Chen, F.-L.; Chung, M.-J. *Mol. Divers.* **2003**, *6*, 213–221.
251. Basso, A.; Banfi, L.; Riva, R.; Guanti, G. *J. Org. Chem.* **2005**, *70*, 575–579.
252. Banfi, L.; Basso, A.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 6637–6640.
253. Urban, R.; Eberle, G.; Marquarding, D.; Rehn, D.; Rehn, H.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 627–628.
254. Behnke, D.; Taube, R.; Illgen, K.; Nerdinger, S.; Herdtweck, E. *Synlett* **2004**, 688–692.
255. Fadel, A. *Synlett* **1993**, 503–505.
256. Fadel, A.; Khesrani, A. *Tetrahedron: Asymmetry* **1998**, *9*, 305–320.
257. Truong, M.; Lecornué, F.; Fadel, A. *Tetrahedron: Asymmetry* **2003**, *14*, 1063–1072.
258. Boesten, W. H. J.; Seerden, J.-P.G.; de Lange, B.; Dielemans, H. J. A.; Elsenberg, H. L.; Kaptein, B.; Moody, H. M.; Kellogg, R. M.; Broterman, Q. B. *Org. Lett.* **2001**, *3*, 1121–1124.
259. (a) Ma, D.; Ding, K. *Org. Lett.* **2000**, *2*, 2515–2517. (b) Ding, K.; Ma, D. *Tetrahedron* **2001**, *57*, 6361–6366.
260. Harwood, L. M.; Drew, M. G. B.; Hughes, D. J.; Vickers, R. J. *J. Chem. Soc., Perkin Trans 1* **2001**, 1581–1583.
261. Kobayashi, S.; Ueno, M.; Suzuki, R.; Ishitani, H. *Tetrahedron Lett.* **1999**, *40*, 2175–2178.
262. Dudot, B.; Chiaroni, A.; Royer, J. *Tetrahedron Lett.* **2000**, *40*, 6355–6359.
263. Loh, T.-P.; Chen, S.-L. *Org. Lett.* **2002**, *4*, 3647–3650.
264. De Vries, A. H. M.; Hof, R. P.; Staal, D.; Kellogg, R. M.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 1539–1543.
265. Annunziata, R.; Cinquini, M.; Cozzi, F.; Molteni, V.; Schupp, O. *Tetrahedron* **1997**, *53*, 9715–9726.
266. Wei, H.-X.; Chen, D.; Guigen Li, X. X.; Paré, P. W. *Tetrahedron: Asymmetry* **2003**, *14*, 971–974.
267. Neumann, H.; Jacobi von Wangelin, A.; Gördes, D.; Spannenberg, A.; Beller, M. *J. Am. Chem. Soc.* **2001**, *123*, 8398–8399.
268. Narkevitch, V.; Megevand, S.; Schenk, K.; Vogel, P. *J. Org. Chem.* **2001**, *66*, 5080–5093.
269. Huang, X.; Craita, C.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4272–4275.
270. (a) Dondoni, A.; Massi, A.; Sabbatini, S. *Tetrahedron Lett.* **2001**, *42*, 4495–4497. (b) Dondoni, A.; Massi, A.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2002**, *67*, 6979–6994. (c) Dondoni, A.; Massi, A.; Minghini, E.; Sabbatini, S.; Bertolasi, V. *J. Org. Chem.* **2003**, *68*, 6172–6183.
271. Hong, C. Y.; Kishi, Y. *J. Am. Chem. Soc.* **1992**, *114*, 7001–7006.
272. Elliot, M. C.; Long, M. S. *Org. Biomol. Chem.* **2004**, *2*, 2003–2011.
273. Petasis, N. A.; Zavialov, I. A. *J. Am. Chem. Soc.* **1997**, *119*, 445–446.
274. Petasis, N. A.; Goodman, A.; Zavialov, I. A. *Tetrahedron* **1997**, *53*, 16463–16470.
275. Petasis, N. A.; Patel, Z. D. *Tetrahedron Lett.* **2000**, *41*, 9607–9611.
276. Currie, G. S.; Drew, M. G. B.; Harwood, L. M.; Hughes, D. J.; Luke, R. W. A.; Vickers, R. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2982–2990.
277. Pye, P. J.; Rossen, K.; Weissman, S. A.; Maliakal, A.; Reamer, R. A.; Ball, R.; Tsou, N. N.; Volante, R. P.; Reider, P. J. *Chem. Eur. J.* **2002**, *8*, 1372–1376.
278. (a) Prakash, G. K. S.; Mandal, M.; Schweier, S.; Petasis, N. A.; Olah, G. A. *J. Org. Chem.* **2002**, *67*, 3718–3723. (b) Sugiura, M.; Hirano, K.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 7182–7183.
279. Koolmeister, T.; Södergren, M.; Scobie, M. *Tetrahedron Lett.* **2002**, *43*, 5969–5970.

280. Tomooka, C. S.; Carreira, E. M. *Helv. Chim. Acta* **2002**, *85*, 3773–3784.
281. Sklute, G.; Amsallem, D.; Shabli, A.; Varghese, J. P.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 11776–11777.
282. (a) Ymaguchi, R.; Hamasaki, T.; Sasaki, T.; Ohta, T.; Utimoto, K.; Kozima, S.; Takaya, H. *J. Org. Chem.* **1993**, *58*, 1136–1143. (b) Haraguchi, Y.; Kozima, S.; Yamaguchi, R. *Tetrahedron: Asymmetry* **1996**, *7*, 443–449.
283. (a) Tailor, J.; Hall, D. G. *Org. Lett.* **2000**, *2*, 3715–3718. (b) Touré, B. B.; Hoveyda, H. R.; Tailor, J.; Ulaczyk-Lesanko, A.; Hall, D. G. *Chem. Eur. J.* **2003**, *9*, 466–474. (c) Touré, B. B.; Hall, D. G. *Angew. Chem., Int. Ed.* **2004**, *43*, 2001–2004. (d) Touré, B. B.; Hall, D. G. *J. Org. Chem.* **2004**, *69*, 8429–8436.
284. Boisbrun, M.; Kovàcs-Kulyassa, A.; Jeannin, L.; Sapi, J.; Toupet, L.; Laronze, J.-Y. *Tetrahedron Lett.* **2000**, *41*, 9771–9775.
285. Zhao, G.; Sun, X.; Bienaymé, H.; Zhu, J. *J. Am. Chem. Soc.* **2001**, *123*, 6700–6701.
286. Du Bois, J.; Tomooka, C. S.; Hong, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1997**, *119*, 3179–3180.
287. (a) Peyronel, J.-F.; Grisoni, S.; Carboni, B.; Courgeon, T.; Carrié, R. *Tetrahedron* **1994**, *50*, 189–198. (b) Garner, P.; Dogan, O. *J. Org. Chem.* **1994**, *59*, 4–6. (c) Enders, D.; Meyer, I.; Runsik, J.; Raabe, G. *Tetrahedron* **1998**, *54*, 10733–10752. (d) Wittland, C.; Risch, N. *J. Prakt. Chem.* **2000**, *342*, 311–315. (e) Chinchilla, R.; Falvello, L. R.; Galindo, N.; Nàjera, C. *Eur. J. Org. Chem.* **2001**, 3133–3140. (f) Onishi, T.; Sebahar, P. R.; Williams, R. M. *Org. Lett.* **2003**, *5*, 3135–3137. (g) Chung, F.; Chauveau, A.; Seltki, M.; Bonin, M.; Micouin, L. *Tetrahedron Lett.* **2004**, *45*, 3127–3130. (i) Dondas, H. A.; Fishwick, C. W. G.; Grigg, R.; Kilner, C. *Tetrahedron* **2004**, *60*, 3473–3485.
288. (a) Anslow, A. S.; Harwood, L. M.; Phillips, H.; Watkin, D. *Tetrahedron: Asymmetry* **1991**, *2*, 997–1000. (b) Anslow, A. S.; Harwood, L. M.; Lilley, I. A. *Tetrahedron: Asymmetry* **1995**, *6*, 2465–2468.
289. Hanselmann, R.; Zhou, J.; Ma, P.; Confalone, P. N. *J. Org. Chem.* **2003**, *68*, 8739–8741.
290. (a) Chiacchio, U.; Corsaro, A.; Gumina, G.; Rescifina, A.; Llanazo, D.; Piperno, A.; Romeo, G.; Romero, R. *J. Org. Chem.* **1999**, *64*, 9321–9327. (b) Merino, P.; Revuelta, J.; Tejero, T.; Chiacchio, U.; Rescifina, A.; Piperno, A.; Romeo, G. *Tetrahedron: Asymmetry* **2002**, *13*, 167–172.
291. Ganguly, A. K.; Seah, N.; Popov, V.; Wang, C. H.; Kuang, R.; Saksena, A. K.; Pramanik, B. N.; Chan, T. M.; McPhail, A. T. *Tetrahedron Lett.* **2002**, *43*, 8981–8983.
292. (a) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959–5989. (b) Tietze, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453–3516.
293. De Meijere, A.; Bräse, S. *J. Organomet. Chem.* **1999**, *576*, 88–110.
294. De Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed.* **1994**, *33*, 2379–2411.
295. Ang, K. H.; Bräse, S.; Steinig, A. G.; Meyer, F. E.; Llebaria, A.; Voigt, K.; de Mejeire, A. *Tetrahedron* **1996**, *52*, 11503–11528.
296. (a) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 6827–6832. (b) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *J. Org. Chem.* **1997**, *62*, 1341–1347. (c) Nguefack, J.-F.; Bolitt, V.; Sinou, D. *Chem. Commun.* **1995**, 1893–1894.
297. Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65–87.
298. Grigg, R.; Santhakumar, V.; Sridharan, V.; Thornton-Pett, M.; Bridge, A. W. *Tetrahedron* **1993**, *49*, 5177–5188.
299. Fox, M. E.; Li, C.; Marino, J. P.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467–5480.
300. Tietze, L. F.; Schirok, H. *J. Am. Chem. Soc.* **1999**, *121*, 10264–10269.
301. Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Eur. J.* **2002**, *7*, 1719–1729.
302. Kojima, A.; Takemoto, T.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem.* **1996**, *61*, 4876–4877.
303. Larock, R. C.; Lee, N. H. *J. Org. Chem.* **1991**, *56*, 6253–6254.
304. Oppolzer, W.; Bienaymé, H.; Genevois-Borella, A. *J. Am. Chem. Soc.* **1991**, *113*, 9660–9661.
305. (a) Torii, S.; Okumoto, H.; Kotani, T.; Nakayasu, S.; Ozaki, H. *Tetrahedron Lett.* **1992**, *33*, 3503–3506. (b) Torii, S.; Okumoto, H.; Ozaki, H.; Nakayasu, S.; Tadokoro, T.; Kotani, T. *Tetrahedron Lett.* **1992**, *33*, 3499–3502.
306. Masters, J. J.; Hegedus, L. S. *J. Org. Chem.* **1993**, *58*, 4547–4554.
307. Nicolaou, K. C.; Chakraborty, T. K.; Piscopio, A. D.; Minowa, N.; Bertinato, P. *J. Am. Chem. Soc.* **1993**, *115*, 4419–4420.
308. Nemoto, H.; Nagamochi, M.; Ishibashi, M.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 74–79.
309. Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153–156.
310. Thorey, C.; Wilken, J.; Hénin, F.; Martens, J.; Mehler, T.; Muzart, J. *Tetrahedron Lett.* **1995**, *36*, 5527–5530.
311. Sugiura, M.; Nakai, T. *Tetrahedron Lett.* **1996**, *37*, 7991–7994.
312. (a) Furuichi, N.; Hara, H.; Osaki, T.; Mori, H.; Katsumura, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 1023–1026. (b) Furuichi, N.; Hara, H.; Osaki, T.; Nakano, M.; Mori, H.; Katsumura, S. *J. Org. Chem.* **2004**, *69*, 7949–7959.
313. Fukuzawa, S.-i.; Tsuchimoto, T.; Hotaka, T.; Hiyama, T. *Synlett* **1995**, 1077–1078.
314. Tang, X.-Q.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 6098–6099.
315. (a) Wood, J. L.; Moniz, G. A. *Org. Lett.* **1999**, *1*, 371–374. (b) Drutu, I.; Krygowski, E. S.; Wood, J. L. *J. Org. Chem.* **2001**, *66*, 7025–7029.
316. Evans, P. A.; Robinson, J. E. *J. Am. Chem. Soc.* **2001**, *123*, 4609–4610.
317. Borsting, P.; Nielsen, P. *Chem. Commun.* **2002**, 2140–2141.
318. Zaja, M.; Blechert, S. *Tetrahedron* **2004**, *60*, 9629–9634.
319. Boyer, F.-D.; Hanna, I.; Ricard, L. *Org. Lett.* **2001**, *3*, 3095–3098.
320. Oesterreich, K.; Klein, I.; Spitzner, D. *Synlett* **2002**, *10*, 1712–1714.
321. Sanière, L.; Leman, L.; Bourguignon, J.-J.; Dauban, P.; Dodd, R. H. *Tetrahedron* **2004**, *60*, 5889–5897.

Biographical sketch

Hélène Pellissier was born in Gap, France. She carried out her PhD under the supervision of Dr. G. Gil in Marseille and then entered the Centre National de la Recherche Scientifique in 1988. After a postdoctoral period in Professor K.P.C. Vollhardt's group, she joined the group of Professor M. Santelli in Marseille in 1992, where she focused on the chemistry of BISTRO and its large application in organic synthesis. Thus, she developed several new very short total syntheses of steroids starting from 1,3-butadiene and benzocyclobutenes.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1667–1674

Heteroarenium salts in synthesis. Highly functionalized tetra- and pentasubstituted pyridines

Andreas Schmidt,[a,*] Thorsten Mordhorst[a] and Martin Nieger[b]

[a]*Clausthal University of Technology, Institute of Organic Chemistry, Leibnizstrasse 6, D-38678 Clausthal-Zellerfeld, Germany*
[b]*Rheinische Friedrich-Wilhelms-Universität Bonn, Institute of Inorganic Chemistry, Gerhard-Domagk-Strasse 1, D-53121 Bonn, Germany*

Received 4 November 2005; revised 24 November 2005; accepted 28 November 2005

Available online 20 December 2005

Abstract—Activation of chloropyridines by heteroarenium substituents allows sequential substitutions by O-, N-, and S-nucleophiles. Reaction of 2,3,5,6-tetrachloropyridine and 4-ethylsulfanyl-2,3,5,6-tetrachloropyridine with 4-(dimethylamino)pyridine, 4-(pyrrolidin-1-yl)pyridine, or 4-aminopyridine results in the formation of 2,6-bis-heteroarenium substituted 3,5-dichloropyridines. On nucleophilic displacement of the heteroarenium substituents by O-, N-, or S-nucleophiles highly functionalized 3,5-dichloropyridines form which possess N^2,S^4,N^6-, O^2,S^4,O^6-, O^2,O^6-, N^2,N^6-, and S^2,S^6-substitution patterns.

1. Introduction

Substitution reactions on halogenated heteroaromatics are widely applied reactions in organic synthesis. An impressive number of monographs and review articles reflect that synthetically, biologically, pharmaceutically, or industrially important pyridines can be synthesized from halogenated precursors.[1–4] Heteroaromatic substitutions proceed by different mechanisms. Mostly, a two-step AE-mechanism[1–3] is observed, but S_N(ANRORC)-,[5] EA-,[6] or S_{RN1}-mechanisms[7] have also been described. It is also known that the 2-, 3-, and 4-positions of the pyridine ring system display different reactivities.[1–3] The 3-position is often inert against nucleophilic attacks,[8] unless EA-mechanisms by amide ions[9] or metal-catalyses are applied.[10]

However, the vast majority of known substitutions was limited to the synthesis of mono- or bisubstituted pyridines. Thus, the reaction of pentachloropyridine with aliphatic amines generates only mono-amino tetrachloropyridines.[11] Vigorous reaction conditions are necessary to form 3,4-bisamino substituted trichloropyridines[12] or lead to mixtures of compounds. These limitations cannot be circumvented by alternative pyridine syntheses such as Hantźsch synthesis,[13] Kröhnke synthesis,[14] gasphase reactions of aldehydes and ketones with acrolein and ammonia,[15] electrocyclic ring closures,[16] ring transformations,[17] cycloadditions,[18] directed metallations,[19] or transition-metal catalysed reactions.[20] As a consequence, the number of reported tetra- and penta-substituted pyridines is very small. The need for these pyridines, however, is reflected in recent publications dealing with sequential controlled substitution reactions on pentafluoropyridines as promising avenues for the synthesis of macrocycles.[21]

As part of an ongoing project we recently described the synthesis and characterization of mono-, tris-, and pentakis-heteroarenium substituted pyridines bearing up to 10 positive charges within a common π-electron system.[22] These heteroarenium salts proved to be valuable starting materials for the regioselective synthesis of hitherto unavailable pyridine ethers[23] and pyridine thioethers.[24] We report here the scope and limitations of reactions leading to first examples of N^2,S^4,N^6-trisubstituted dichloropyridines, and to a variety of O^2,S^4,O^6-trisubstituted as well as O^2,O^6-, N^2,N^6-, and S^2,S^6-disubstituted dichloropyridines, which are symmetrically ($R^2=R^3$, Fig. 1) or non-symmetrically substituted ($R^2\neq R^3$).

2. Results and discussion

2.1. Activation of pentachloropyridine by heteroarenium substituents

Our earlier work reveals that the 4-chlorine atom of pentachloropyridine is the most susceptible leaving group toward substitution reactions with nucleophilic

Keywords: Heteroarenium; Pyridines; Nucleophiles.
* Corresponding author. Tel.: +49 5323 723861; fax: +49 5323 722858; e-mail: schmidt@ioc.tu-clausthal.de

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.065

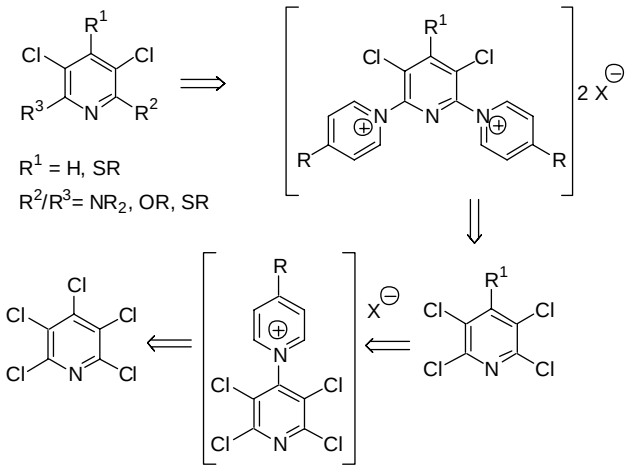
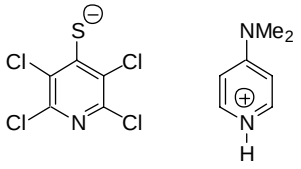


Figure 1. Retrosynthesis of substituted pyridines, available by sequential regioselective substitutions on heteroarenium activated chlorinated pyridines.

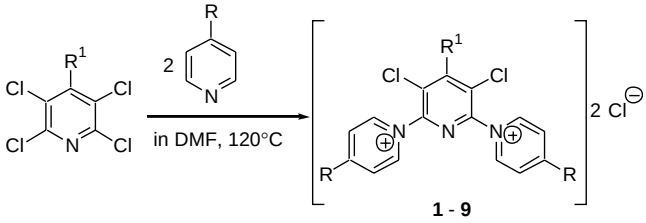
heteroaromatics such as 4-(dimethylamino)pyridine (DMAP), 4-(pyrrolidino)pyridine, and 1-methylimidazole.[22] We therefore focussed our interest on substitution reactions on pyridines without chlorine in the 4-position. In view of the interest in 4-sulfanyl-substituted pyridines (most of which are patented[25]) and other pyridine thioethers as bacterizides,[26] pesticides,[27] and intermediates for the synthesis of fungicides[28] and other biologically active compounds,[29] we focussed our interest on tetrachloro-4-sulfanylpyridines as starting materials. No substitution, however, was observable starting from 2,3,5,6-tetrachloropyridine-4-thiol or tetrachloropyridines with oxygen-or amino-groups in the 4-position under the reaction conditions applied. Deprotonation of acidic groups such as the SH-group resulted in a considerably decreased leaving group tendency of the α-chlorine substituents. Thus, treatment of 2,3,5,6-tetrachloro-pyridine-4-thiol with DMAP gave the salt 4-(dimethylamino)pyridinium 2,3,5,6-tetrachloropyridine-4-thiolate in quantitative yield (Scheme 1).



Scheme 1.

We found that 4-ethylsulfanyl-2,3,5,6-tetrachloropyridine, prepared regioselectively in 93% yield starting from 4-dimethylamino-(2,3,5,6-tetrachloropyridin-4-yl)pyridinium chloride,[24] does react with 4-aminopyridine, 4-(dimethylamino)pyridine, and 4-(pyrrolidino)pyridine to the bis-heteroarenium salts **1**, **4**, and **7**, respectively, (Table 1). Correspondingly, 4-(2-propylsulfanyl)-2,3,5,6-tetrachloro-pyridine gives **2**, **5**, and **8**. 2,3,5,6-Tetrachloro-pyridine affords the bis-heteroarenium salts **3**, **6**, and **9** in very good to excellent yields. All reactions were conducted at 120 °C in DMF, from which the salts precipitated in analytical purity on addition of ethyl acetate. The salts **1**–**9** are soluble in water, alcohols, amines, thiols, and DMF,

Table 1. Preparation of the bis-heteroarenium substituted pyridines



1 - 9

	R^1	R	Bis-hetero-arenium salt	Yield (%)
1	S–Et	$–NH_2$	**1**	54
2	S–*i*Pr	$–NH_2$	**2**	61
3	H	$–NH_2$	**3**	73
4	S–Et	$–N(CH_3)_2$	**4**	90
5	S–*i*Pr	$–N(CH_3)_2$	**5**	89
6	H	$–N(CH_3)_2$	**6**	95
7	S–Et	Pyrrolidin-1-yl	**7**	65
8	S–*i*Pr	Pyrrolidin-1-yl	**8**	66
9	H	Pyrrolidin-1-yl	**9**	99

stable on storage in air and on heating to 150 °C. The amino derivatives (**1**, **2**, **3**) are slightly hygroscopic.

Suitable single crystals of the bis-heteroarenium salt **5** as tetrafluoroborate were obtained by slow evaporation of a concentrated solution in H_2O:EtOH:HBF_4 (50% in H_2O)= 1:1:1. The molecular structure and the crystallographic numbering are shown in Figure 2. The dication **5** crystallized triclinic. The two pyridinium rings are twisted. Two different dihedral angles N1–C2–N21–C22 [123.4(3)°] and N1–C6–N61–C66 [115.3(3)°] were determined. The corresponding C2–N21 and C6–N61 bond distances (crystallographic numbering) are 144.2(3) pm, which corresponds to long C(sp^2)–N bonds. The dimethylamino group is joined to the pyridinium ring by a shortened C–N bond, the bond length of which was determined to be 133.2(4) and 133.2(4) pm. Bond distances of C22–C23 = 134.6(4) and C62–C63 = 134.9(4) pm do not hint at quinoidal characters of the pyridinium substituents.

2.2. Reaction of the bis-heteroarenium salts

Scope and limitations of substitution reactions of bis-heteroarenium salts to highly functionalized and hitherto unknown pyridines were investigated by examining first the reaction with O-, N-, and S-nucleophiles. 4-(Pyrrolidin-1-yl)pyridine gave the highest yields of the corresponding bis-heteroarenium salts **7**–**9**, but to our experience 4-(dimethylamino)pyridinium had the best leaving group tendencies for substitution reactions. Table 2 shows the reactions of the DMAP derivatives **4**, **5**, and **6** with oxygen nucleophiles. Sodium methanolate in methanol changed the heteroarenium substituents of **4** to methoxy groups to give **10**, which is a new substance (Table 2, entry 1). Likewise, the same reaction conditions converted **5** to **14** and **6** to **18** (entries 5 and 9, respectively). The synthesis of 3,5-dichloro-2,6-dimethoxypyridine **18** was described earlier. It was formed on reaction of 2,3,5,6-tetrachloropyridine with sodium methanolate in moderate yield.[30] No reaction occured on treatment of **4**, **5**, and **6** with 4-methoxyphenol in

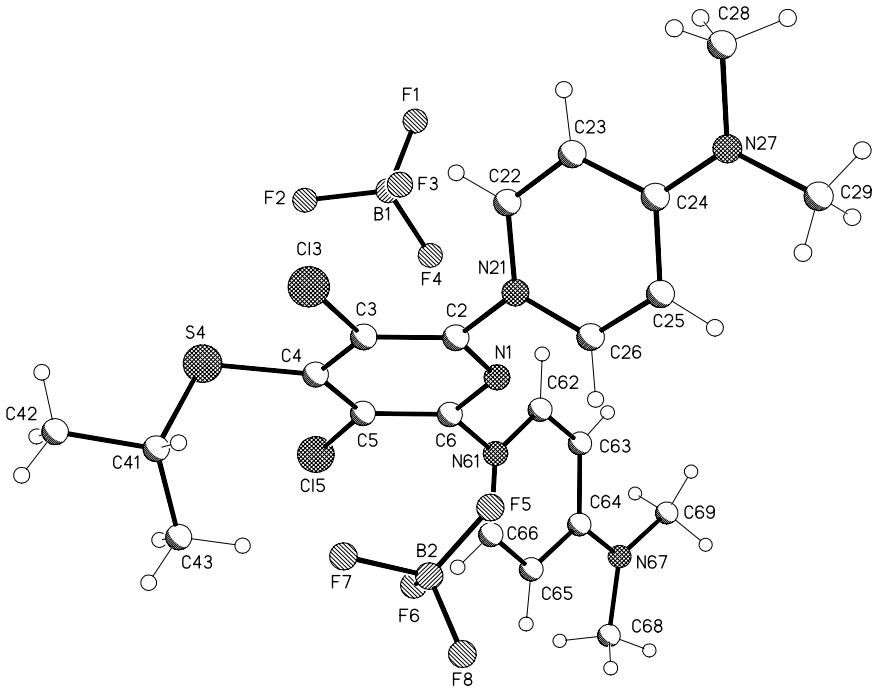
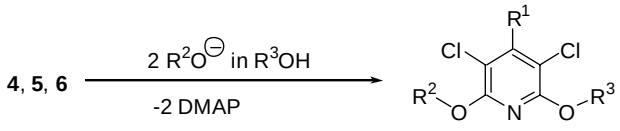


Figure 2. Molecular structure of **5**.

Table 2. Reaction of the dications **4**, **5**, and **6** with O-nucleophiles

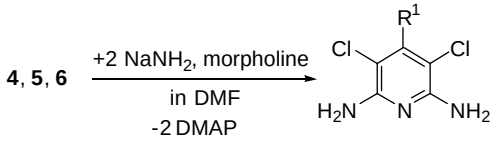


10 - 21

Entry	Starting material	R^1	R^2	R^3	Base added	Method	Product	Yield (%)
1	**4**	S–Et	Me	Me	Na	3 h/64 °C	**10**	57
2	**4**	S–Et	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**11**	23
3	**4**	S–Et	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**12**	20
4	**4**	S–Et	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**13**	45
5	**5**	S–*i*Pr	Me	Me	Na	3 h/64 °C	**14**	59
6	**5**	S–*i*Pr	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**15**	43
7	**5**	S–*i*Pr	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**16**	15
8	**5**	S–*i*Pr	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**17**	42
9	**6**	H	Me	Me	Na	3 h/64 °C	**18**	55
10	**6**	H	4-MeO-Ph	Me	$NaNH_2$	6 h/64 °C	**19**	40
11	**6**	H	4-MeO-Ph	*i*Pr	$NaNH_2$	6 h/82 °C	**20**	14
12	**6**	H	4-MeO-Ph	4-MeO-Ph	$NaNH_2$	6 h/82 °C	**21**	43

DMF in the presence of sodium amide. Non-symmetrically substituted pyridines ($R^1 \neq R^2 \neq R^3$), however, were obtained in a one-pot reaction of 4-methoxyphenol and $NaNH_2$ in methanol, although in moderate to low yields. Applying this reaction conditions pyridine thioethers with two different alkoxy groups in the α-positions of pyridine (**11**, **15**, **19**) were obtained. Thus, treatment of bis-heteroarenium salt **4** with 4-methoxyphenol in the presence of sodium amide in methanol gave 3,5-dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-methoxypyridine **11** (R^3=Me; entry 2). 2-Propanol as solvent resulted in the formation of a mixture of symmetrically and non-symmetrically substituted pyridines. The main products in the reactions of the bis-heteroarenium salts with 4-methoxyphenol in 2-propanol as solvent are the 2,6-(4-methoxyphenol)-substituted pyridines **13**, **17**, and **21** (Table 2, entries 4, 8 and 12), which can easily be separated from the non-symmetrically substituted α-(2-propoxy)pyridines **12**, **16**, and **20** (entries 3, 7 and 11) by column chromatography (silica gel; EtOAC/petrol ether=1:1), respectively. To the best of our knowledge, the compounds **10–17** are the first representatives of O^2,S^4,O^6-substituted 3,5-dichloropyridines. Even without chlorine in the β-positions this substitution pattern is very rare; we found that only five O^2,S^4,O^6-substituted pyridines have been synthesized by multi-step procedures[31] and patented[32] to date. O^2,O^6-substituted 3,5-dichloropyridines with hydrogen in the 4-position are pharmacologically interesting

Table 3. Reaction of the bis-heteroarenium salts **4**, **5**, and **6** with sodium amide



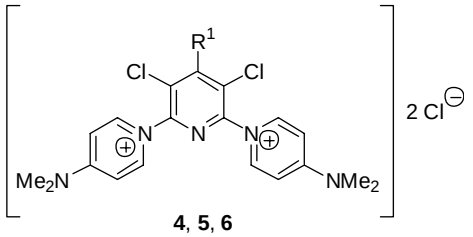
22 - 24

Entry	Starting material	R^1	Product	Yield (%)
1	**4**	S–Et	**22**	30
2	**5**	S–*i*Pr	**23**	55
3	**6**	H	**24**	20

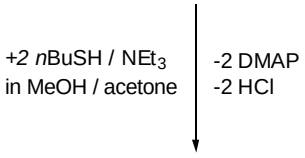
compounds; some derivatives with a broad variety of biological activities were prepared by multi-step procedures earlier.[33]

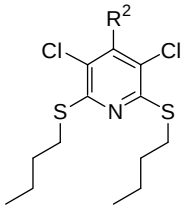
We next examined nitrogen nucleophiles. The dications **4** and **5** are attacked by amide in DMF in the presence of morpholine (or piperidine) to give the 2,6-diamino-4-sulfanylpyridines **22** and **23** (Table 3). Seemingly, these compounds are the first examples of N^2,S^4,N^6-substituted dichloropyridines. The bis-heteroarenium salt **6** affords 2,6-diamino-3,5-dichloropyridine **24** in low yield, which is also available starting from tetrachloroisonicotinic acid and ammonia at 200 °C in a sealed tube,[34] or from 2,6-diaminopyridine and hydrogen peroxide in hydrochloric acid in 60% yield.[35] No traces of the morpholine-substituted pyridines were isolable.

Table 4. Reaction of the dications with *n*-butylthiolate



4, 5, 6





25, 26

Entry	Starting material	R^1	R^2	Product	Yield (%)
1	**4**	S–Et	S–*n*Bu	**25**	46
2	**5**	S–*i*Pr	S–*n*Bu	**25**	40
3	**6**	H	H	**26**	25

Finally, we examined thiolates as reagents. In acetone, methanol, or mixtures of both and triethylamine as base substitutions were observed, and the pyridinium rings were replaced. Surprisingly, the ethylsulfanyl- and the 2-propylsulfanyl group at C-4 of **4** and **5** were substituted as well to yield **25**. The bis-heteroarenium salt **6** reacted in low yields to the bis-sulfanyl derivative **26** (Table 4).

In summary, we present an approach to highly functionalized pyridines possessing rare or hitherto unknown substitution patterns, which are of interest from chemical and biological viewpoints.

3. Experimental

3.1. General

The ^{1}H and ^{13}C NMR spectra were recorded on Bruker Digital FT-NMR Avance 400 and Avance DPX 200 spectrometers. Multiplicities are described by using the following abbreviations: s = singlet, d = doublet, m = multiplet. ^{15}N NMR spectra: reference $MeNO_2$. FT-IR spectra were obtained on a Bruker Vektor 22 in the range of 400–4000 cm^{-1} (2.5% pellets in KBr). The electrospray ionisation mass spectra (ESIMS) were measured with an Agilent LCMSD Series HP1100 with APIES. Samples were sprayed from methanol at 0 V fragmentor voltage. Melting points are uncorrected. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 287940. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk). Some crystal data of **5**: $[C_{22}H_{27}Cl_2N_5S]^{2+}2\,[BF_4]^-$, M = 638.07; space group P-1 (No. 2); dimensions 0.40×0.20×0.10 mm, a = 9.2815(6), b = 9.5981(4), c = 15.9010(9) Å; α = 93.103(3)°, β = 90.874(3)°; γ = 94.325(3)°, V = 1410.16(13) $Å^3$, D_c = 1.503 Mg m^{-3}, Z = 2, μ(Mo Kα) = 0.380 mm^{-1}; T = 123(2) K; $F(000)$ = 652, 10104 reflections were collected in a Nonius KappaCD diffractometer ($2\Theta_{max}$ = 50°, $-11 \le h \le 10$, $-11 \le k \le 11$, $-16 \le l \le 18$), 4934 symmetry independent reflections (R_{int} = 0.0347) were used for the structure solution (direct methods)[36] and refinement (full-matrix least-squares on F^2,[37] 365 parameters), non-hydrogen atoms were refined anisotropically, H atoms localized by difference electron density, and were defined using a riding model; $wR2$ (all data) = 0.1182 [$R1$ = 0.0482 for 3741 $I > 2\sigma(I)$].

3.2. General procedure for the preparation of dications (1–9)

2,3,5,6-Tetrachloropyridine (2.17 g, 10 mmol) or 2,3,5,6-tetrachloro-4-ethylsulfanylpyridine[24] (2.77 g, 10 mmol) or 2,3,5,6-tetrachloro-4-(2-propylsulfanyl)pyridine (2.91 g, 10 mmol) and 4-aminopyridine (1.88 g, 20 mmol) or 4-dimethylaminopyridine (2.44 g, 20 mmol) or 4-(pyrrolidin-1-yl)pyridine (2.96 g, 20 mmol) were dissolved in 200 mL of DMF and stirred for 3 h at 120 °C. After cooling to room temperature 200 mL of ethyl acetate were added whereupon yellow precipitates formed, which were filtered off, washed with ethyl acetate, and dried in vacuo.

3.2.1. 1,1′-Bis[4-amino-(3,5-dichloro-4-ethylsulfanyl-pyridine-2,6-diyl)pyridinium]dichloride (1). Yellow solid, mp 317 °C (Found: C, 43.54; H, 4.56; N, 15.13. $C_{17}H_{17}Cl_4N_5S$ requires C, 43.89; H, 3.68; N, 15.05); δ_H [D_2O–CD_3OD (1/1)] 8.34 (d, ^3J=7.9 Hz, 4H), 7.05 (d, ^3J=7.9 Hz, 4H), 3.32 (q, 2H; ^3J=7.4 Hz, CH_2), 1.33 (d, ^3J=7.4 Hz, 3H; CH_3), no signals of the amino groups were detectable due to H/D exchange; δ_C [D_2O–CD_3OD (1/1)] 160.3, 153.5, 146.4, 141.7, 132.4, 109.2, 29.9, 14.3; ν_{max} (KBr) (cm^{-1}) 1655, 1543, 1376, 1202, 843.

3.2.2. 1,1′-Bis[4-amino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (2). Yellow solid, dec>260 °C (Found: C, 43.74; H, 4.73; N, 14.60. $C_{18}H_{19}Cl_4N_5S$ requires C, 45.11; H, 4.00; N, 14.61); δ_H [DMSO] 9.47 (s, 4H; NH_2), 8.58 (d, ^3J=7.3 Hz, 4H), 7.16 (d, ^3J=7.3 Hz, 4H), 3.94 (h, ^3J=6.6 Hz, 1H), 1.32 (d, ^3J=6.6 Hz, 6H); δ_C [DMSO] 160.1, 150.6, 146.3, 141.9, 132.7, 109.0, 41.2, 23.4; ν_{max} (KBr) (cm^{-1}) 3433, 3257, 3095, 1661, 1542, 1376, 1198, 1165, 1103, 846.

3.2.3. 1,1′-Bis[4-amino-(3,5-dichloro-pyridine-2,6-diyl)-pyridinium]dichloride (3). Yellow solid, mp 255 °C (Found: C, 43.72; H, 4.20; N, 17.20. $C_{15}H_{13}Cl_4N_5\cdot{}^1/_2\ H_2O$ requires C, 43.50; H, 3.41; N, 16.91); δ_H [DMSO–D_2O (1/1)] 8.97 (s, 1H), 8.53 (d, ^3J=7.6 Hz, 4H), 7.11 (d, ^3J=7.6 Hz, 4H), no signals of the amino groups detectable due to H/D exchange; δ_C [DMSO–D_2O (1/1)] 159.7, 145.8, 144.5, 141.8, 127.4, 108.9; ν_{max} (KBr) (cm^{-1}) 3059, 1663, 1542, 1387, 1285, 1189, 1105, 842.

3.2.4. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-4-ethylsulfanyl-pyridine-2,6-diyl)pyridinium]dichloride (4). Yellow solid, mp 238 °C (Found: C, 45.38; H, 5.14; N, 13.46; S, 5.57. $C_{21}H_{25}Cl_4N_5S\cdot2H_2O$ requires C, 45.25; H, 5.24; N, 12.57; S, 5.75); δ_H [DMSO] 8.80 (d, ^3J=7.8 Hz, 4H), 7.32 (d, ^3J=7.8 Hz, 4H), 3.37 (q, ^3J=7.3 Hz, 2H), 3.36 (s, 12H), 1.32 (t, ^3J=7.3 Hz, 3H); δ_C [DMSO] 156.5, 151.2, 146.1, 141.1, 132.0, 107.6, 40.5, 29.8, 15.3; ν_{max} (KBr) (cm^{-1}) 1648, 1577, 1543, 1406, 1380, 1219, 829.

3.2.5. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (5). Yellow solid, mp 215 °C (Found: C, 49.34; H, 4.95; N, 12.69; $C_{22}H_{27}Cl_4N_5S$ requires: C, 49.36; H, 5.08; N, 13.08); δ_H [DMSO] 8.82 (d, ^3J=7.8 Hz, 4H), 7.33 (d, ^3J=7.8 Hz, 4H), 4.00 (h, ^3J=6.6 Hz, 1H), 3.36 (s, 12H), 1.37 (d, ^3J=6.6 Hz, 6H); δ_C [DMSO] 156.5, 150.5, 146.2, 141.1, 133.0, 107.6, 48.4, 40.4, 23.4; ν_{max} (KBr) (cm^{-1}) 3409, 1648, 1578, 1407, 1380, 1222, 1163.

3.2.6. 1,1′-Bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]dichloride (6). Yellow solid, mp 134 °C (Found: C, 43.45; H, 6.04; N, 14.07; $C_{19}H_{21}Cl_4N_5\cdot3{,}5H_2O$ requires C, 43.57; H, 5.38; N, 13.36); δ_H [DMSO] 9.20 (s, 1H), 8.75 (d, ^3J=7.8 Hz, 4H), 7.29 (d, ^3J=7.8 Hz, 4H), 3.34 (s, 12H); δ_C [DMSO] 156.5, 145.9, 144.4, 140.9, 127.5, 107.6, 40.5; ν_{max} (KBr) (cm^{-1}) 1649, 1582, 1562, 1429, 1406, 1230, 1212, 1105, 832.

3.2.7. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-4-(ethylsulfanyl)-pyridine-2,6-diyl)pyridinium]dichloride (7). Yellow solid, mp 204 °C (Found: C, 49.99; H, 5.66; N, 12.41; S, 5.02; $C_{25}H_{29}Cl_4N_5S\cdot2H_2O$ requires C, 49.27; H, 5.46; N, 11.49; S, 5.26); δ_H [DMSO–CD_3OD (1/1)] 8.68 (d, ^3J=7.7 Hz, 4H), 7.31 (d, ^3J=7.7 Hz, 4H), 4.51 (q, ^3J=6.9 Hz, 2H), 3.90–4.10 (m, 8H), 2.40–2.60 (m, 8H), 1.68 (t, ^3J=6.9 Hz, 3H); δ_C [DMSO–CD_3OD (1/1)] 154.2, 146.6, 145.0, 140.8, 129.9, 107.6, 49.2, 29.9, 24.6, 14.2; ν_{max} (KBr) (cm^{-1}) 1648, 1572, 1430, 1214, 1087, 828.

3.2.8. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-4-(2-propylsulfanyl)-pyridine-2,6-diyl)-pyridinium]dichloride (8). Yellow solid, mp 214 °C (Found: C, 47.22; H, 6.15; N, 11.38; S, 4.81; $C_{26}H_{31}Cl_4N_5S\cdot4H_2O$ requires C, 47.35; H, 5.96; N, 10.62; S, 4.81); δ_H [DMSO] 8.74 (d, ^3J=7.7 Hz, 4H), 7.13 (d, ^3J=7.7 Hz, 4H), 3.97 (h, ^3J=6.8 Hz, 1H), 3.65 (s, 8H), 2.03 (s, 8H), 1.34 (d, ^3J=6.8 Hz, 6H); δ_C [DMSO] 153.6, 150.5, 146.3, 141.0, 132.9, 108.3, 49.1, 41.3, 24.5, 23.4; ν_{max} (KBr) (cm^{-1}) 1647, 1571, 1548, 1429, 1215, 1087, 828.

3.2.9. 1,1′-Bis[4-pyrrolidino-(3,5-dichloro-pyridine-2,6-diyl)-pyridinium]dichloride (9). Pale yellow solid, mp 232 °C (Found: C, 48.95; H, 5.87; N, 12.82; $C_{23}H_{25}Cl_4N_5\cdot3H_2O$ requires C, 48.69; H, 5.51; N, 12.34); δ_H [DMSO] 9.22 (s, 1H), 8.76 (d, ^3J=7.7 Hz, 4H), 7.15 (d, ^3J=7.7 Hz, 4H), 3.68 (s, 8H), 2.06 (s, 8H); δ_C [DMSO] 153.6, 146.0, 144.4, 140.9, 127.5, 108.3, 49.1, 24.5; ν_{max} (KBr) (cm^{-1}) 1648, 1573, 1429, 1389, 1351, 1206, 1105, 831.

3.3. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with sodium methanolate to 10, 14, and 18

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol) and sodium methanolate (2.70 g, 50 mmol), respectively. After 6 h stirring at reflux temperature the solvent was distilled off, and the residue was worked up by chromatography (silica gel 60 HF_{254} from Merck, ethyl acetate–petrol ether (1/1)).

3.3.1. 3,5-Dichloro-4-ethylsulfanyl-2,6-dimethoxypyridine (10). Colourless liquid; (Found: C, 40.04; H, 3.71; N, 5.14; S, 11.81; $C_9H_{11}Cl_2NO_2S$ requires C, 40.31; H, 4.18; N, 5.22; S, 11.96); δ_H [$CDCl_3$] 4.01 (s, 6H), 3.04 (q, ^3J=7.4 Hz, 2H), 1.23 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 156.0, 145.8, 113.2, 54.6, 29.1, 14.8; ν_{max} (NaCl) (cm^{-1}) 2984, 2950, 2867, 1562, 1538, 1470, 1448, 1370, 1318, 1200, 1121, 1098, 1031, 787, 746; GC–MS: m/z=268 (M, 100); 237 (M−C_2H_5, 9); 199 (M−C_5H_5–Cl, 13) amu.

3.3.2. 3,5-Dichloro-2,6-dimethoxy-4-(2-propylsulfanyl)-pyridine (14). Colourless liquid; (Found: C, 42.58; H, 4.66; N, 4.96; S, 10.93; $C_{10}H_{13}Cl_2NO_2S$ requires C, 42.56; H, 4.64; N, 4.96; S, 11.36); δ_H [$CDCl_3$] 4.02 (s, 6H), 3.74 (h, ^3J=6.7 Hz, 1H), 1.27 (d, ^3J=6.7 Hz, 6H); δ_C [$CDCl_3$] 156.1, 145.9, 113.6, 54.6, 39.4, 23.1; ν_{max} (NaCl) (cm^{-1}) 2951, 2866, 1558, 1538, 1471, 1446, 1369, 1317, 1244, 1199, 1121, 1097, 786, 749; GC–MS: m/z=282 (M, 100); 238 (M−C_3H_7, 5) amu.

3.3.3. 3,5-Dichloro-2,6-dimethoxypyridine (18). White solid, mp 48 °C (Found: C, 40.41; H, 3.62; N, 6.67;

$C_7H_7Cl_2NO_2$ requires C, 40.41; H, 3.39; N, 6.73); δ_H [$CDCl_3$] 7.58 (s, 1H), 4.00 (s, 6H); δ_C [$CDCl_3$] 156.0, 139.9, 107.8, 54.4; ν_{max} (KBr) (cm^{-1}) 1582, 1470, 1398, 1225, 1095, 1009, 786, 739; GC–MS: m/z=208 (M, 100), 177 (M−CH_3O, 52) amu.

3.4. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with 4-methoxyphenol in methanol to 11, 15, and 19

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and 4-methoxyphenol (2.48 g, 20 mmol), respectively. Then, sodium amide (0.78 g, 20 mmol) was added and the mixture was heated under reflux for 6 h. After this period the solvent was distilled off and the residue was worked up chromatographically (silica gel 60 HF_{254} from Merck, ethyl acetate–petrol ether (1/1)).

3.4.1. 3,5-Dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-methoxypyridine (11). Pale yellow liquid; (Found: C, 49.32; H, 4.29; N, 4.35; $C_{15}H_{15}Cl_2NO_3S$ requires C, 50.01; H, 4.20; N, 3.89); δ_H [$CDCl_3$] 7.07 (d, ^3J=9.2 Hz, 2H), 6.89 (d, ^3J=9.2 Hz, 2H), 3.82 (s, 3H), 3.67 (s, 3H), 3.09 (h, ^3J=7.4 Hz, 2H), 1.27 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 157.2, 156.7, 156.0, 146.9, 145.8, 122.4 (overlapped), 114.1, 113.2, 55.5, 54.6, 29.1, 14.9; ν_{max} (NaCl) (cm^{-1}) 2951, 1561, 1504, 1460, 1369, 1247, 1198, 1101, 1033; GC–MS: m/z=361 (MH^+, 100) amu.

3.4.2. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-methoxy-4-(2-propylsulfanyl)pyridine (15). Colourless liquid; (Found: C, 50.46; H, 4.24; N, 3.73; $C_{16}H_{17}Cl_2NO_3S$ requires C, 51.34; H, 4.58; N, 3.74); δ_H [$CDCl_3$] 7.01–7.11 (m, 2H), 6.82–6.92 (m, 2H), 3.78 (h, ^3J=6.7 Hz, 1H), 3.77 (s, 3H), 3.65 (s, 3H), 1.29 (d, ^3J=6.7 Hz, 6H); δ_C [$CDCl_3$] 156.6, 155.9, 155.4, 146.8, 146.7, 122.3, 115.5, 114.0, 113.8, 55.3, 54.4, 39.5, 23.1; ν_{max} (NaCl) (cm^{-1}) 2951, 1558, 1505, 1462, 1367, 1246, 1196, 1097, 1034, 843; GC–MS: m/z=389 (M, 100) amu.

3.4.3. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-methoxypyridine (19). Colourless liquid; (Found: C, 52.02; H, 3.69; N, 4.67; $C_{13}H_{11}Cl_2NO_3$ requires C, 50.57; H, 3.21; N, 4.75); δ_H [$CDCl_3$] 7.62 (s, 1H), 7.00–7.10 (m, 2H), 6.82–6.92 (m, 2H), 3.78 (s, 3H), 3.64 (s, 3H); δ_C [$CDCl_3$] 156.6, 155.8, 155.3, 146.8, 140.5, 122.3, 114.1, 109.9, 108.5, 55.4, 54.4; ν_{max} (NaCl) (cm^{-1}) 2954, 1578, 1506, 1469, 1409, 1380, 1222, 1192, 1095, 1036, 988, 837; GC–MS: m/z=329 (MH^+, 100), 264 (M−C_3H_7, 83), 108 (C_7H_7O, 53) amu.

3.5. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with 4-methoxyphenol in 2-propanole to 12, 13, 16, 17, 20, and 21

In 100 mL of 2-propanol were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and 4-methoxyphenol (2.48 g, 20 mmol), respectively. Then, sodium amide (0.78 g, 20 mmol) was dissolved and the mixture was heated at reflux temperature for 6 h. After this period the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)).

3.5.1. 3,5-Dichloro-4-ethylsulfanyl-2-(4-methoxyphenoxy)-6-(2-propoxy)-pyridine (12). Colourless liquid; (Found: C, 51.02; H, 4.71; N, 3.70; $C_{17}H_{19}Cl_2NO_3S$ requires C, 52.58; H, 4.93; N, 3.61); δ_H [$CDCl_3$] 7.05 (m, 2H), 6.89 (m, 2H), 4.70 (h, ^3J=6.2 Hz, 1H), 3.83 (s, 3H), 3.09 (h, ^3J=7.3 Hz, 2H), 1.28 (t, ^3J=7.3 Hz, 3H), 1.27 (d, ^{3}J=6.2 Hz, 6H); δ_C [$CDCl_3$] 160.4, 156.7, 155.2, 147.0, 146.4, 122.5, 122.4, 114.5, 114.1, 70.9, 55.6, 29.2, 21.6, 15.0; ν_{max} (NaCl) (cm^{-1}) 2979, 2931, 1557, 1504, 1374, 1246, 1195, 1095, 1036, 945; GC–MS: m/z=389 (MH^+, 100) amu.

3.5.2. 3,5-Dichloro-4-ethylsulfanyl-2,6-bis(4-methoxyphenoxy)-pyridine (13). Colourless solid, mp 82 °C; (Found: C, 55.41; H, 4.42; N, 3.10; S, 6.92; $C_{21}H_{19}Cl_2NO_4S$ requires C, 55.76; H, 4.23; N, 3.10; S, 7.09); δ_H [$CDCl_3$] 6.80–6.87 (m, 4H), 6.64–6.73 (m, 4H), 3.77 (s, 6H), 3.13 (q, ^3J=7.4 Hz, 2H), 1.31 (t, ^3J=7.4 Hz, 3H); δ_C [$CDCl_3$] 156.6, 155.3, 147.4, 146.5, 122.4, 115.2, 113.9, 55.4, 29.4, 15.0; ν_{max} (KBr) (cm^{-1}) 1559, 1501, 1369, 1249, 1193, 1029, 828; GC–MS: m/z=452 (M, 100) amu.

3.5.3. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-(2-propoxy)-4-(2-propylsulfanyl)pyridine (16). Pale yellow liquid; (Found: C, 53.34; H, 5.64; N, 3.56; $C_{18}H_{21}Cl_2NO_3S$ requires C, 53.73; H, 5.26; N, 3.48); δ_H [$CDCl_3$] 7.00–7.10 (m, 2H), 6.85–6.95 (m, 2H), 4.70 (h, ^3J=6.3 Hz, 1H), 3.83 (s, 3H), 3.80 (h, ^3J=6.5 Hz, 1H), 1.31 (d, ^3J=6.3 Hz, 6H), 1.17 (d, ^3J=6.5 Hz, 6H); δ_C [$CDCl_3$] 156.7, 155.5, 155.3, 147.0, 146.5, 122.5, 115.9, 114.2, 113.4, 70.9, 55.6, 39.5, 23.3, 21.6; ν_{max} (NaCl) (cm^{-1}) 2977, 2931, 1558, 1503, 1374, 1246, 1196, 1109, 1037, 946, 832; GC–MS: m/z=403 (MH^+, 100), 359 (M−C_3H_7, 15), 317 (M−$2C_3H_7$, 28), 280 (M−$2C_3H_7$–Cl, 21) amu.

3.5.4. 3,5-Dichloro-2,6-bis(4-methoxyphenoxy)-4-(2-propylsulfanyl)pyridine (17). Pale yellow solid, mp 52 °C; (Found: C, 56.22; H, 4.78; N, 3.00; S, 6.80; $C_{22}H_{21}Cl_2NO_4S$ requires C, 56.66; H, 4.54; N, 3.00; S, 6.88); δ_H [$CDCl_3$] 6.86–6.90 (m, 2H), 6.62–6.72 (m, 2H), 3.84 (h, ^3J=6.6 Hz, 1H), 3.76 (s, 6H), 1.34 (d, ^3J=6.6 Hz, 6H); δ_C [$CDCl_3$] 156.6, 155.3, 147.5, 146.5, 122.5, 115.7, 113.9, 55.4, 39.7, 23.3; ν_{max} (KBr) (cm^{-1}) 2957, 2834, 1551, 1505, 1369, 1264, 1193, 1036, 825; GC–MS: m/z=467 (M, 100) amu.

3.5.5. 3,5-Dichloro-2-(4-methoxyphenoxy)-6-(2-propoxy)-pyridine (20). Colourless liquid; (Found: C, 54.41; H, 4.39; N, 4.35; $C_{15}H_{15}Cl_2NO_3$ requires C, 54.90; H, 4.61; N, 4.27); δ_H [$CDCl_3$] 7.66 (s, 1H), 7.00–7.08 (m, 2H), 6.85–6.93 (m, 2H), 4.71 (h, ^3J=6.3 Hz, 1H), 3.82 (s, 3H), 1.17 (d, ^3J=6.3 Hz, 6H); δ_C [$CDCl_3$] 156.7, 155.3, 155.2, 147.0, 140.5, 122.5, 114.1, 110.3, 107.7, 70.7, 55.6, 21.6; ν_{max} (NaCl) (cm^{-1}) 2980, 1569, 1505, 1436, 1247, 1218, 1191, 1092, 1036, 833; GC–MS: m/z=329 (MH^+, 100) amu.

3.5.6. 3,5-Dichloro-2,6-bis(4-methoxyphenoxy)pyridine (21). Colourless solid, mp 104 °C; (Found: C, 58.00; H, 3.49; N, 3.48; $C_{19}H_{15}Cl_2NO_4$ requires C, 58.18; H, 3.85; N, 3.57); δ_H [$CDCl_3$] 7.75 (s, 1H), 6.79–6.89 (m, 4H), 6.63–6.73 (m, 4H), 3.77 (s, 6H); δ_C [$CDCl_3$] 156.5, 155.2, 146.6, 141.1, 122.4, 113.9, 110.1, 55.5; ν_{max} (KBr) (cm^{-1}) 2958,

1574, 1508, 1428, 1249, 1221, 1180, 1091, 1034, 829; GC–MS: $m/z=392$ (M, 100) amu.

3.6. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 with sodium amide in DMF to 22–24

In 100 mL of DMF were dissolved the salt **4** (5.21 g, 10 mmol), or **5** (5.35 g, 10 mmol), or **6** (4.61 g, 10 mmol), and morpholine (8.2 g, 0.1 mol) as well as sodium amide (3.9 g, 0.1 mol), respectively. The mixture was stirred at 100 °C for 6 h. Then, the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)).

3.6.1. 2,6-Diamino-3,5-dichloro-4-ethylsulfanylpyridine (22). Yellow solid, mp 63 °C; (Found: C, 35.83; H, 4.11; N, 17.09; S, 13.62; $C_7H_9Cl_2N_3S$ requires C, 35.31; H, 3.81; N, 17.65; S, 13.46); δ_H [$CDCl_3$] 4.81 (s, 4H), 3.00 (q, $^3J=7.4$ Hz, 2H), 1.24 (t, $^3J=7.4$ Hz, 3H); δ_C [$CDCl_3$] 152.1, 142.5, 108.0, 29.2, 14.9; ν_{max} (KBr) (cm^{-1}) 3397, 3319, 1605, 1426, 1409, 1263, 746; GC–MS: $m/z=238$ (MH^+, 100) amu.

3.6.2. 2,6-Diamino-3,5-dichloro-4-(2-propylsulfanyl)-pyridine (23). Yellow solid, mp 64 °C; (Found: C, 38.49; H, 4.55; N, 15.98; S, 12.61; $C_8H_{11}Cl_2N_3S$ requires C, 38.10; H, 4.40; N, 16.66; S, 12.72); δ_H [$CDCl_3$] 4.89 (s, 4H), 3.65 (h, $^3J=6.6$ Hz, 1H), 1.27 (d, $^3J=6.6$ Hz, 6H); δ_C [$CDCl_3$] 152.1, 142.7, 108.3, 39.3, 23.2; ν_{max} (KBr) (cm^{-1}) 3425, 3323, 1627, 1603, 1531, 1412; GC–MS: $m/z=253$ (MH^+, 100); 208 ($M-C_3H_7$, 31); 175 ($M-C_3H_7S$, 43) amu.

3.6.3. 2,6-Diamino-3,5-dichloropyridine (24). Yellow solid, mp 202 °C; (Found: C, 33.87; H, 2.70; N, 24.00; $C_5H_5N_3Cl_2$ requires C, 33.73; H, 2.83; N, 23.60); δ_H [$CDCl_3$–CD_3OD (1/2)] 7.68 (s, 1H), the protons of the amino groups gave no signal due to H/D-exchange; δ_C [$CDCl_3$–CD_3OD (1/2)] 161.1, 140.0, 104.7; ν_{max} (KBr) (cm^{-1}) 3457, 3409, 3317, 1626, 1458, 1295, 902, 737; GC–MS: $m/z=180$ (MH^+, 100) amu.

3.7. General procedure for the reaction of the 1,1′-bis[4-dimethylamino-(3,5-dichloro-pyridine-2,6-diyl)pyridinium]-dichlorides 4, 5, and 6 to 2,4,6-tris(*n*-butylsulfanyl)-3,5-dichloropyridine (25)

In 100 mL of methanol were dissolved the salt **4** (5.21 g, 10 mmol) or **5** (5.35 g, 10 mmol), *n*-butylthiol (5.4 g, 50 mmol) and triethylamine (5.2 g, 50 mmol). The mixture was then stirred for 18 h at room temperature. Then, the solvent was distilled off and the residue was chromatographed (silica gel, ethyl acetate–petrol ether (1/1)).

3.7.1. 2,4,6-Tris(*n*-butylsulfanyl)-3,5-dichloropyridine (25). Colourless liquid; (Found: C, 49.79; H, 6.64; N, 3.05; S, 24.30; $C_{17}H_{27}Cl_2NS_3$ requires C, 49.50; H, 6.60; N, 3.40; S, 23.32); δ_H [$CDCl_3$] 3.17 (t, $^3J=7.5$ Hz, 4H), 2.97 (t, $^3J=7.1$ Hz, 2H), 1.72 (m, 4H), 1.66 (m, 2H), 1.46 (m, 4H), 1.43 (m, 2H), 0.95 (t, $^3J=7.5$ Hz, 6H), 0.89 (t, $^3J=7.1$ Hz, 3H); δ_C [$CDCl_3$] 155.4, 142.4, 127.7, 34.9, 31.8, 31.2, 30.7, 22.2, 21.7, 13.7, 13.5; ν_{max} (NaCl) (cm^{-1}) 2959, 2930, 2872, 1492, 1464, 1287, 1209, 1187, 1076, 806; GC–MS: $m/z=414$ (MH^+, 80); 376 (M−Cl, 100), 334 (M−Cl–C_3H_7, 38) amu.

3.7.2. Preparation of 2,6-bis(*n*-butylsulfanyl)-3,5-dichloro-pyridine (26). In 100 mL of methanol were dissolved 1,1′-bis[4-dimethylamino-(3,5-dichloropyridine-2,6-diyl)pyridinium]dichloride (5.21 g, 10 mmol), *n*-butylthiol (5.4 g, 50 mmol), and triethylamine (5.2 g, 50 mmol). The mixture was stirred for 18 h at room temperature. Then, the solvent was distilled off and the residue was chromatographed (silica gel 60, ethyl acetate–petrol ether (1/1)). Pale yellow liquid; (Found: C, 48.85; H, 6.22; N, 2.84; $C_{13}H_{19}Cl_2NS_2$ requires C, 48.14; H, 5.90; N, 4.32); δ_H [$CDCl_3$] 7.42 (s, 1H), 3.19 (t, $^3J=7.4$ Hz, 4H), 1.62–1.79 (m, 4H), 1.39–1.54 (m, 4H), 0.95 (t, $^3J=7.2$ Hz, 6H); δ_C [$CDCl_3$] 154.2, 135.2, 123.6, 38.8, 31.3, 22.2, 13.7; ν_{max} (NaCl) (cm^{-1}) 2957, 2930, 2873, 1545, 1515, 1464, 1371, 1334, 1218, 1147, 1062; GC–MS: $m/z=325$ (M, 100); 288 (M−Cl, 41), 266 (M−C_4H_9, 10) amu.

Acknowledgements

The Deutsche Forschungsgemeinschaft (DFG) is greatfully acknowledged for financial support. We thank Prof. F. Vögtle, Prof. K.-H. Dötz, and Prof. E. Niecke (University of Bonn) for providing the X-ray facilities.

References and notes

1. Spitzner, D. In Black, D. S. C., Ed.; Science of Synthesis; Thieme: Stuttgart, 2004; Vol. 15, pp 11–284.
2. Spitzner, D. In Kreher, E., Ed.; Houben-Weyl, Methoden der Organischen Chemie; Thieme: Stuttgart, 1994; Vol. E7b, pp 286–686.
3. *The Chemistry of Heterocyclic Compounds*, Weissberger A., Taylor, E. C., Eds.; Vol. 14: Pyridine and its Derivatives, Suppl. 1–4, Abramovitch, A., Ed., Wiley-Interscience: New York, 1974 and 1975.
4. Belen'kii, L. I.; Kruchkovskaya, N. D.; Gramenitskaya, V. N. *Adv. Heterocycl. Chem.* **1999**, *73*, 295.
5. de Bie, D. A.; Geurtsen, B.; Berg, I. E.; van der Plas, H. C. *J. Org. Chem.* **1986**, *51*, 3209.
6. (a) Hoffmann, R. W. *Dehydrobenzene and Cycloalkynes*; Chemie: Weinheim, 1967. (b) Kauffmann, T.; Wirthwein, R. *Angew. Chem.* **1971**, *83*, 21. Angew. Chem., Int. Ed. Engl. **1971**, *10*, 20. (c) Reinecke, M. G. *Tetrahedron* **1982**, *38*, 427.
7. (a) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1. (b) Boy, P.; Combellas, C.; Thiebault, A. *Synlett* **1991**, 923. (c) Beugelmans, R.; Chastanet, J. *Tetrahedron* **1993**, *49*, 7883.
8. (a) Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027. (b) Connon, S.-J.; Hegarty, A. F. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1245. (c) Kim, C.-S.; Russell, K. C. *J. Org. Chem.* **1998**, *23*, 8229. (d) Barlocco, D.; Cignarella, G.; Tondi, D.; Vianello, P.; Villa, S. *J. Med. Chem.* **1998**, *41*, 674.
9. Berry, D. J.; Wakefield, B. J. *J. Chem. Soc. C* **1969**, 2342.

10. (a) Gradel, B.; Brenner, E.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 568. (b) Sakamoto, T.; Kondo, Y.; Murata, N.; Yamanaka, H. *Tetrahedron Lett.* **1992**, *33*, 5373. (c) Sakamoto, T.; Shiga, F.; Yasuhara, A.; Uchiyama, D.; Kondo, Y.; Yoshinori, Y. *Synthesis* **1992**, *8*, 746. (d) Ji, J.; Li, T.; Brunelle, W. H. *Org. Lett.* **2003**, *5*, 4611.
11. (a) Vorbrüggen, H. *Adv. Heterocycl. Chem.* **1990**, *49*, 117. (b) Collins, I.; Suschitzky, H. *J. Chem. Soc. C* **1970**, 1523. (c) Roberts, S. M.; Suschitzky, H. *Chem. Commun.* **1967**, 893.
12. (a) Bratt, J.; Iddon, B.; Mack, A. G.; Suschitzky, H.; Taylor, J. A.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 648. (b) Julia, L.; Rius, J.; Suschitzky, H. *Heterocycles* **1992**, *34*, 1539.
13. Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269.
14. Kröhnke, F. *Synthesis* **1976**, 1.
15. Beschke, H. *Aldrichim. Acta* **1981**, *14*, 13.
16. Jutz, J. C. *Top. Curr. Chem.* **1978**, *73*, 125.
17. Katritzky, A. R. *Tetrahedron* **1980**, *36*, 679.
18. Boger, D. L. *Chem. Rev.* **1986**, *86*, 781.
19. (a) Queguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (b) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436. (c) Comins, D. L.; La Munyon, D. H. *Tetrahedron Lett.* **1988**, *29*, 773.
20. Undheim, K.; Benneche, T. *Adv. Heterocycl. Chem.* **1995**, *62*, 305.
21. (a) Sandford, G. *Eur. J. Org. Chem.* **2003**, *9*, 1465. (b) Chambers, R. D.; Hoskin, P. R.; Sandford, G.; Yufit, D. S.; Howard, A. A. K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2788. (c) Chambers, R. D.; Hoskin, P. R.; Kenwright, A. R.; Richmond, P.; Sandford, G.; Yufit, M. S.; Howard, J. A. K. *Org. Biomol. Chem.* **2003**, *1*, 2137.
22. (a) Schmidt, A.; Mordhorst, T.; Nieger, M. *Org. Biomol. Chem.* **2005**, *3*, 3788. (b) Schmidt, A.; Mordhorst, T.; Habeck, T. *Org. Lett.* **2002**, *4*, 1375.
23. Schmidt, A.; Mordhorst, T. *Synthesis* **2005**, 781.
24. Schmidt, A.; Mordhorst, T. *Z. Naturforsch.* **2005**, *60b*, 683.
25. Johnston, H. (Dow Chemical Co.). U.S. Patent 3,549,647; *Chem. Abstr.* **1971**, *75*, 5715.
26. Kyriacou, D. (Dow Chemical Co.). U.S. Patent 3,829,430; *Chem. Abstr.* **1975**, *82*, 43181.
27. Gilmore, C. J.; MacNicol, D. D. *Tetrahedron Lett.* **1984**, *25*, 4303.
28. Johnston, H. (Dow Chemical Co.). U.S. Patent 3,364,223; *Chem. Abstr.* **1968**, *69*, 27254.
29. (a) Ugryumov, E. P.; Kaklyugin, V. Y. *Agrokhimiya* **1995**, *2*, 73. *Chem. Abstr.* **1995**, *122*, 308690. (b) Kukhar, V. P.; Cherepenko, T. I.; Pavlenko, A. F. *Dopov. Akad. Nauk Ukr. RSR, Ser. B: Geol., Khim. Biol. Nauki* **1982**, *12*, 60. *Chem. Abstr.* **1983**, *98*, 121208. (c) Dzyuban, A. D.; Protopopova, G. V.; Reidalova, L. I.; Sologub, S. L.; Zalesskii, G. A.; Moshchitskii, S. D.; Pavlenko, A. F. *Fiziol. Akt. Veshchestva* **1974**, *6*, 76. *Chem. Abstr.* **1975**, *82*, 165834.
30. Xu, X.; Qian, X.; Li, Z.; Song, G. *J. Fluorine Chem.* **1998**, *88*, 9.
31. (a) Efremov, I. V.; Sipyagin, A. M.; Pomytkin, I. A. *Chem. Heterocycl. Compd. (Engl. Transl.)* **1996**, *32*, 796. (b) Boehme, H.; Ahrens, G. *Liebigs Ann. Chem.* **1982**, *6*, 1030. (c) Tominaga, Y. *Chem. Pharm. Bull.* **1977**, *25*, 1519.
32. Yamanouchi Pharm., DE 2727686, 1978; *Chem. Abstr.* **1978**, *88*, 136637.
33. Phillips, G. B.; Buckman, B. O.; Davey, D. D.; Eagen, K. A.; Guilford, W. J.; Hinchman, J.; Ho, E.; Koovakkat, S.; Liang, A.; Light, D. R.; Mohan, R.; Ng, H. P.; Post, J. M.; Shaw, K. J.; Smith, D.; Subramanyam, B.; Sullivan, M. E.; Trinh, L.; Vergona, R.; Walters, J.; White, K.; Whitlow, M.; Wu, S.; Xu, W.; Morrissey, M. M. *J. Med. Chem.* **1998**, *41*, 3557.
34. (a) Sell, W. J.; Dootson, F. W. *J. Chem. Soc.* **1897**, *71*, 1082. (b) Sell, W. J.; Dootson, F. W. *J. Chem. Soc.* **1898**, *73*, 441.
35. Chen, T. K.; Flowers, W. T. *J. Chem. Soc., Chem. Commun.* **1980**, *23*, 1139.
36. Sheldrick, G. M. *SHELXS-97, Acta Crystallogr., Sect. A* **1990**, *46*, 467.
37. Sheldrick, G. M. *SHELXL-97*, University of Göttingen: Göttingen, Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1675–1689

The biomimetic synthesis of SNF4435C and SNF4435D, and the total synthesis of the polyene metabolites aureothin, *N*-acetyl-aureothamine and spectinabilin

Mikkel F. Jacobsen, John E. Moses, Robert M. Adlington and Jack E. Baldwin*

Chemistry Research Laboratory, University of Oxford, Mansfield road, Oxford, OX1 3TA, United Kingdom

Received 19 October 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—Full details of the biomimetic conversion of polyene metabolite spectinabilin (**5**) into the isomeric natural products SNF4435C (**1**) and SNF4435D (**2**) by a cascade of *E*/*Z*-isomerizations and electrocyclizations are reported. Additionally, short total syntheses of the related natural products (±)-aureothin (**3**), (±)-*N*-acetyl-aureothamine (**4**) and (±)-spectinabilin (**5**) are presented. The key steps in the synthesis of (±)-**3**, (±)-**4** and (±)-**5** are the construction of the tetrahydrofuran motif using a palladium-catalyzed cycloaddition and the ruthenium-catalyzed cross metathesis of alkene **17** to form the common intermediate, boronic ester **24**, which was further transformed using a trans-selective Suzuki coupling with a dibromide and a stereospecific Negishi-type methylation.

1. Introduction

In recent years, a plethora of polypropionates metabolites have been isolated from various terrestrial and marine systems as phylogenetically diverse as bacteria and sponges. Several of these compounds not only feature interesting biological activities, including immunosuppression, cytotoxicity and antibacterial effects, but also possess structurally interesting and complex motifs. Our continued interest in polypropionate natural products and biomimetic synthesis motivated us to consider the recently isolated nitrophenyl pyrones SNF4435C (**1**) and SNF4435D (**2**) reported by Snow Brand Milk Products Co., Ltd, Japan as targets for synthesis (Fig. 1).[1–3]

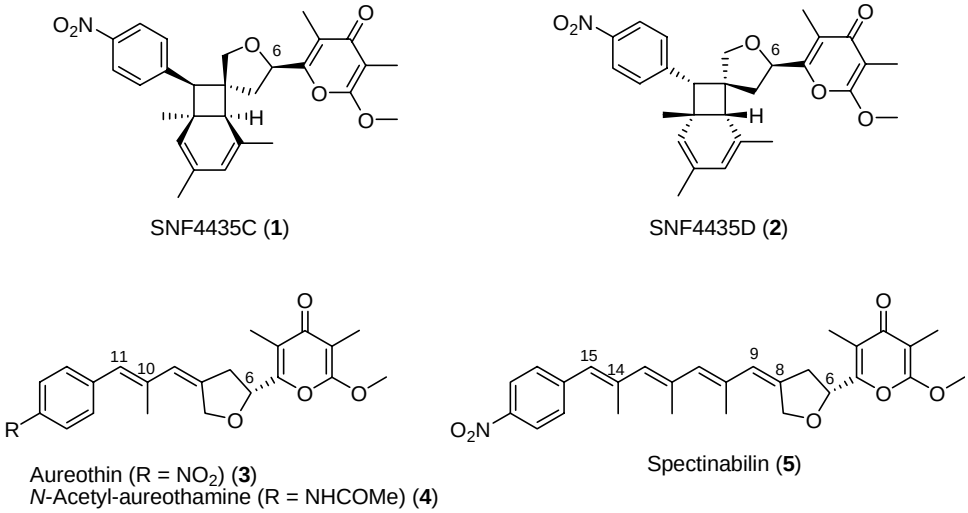


Figure 1. Metabolites from Streptomyces.

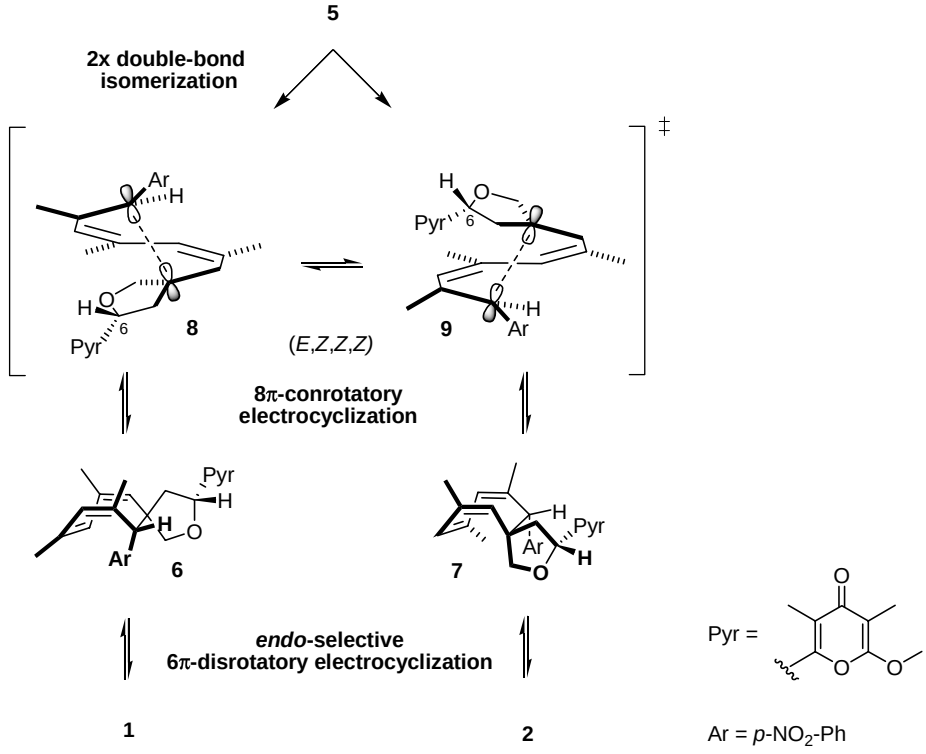
Keywords: Metabolite; Total synthesis; Metathesis; C–C coupling reaction; Biomimetic synthesis; Electrocyclization; Isomerization.
* Corresponding author. Tel.: +44 865 275 671; fax: +44 865 275 6732; e-mail: jack.baldwin@chem.ox.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.058

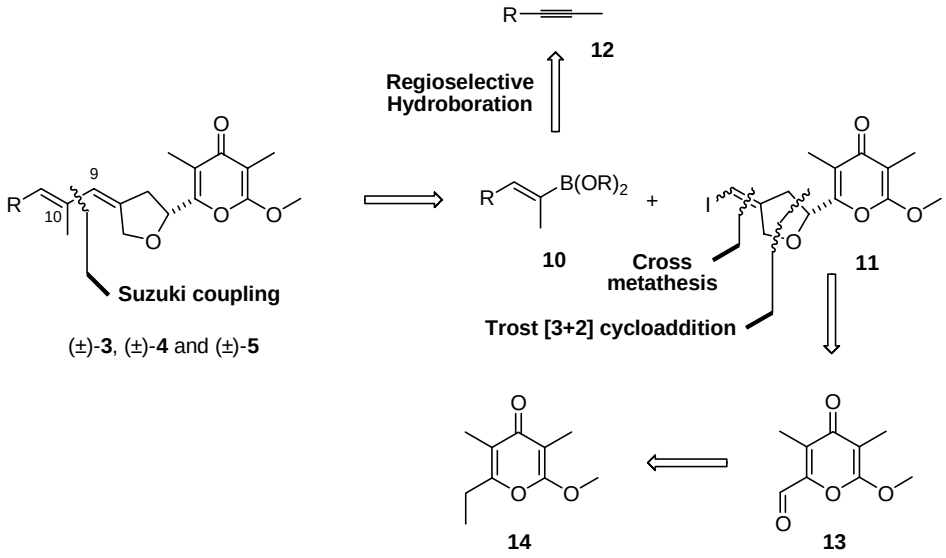
Biologically, the SNF compounds are potent immunosuppressants, exhibiting activities at submicromolar concentrations, isolated from a strain of *Streptomyces spectabilis* found in a soil sample collected on the main island of Okinawa, Japan. Structurally, the SNF compounds are pentacyclic structures featuring a rare hexasubstituted bicyclo[4.2.0] core connected to a spirofuran unit, which in turn is linked to a γ-pyrone moiety. The tetrahydrofuran ring-substituted γ-pyrone motif is also found in the related polyenes aureothin (**3**) (*Streptomyces thioluteu*),[4,5] *N*-acetyl-aureothamine (**4**) (*Streptomyces netropsis*)[6] and spectinabilin (**5**) (*S. spectabilis*).[7–9] *N*-Acetyl-aureothamine (**4**) has been shown to be a highly selective agent against *Helicobacter pylori*, a common cause of chronic gastritis.[6] Recently, studies on the biosynthesis of **3** have revealed that two novel oxygenases are involved.[10,11] An *N*-oxygenase catalyzes the oxidation of *p*-aminobenzoate to the corresponding nitro compound, which serves as starter unit for the polyketide synthase (PKS) resulting in **3**.[10] Secondly, a cytochrome P450 monooxygenase catalyzes the formation of the exomethylene tetrahydrofuran ring.[11] The biosynthesis of **5** is likely to proceed in a similar manner.[12]

It is apparent that spectinabilin (**5**) is a constitutional isomer of **1** and **2**. Interestingly, it has been isolated from the same actinomycete producing the SNF compounds.[3] These observation have led us[13,14] and others[15,16] to propose a biogenetic hypothesis for the transformation of **5** into **1** and **2**,[17] resembling Black's hypothesis for the formation of the endiandric acids,[18] which has been experimentally corroborated by the work of Nicolaou.[19] We envisaged that **1** and **2** could be formed from **5** via a cascade of *E*/*Z*-isomerizations and electrocyclisations. Firstly, the (*E*,*E*,*E*,*Z*)-configuration of **5** could be changed to (*E*,*Z*,*Z*,*Z*) via double *E* to *Z* isomerization. Secondly, the transformed (*E*,*Z*,*Z*,*Z*)-isomer of **5** could undergo a thermally allowed conrotatory 8π-electrocyclization with some bias towards **6** versus **7** via 1,3-asymmetric induction from the C6-stereocenter, followed by an *endo*-selective disrotatory 6π-electrocyclization to form **1** and **2** (Scheme 1). The transition structures **8** and **9** may possess a helical geometry in accord with studies of conrotatory 8π-electrocyclizations using ab initio molecular orbital theory.[20]

In the course of this work, Parker and co-workers have synthesized (−)-**1** and (+)-**2**, both of approximately 70% ee, by forming the (*E*,*Z*,*Z*,*Z*)-isomer in situ via a Stille coupling.[16] Similarly (−)-aureothin (**3**) of 27% ee has previously been synthesized,[21] but the approach employed lacked efficiency (0.01% overall yield) and we believed that it would not be compatible with the more complex tetraene **5**. In order to achieve the synthesis of tetraene **5**, we initially chose the simpler dienes **3** and **4** as model systems.[22] It is reported that both **3**[21] and **5**[9] are prone to racemization even under mild conditions due to the labile C6-proton. Accordingly, any intermediate bearing similar allylic proton(s) in the γ-position to the ketone of a γ-pyrone motif may suffer from such racemization/epimerization. Therefore, we chose instead to devise novel synthesis of (±)-**3**, (±)-**4** and (±)-**5**. We have previously communicated our main findings in these synthetic endeavors and in the biomimetic conversion of **5** to **1** and **2**.[14,22] We now report full details of these studies.



Scheme 1. Biogenetic hypothesis for the formation of **1** and **2** from **5**.

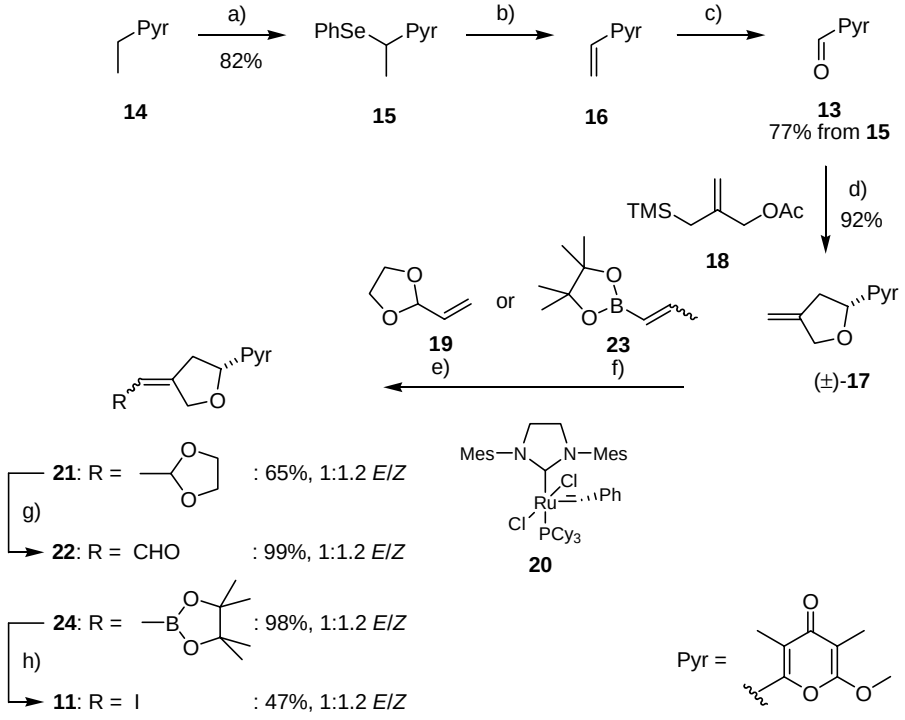


Scheme 2. First retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.

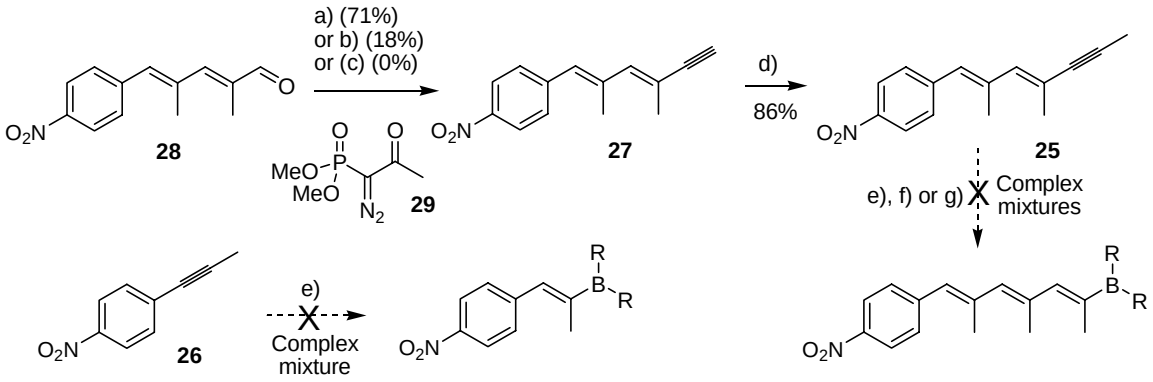
2. Results and discussion

2.1. Synthesis of key boronic ester 24 and initial synthetic studies towards (±)-3, (±)-4 and (±)-5

Our initial retrosynthetic analysis of the polyenes **3**–**5** revealed that the C9–C10 double bond may be formed from the Suzuki coupling of boronic ester **10** with the advanced intermediate, alkenyl iodide **11** (Scheme 2). The former would be formed by regioselective hydroboration of alkyne **12**. We believed that subjection of known aldehyde **13**[21,23] to a sequence of Trost [3+2] cycloaddition, cross metathesis (CM) and iodination should furnish **11**. Our synthesis of **11** started from ethyl pyrone **14**, which was converted to the phenylselenyl compound **15**, and oxidation–elimination of **15** yielded the unstable alkene **16** (Scheme 3). **16** was subjected to the Lemieux–Johnson protocol[24] to afford aldehyde **13** in excellent overall yield (63% from **14**). This route to **13** is a considerable improvement compared to the previously reported route.[23] We were pleased to find that aldehyde **13** reacted smoothly with the palladium-bound trimethylenemethane complex generated from 2-[(tributylstannyl)methyl]-2-propen-1-yl acetate and $Pd(OAc)_2/PPh_3$ to afford the alkene **17** in 88%



Scheme 3. Synthesis of tetrahydrofuran fragments **11** and **24**. (a) KHMDS, PhSeBr, THF, −78 °C→rt; (b) $NaIO_4$, cat. $NaHCO_3$, aq MeOH, rt; (c) cat. OsO_4, $NaIO_4$, aq THF, rt; (d) **18**, 5 mol% $Pd(PPh_3)_4$, 10 mol% $In(acac)_3$, PhMe, reflux; (e) **19** (3.0 equiv), 5 mol% **20**, CH_2Cl_2, reflux; (f) **23** (2.0 equiv), 5 mol% **20**, CH_2Cl_2, reflux; (g) PTSA, acetone–H_2O, rt; (h) I_2, aq NaOH, THF, rt.



Scheme 4. Synthesis of alkyne **25** and attempted hydroborations of **25** and **26**. (a) $TMSCHN_2$, LHMDS, THF, −78 °C; (b) $Ph_3PCHBr^+Br^-$, KO′Bu, THF, −78 °C; (c) **29**, K_2CO_3, MeOH, rt; (d) LHMDS, MeI, rt; (e) catecholborane, neat, 70 °C; (f) 9-BBN; (g) pinacolborane.

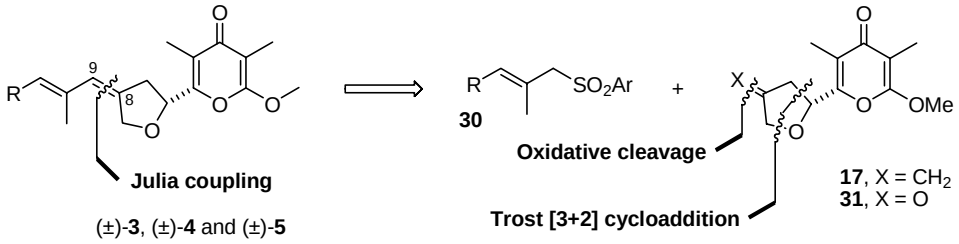
yield.[25] A minor improvement in yield (93%) was observed by employing the silyl acetate **18** instead and $In(acac)_3$ as co-catalyst.[26] Pleasingly, the sequence **14**→**17** can be performed without column chromatography; simple crystallizations of the crude products from CH_2Cl_2-pentanes is sufficient.

The recent report of 1,1-disubstituted alkenes as excellent substrate for CM with alkenyl boronic esters led us to attempt such transformations with **17**.[27] Initially, we attempted the CM with **19** and catalyst **20**. In our hands, this led to a good yield of acetal **21** provided that **19** was added slowly to the reaction mixture to suppress homodimerisation of itself. Treatment of acetal **21** with PTSA smoothly furnished **22**, a potentially useful building block. On the other hand, boronic ester **23** reacted with **17** without the need for slow addition and furnished **24** in almost quantitative yield, albeit with low *E*/*Z*-selectivity.[28] The stereochemistry of (*E*)-**24** and (*Z*)-**24** was confirmed by NOE experiments. **24** could easily be converted to the required iodides **11** in 47% yield (14% recovered **24**) with retention of the *E*/*Z* ratio (1:1.2 *E*/*Z*) upon treatment with I_2 and NaOH in aq THF.[27a]

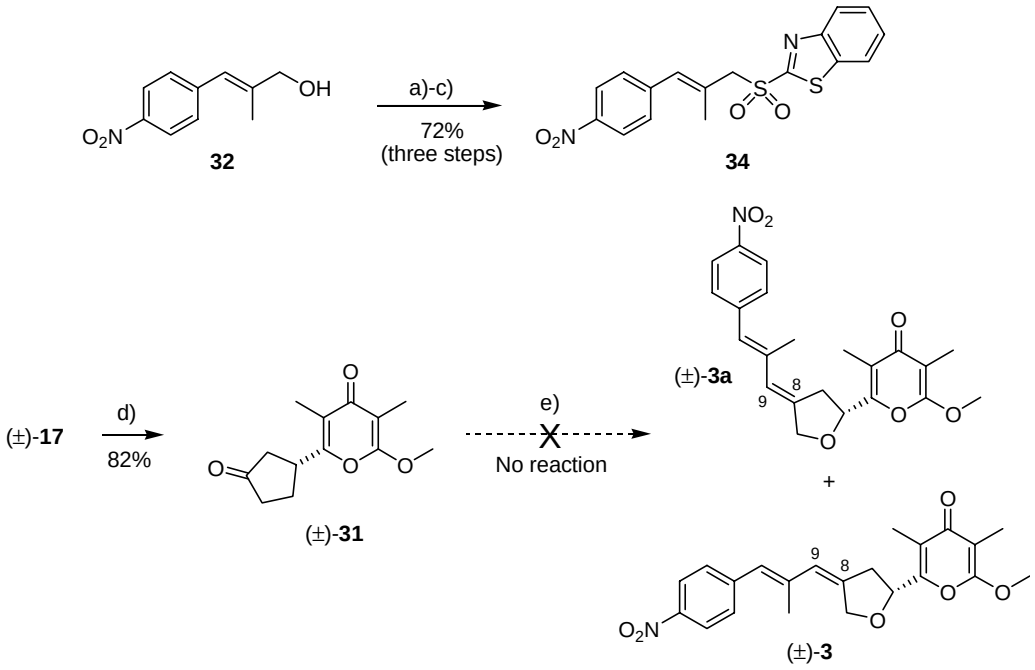
Next, we turned our attention towards the hydroboration of the alkynes **25** and **26**[29] (Scheme 4). Initially, alkyne **27** was synthesized by reacting known aldehyde **28** with the lithium anion of $TMSCHN_2$.[30] The use of a Wittig dehalogenation procedure instead furnished a lower yield (18%) of **27**,[31] while employing the Ohira reagent **29**[32] only led to the decomposition of **28**. Subsequently, facile methylation of **27** provided **25**. To our disappointment, the hydroboration of either **25** or **26** under a variety of conditions proved fruitless, as this only led to intractable tarry product mixtures. Instead, we decided to evaluate a modified Julia coupling of sulfone **30** with (±)-aureonone **31** for the disconnection of the C8–C9 double bond in (±)-**3**, (±)-**4** and (±)-**5** (Scheme 5). The known alcohol **32** reacted with MsCl and Et_3N to afford a mesylate **33**, which was then efficiently converted to sulfone **34** [substitution of **33** with the sodium anion of 2-mercaptobenzothiazole to the yield a sulfide **35**, followed by ammonium molybdate-mediated oxidation to **34**].[33] (±)-Aureonone **31** was easily obtained from alkene (±)-**17** by oxidative cleavage with OsO_4/$NaIO_4$, and the spectral data (IR, ^1H and ^{13}C NMR) were in excellent agreement with those previously reported.[21] Unfortunately, treatment of the lithium anion of sulfone **34** with aureonone **31** did not provide detectable amounts of **3** and/or **3a** presumably due to the stability of the anion of **34**. We were therefore impelled to consider alternative pathways to (±)-**3**, (±)-**4** and (±)-**5** (Scheme 6).

2.2. Completion of the synthesis of (±)-aureothin (3), (±)-*N*-acetyl-aureothamine (4) and (±)-spectinabilin (5)

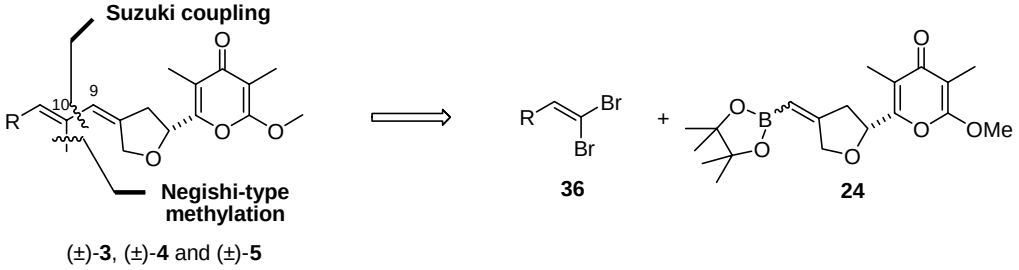
Since we had already established an efficient route to **24**, the use of it in a trans-selective Suzuki coupling with a dibromide **36** to form the C9–C10 double bond followed by a Negishi-type methylation seemed an attractive approach to (±)-**3**, (±)-**4** and (±)-**5** (Scheme 7). Therefore, the Suzuki coupling of **24** and **37**[34] was examined under the influence of various bases (Scheme 8 and Table 1). While NaOH afforded exclusively the dehydrohalogenated product, alkyne **38** (entry 1), Tl_2CO_3 gave rise to a mixture of products, **38**, **39** and **40** (entry 2). Gratifyingly, the use of TlOEt afforded (*E*)-**40** and (*Z*)-**40** as a separable mixture of isomers (1:1.2 *E*/*Z*) in 72% yield (entry 3).[35] The stereochemistry of the C9–C10 double-bond of (*Z*)-**40**,



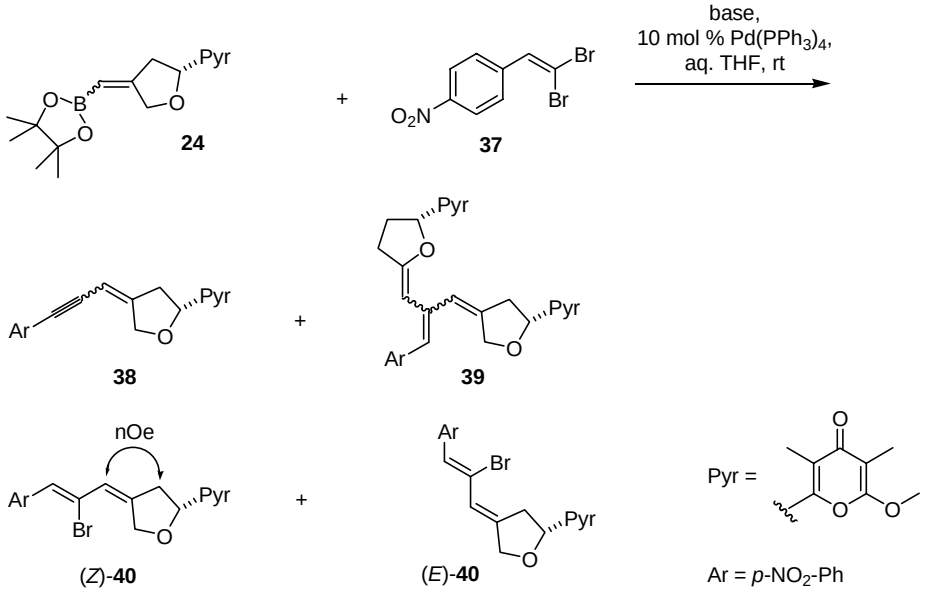
Scheme 5. Second retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.



Scheme 6. Synthesis of Julia–Kocienski fragment **34** and (±)-aureonone **31**, and attempted Julia–Kocienski coupling to form (±)-**3** and/or (±)-**3a**. (a) MsCl, Et_3N, CH_2Cl_2, −10→−15 °C; (b) 2-mercaptobenzothiazole, NaH, DMF, 0 °C→rt; (c) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH:THF, 0 °C→rt; (d) OsO_4, $NaIO_4$, aq THF, rt; (e) LHMDS, **34**, THF, −78 °C→rt.



Scheme 7. Third retrosynthesis of (±)-**3**, (±)-**4** and (±)-**5**.



Scheme 8. Influence of base on Suzuki coupling of **24** with **37** (see Table 1).

Table 1. Influence of base on the Suzuki coupling of **24** with **37** (see Scheme 8)[a,b,c]

Entry	Base (equiv)	Yield **38** (%)	Yield **39** (%)	Yield **40** (%)
1	NaOH (1.5)	70	—	—
2	Tl_2CO_3 (1.5)	20	20	20
3	TlOEt (1.8)	—	—	72

[a] The ratio of **38**, **39** and **40** was determined by ^{1}H NMR analysis of the crude product.
[b] Compounds **38** and **40** were obtained as 1:1.2 *E*/*Z* mixtures of isomers.
[c] Compound **39** was obtained as a mixture of isomers.

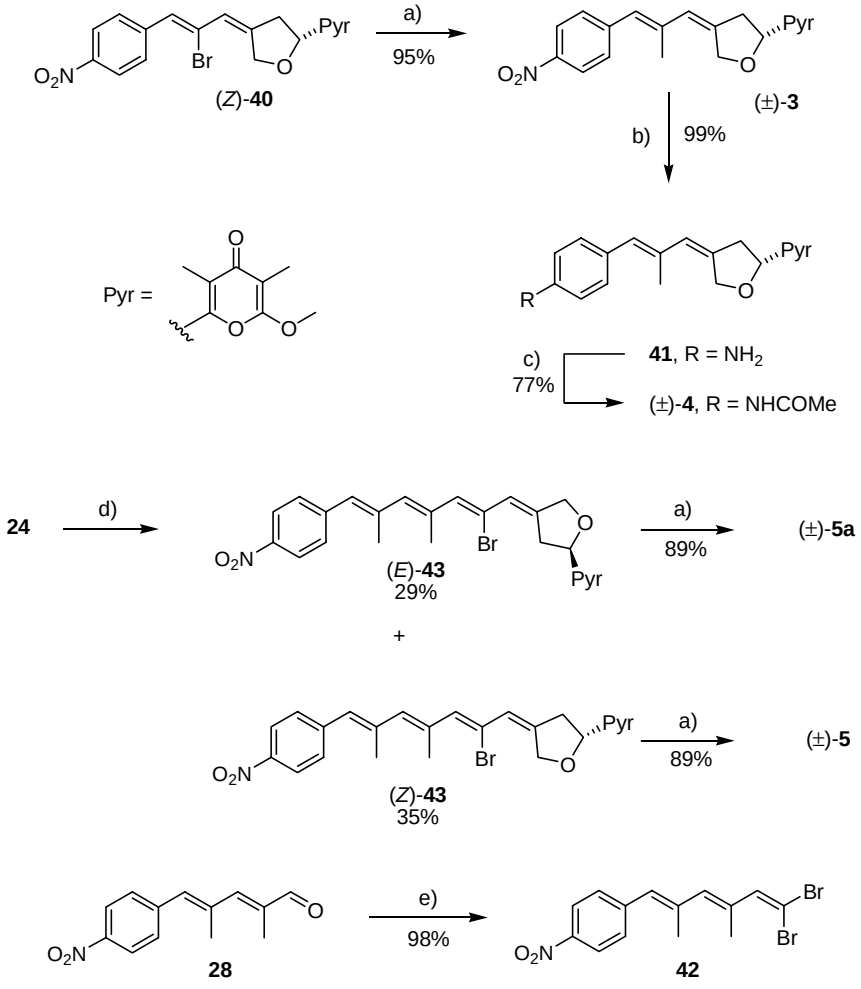
was confirmed by a NOESY experiment. The precursor (*Z*)-**40** of (±)-aureothin (**3**) was methylated under the recently reported Negishi-type conditions (cat. Pd(^{t}Bu$_3$P), Me_2Zn) to afford (±)-**3** in excellent yield with complete retention of stereochemistry (Scheme 9).[36] (±)-**3** was subjected to Zn-mediated reduction under aqueous conditions to furnish pure (±)-aureothamine (**41**) in high yield,[4] which was then acetylated to afford the antibiotic (±)-*N*-acetyl-aureothamine (**4**).[6] The spectral data for (±)-**3**[21] and (±)-**4**[6] (IR, ^{1}H and ^{13}C NMR) were in excellent agreement with those previously reported.

In a similar manner boronic ester **24** was subjected to Suzuki coupling with dibromide **42** (made from aldehyde **28**[37]) to afford the isomers (*E*)-**43** and (*Z*)-**43** in a combined yield of 64%, which could be separated by silica gel chromatography. The light sensitive (*Z*)-**43** reacted smoothly with Me_2Zn under palladium catalysis to yield (±)-spectinabilin (**5**) in 89% yield, while (*E*)-**43** was converted to **5a**, the (*E*,*E*,*E*,*E*)-isomer of **5**. (±)-**5** exhibited identical ^{1}H NMR spectra to that of an authentic sample, and the spectral data (^{1}H, ^{13}C NMR and IR) were in excellent agreement with those previously reported.[7] The previously tentative assignment[7] of the (*E*,*E*,*E*,*Z*)-geometry to **5** was confirmed by 1D NOE experiments.

2.3. The biomimetic conversion of (±)-5 to (±)-1 and (±)-2

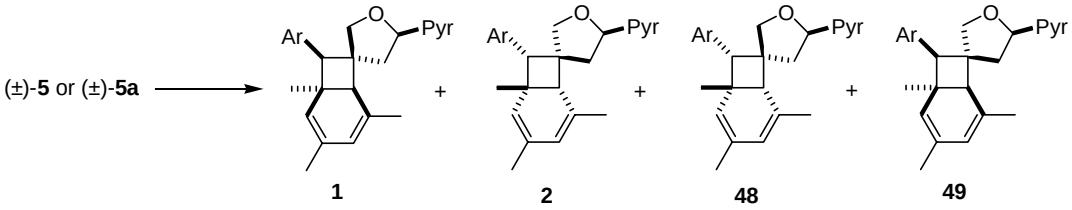
Since we were not aware of the specific conditions by which Nature might convert **5** to **1** and **2**, we examined three types of reaction conditions in attempts to affect the required *E*/*Z* isomerizations and initiate the cascade of electrocyclizations in vitro: light, heat and a Pd(II) source.

During initial exposure of **5** to sunlight in solution, it underwent *E* to *Z* isomerization of the C14–C15 double bond as observed by ^{1}H NMR. The same is true for the C10–C11 double bond in aureothin (**3**). Unfortunately, prolonged exposure of (±)-**5** in solution to sunlight resulted ultimately in very complex product mixtures in which neither **1** nor **2**



Scheme 9. Completion of the total synthesis of (±)-**3**, (±)-**4** and (±)-**5**. (a) Me_2Zn, 2 mol% Pd(^{t}Bu$_3$P)$_2$, THF, rt; (b) Zn, NH_4Cl, aq acetone, rt; (c) AcCl, pyridine, CH_2Cl_2, 0 °C; (d) **42**, 10 mol% $Pd(PPh_3)_4$, TlOEt, aq THF, rt; (e) CBr_4, Zn, PPh_3, pyridine, CH_2Cl_2, rt.

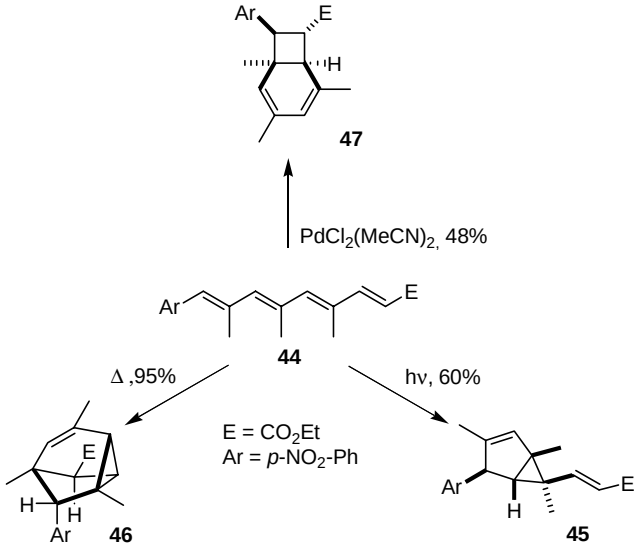
Table 2. Synthesis of (±)-SNF4435C (**1**), (±)-SNF4435D (**2**) and isomers **48** and **49** from (±)-**5** and (±)-**5a**[a,b]



Entry	Substrate	$PdCl_2(MeCN)_2$ (Mol%)	Temperature (°C)	Ratio/**1**:**2**:**48**:**49**[c]	Yield (%)
1	**5**	0	70	3.6:1.0:0:0	23
2	**5**	25	20	4.5:1.0:4.5:1.7	<5[d]
3	**5**	25	70	2.8:1.1:2.1:1.0	40
4	**5**	25	50	3.9:1.0:2.8:1.2	nd
5	**5**	25	110	2.9:1.0:2.0:1.1	nd
6	**5**	100	70	nd	~0
7	**5a**	25	70	2.0:1.0:5.7:3.0	31

[a] Reactions were performed in DMF in the dark.
[b] nd, not determined.
[c] Ratio of **1**, **2**, **48** and **49** was determined from analysis of ^{1}H NMR spectra of crude product.
[d] Estimated from analysis of ^{1}H NMR spectra of crude product.

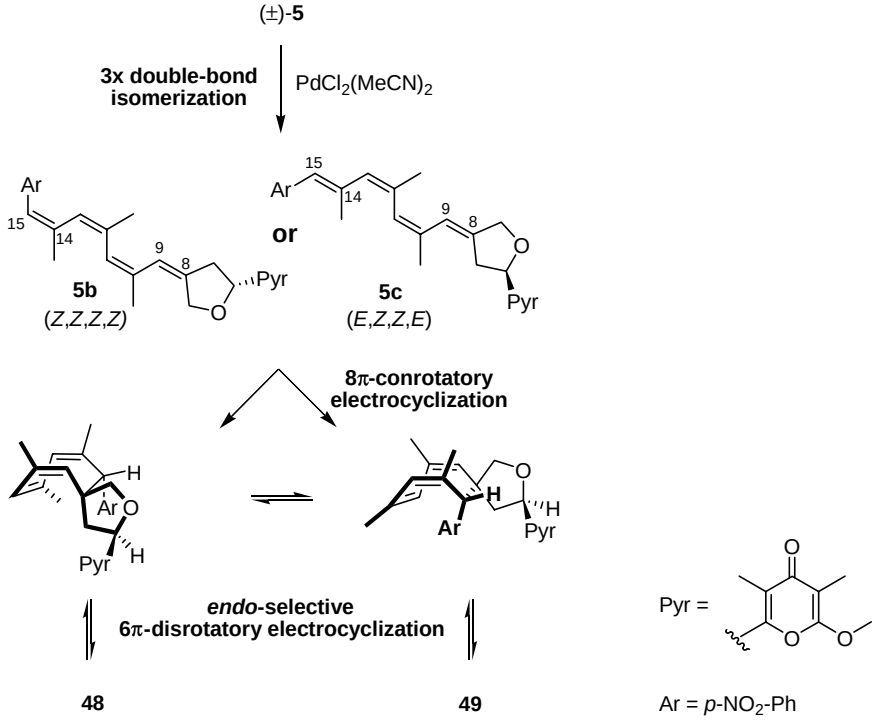
could be detected by ^{1}H NMR. On the other hand, heating a solution of (±)-**5** in DMF at 70 °C for 3 days resulted in 23% of (±)-**1** and (±)-**2** as a 3.6:1 mixture after extensive purification by preparative TLC (Table 2, entry 1). Interestingly, the related tetraene **44** having an electron-withdrawing ester group behaved differently (Scheme 10). The crispatene core structure **45** was produced when **44** was subjected to light, while heat afforded the tricyclic structure **46** in high yield (Scheme 10).[37,38]



Scheme 10. Cascade electrocyclization pathways of tetraene ester **44**.

Previous results in our group have demonstrated that the bicyclo[4.2.0]octadiene core of **1** and **2** can be obtained from (*E*,*E*,*E*,*E*)-tetraenes by employing a palladium(II) source ($PdCl_2(MeCN)_2$) for the requisite *E* to *Z* isomerization, that is, (*E*,*E*,*E*,*E*) to (*E*,*Z*,*Z*,*E*), exemplified by the conversion of **44** to **47** in 48% yield.[13,37,38] However, when **5** was subjected to the standard conditions at rt only small amounts of **1** and **2** could be detected, suggesting that the *E*/*Z*-isomerizations were too slow at this temperature (entry 2). By varying both the catalyst loading and temperature, we found the best conditions to involve heating a solution of **5** in DMF with 25 mol% $PdCl_2(MeCN)_2$ at 70 °C for 1 day in the dark (entry 3). This afforded 22% of (±)-SNF4435C (**1**) and (±)-SNF4435D (**2**) in a slightly different ratio of 2.5:1 compared to that resulting from heating alone (entry 1 vs 3). Surprisingly, 18% of two unexpected isomers **48** and **49** could also be isolated in a 2.1:1 ratio from the reaction mixture. Apparently, their formation is intrinsically related to the use of the Pd(II) source, as neither **48** nor **49** could be detected by heating alone. Lower temperatures led to a more complex reaction mixture (entry 4), whereas elevated temperatures or higher catalyst loading led to increased decomposition (entries 5 and 6). Also, the individual ratios **1**:**2** and **48**:**49** decreased with increasing temperature, while the overall ratio of **1** and **2** to **48** and **49** remained nearly constant (entries 2–4). Interestingly, the ratios of **1** and **2** are close throughout to that found in Nature (2.3:1),[2a] thus supporting our biogenetic hypothesis for their formation. The 1,3-diastereoselection induced from the C6-stereocenter in the 8π-electrocyclization step is almost of the same magnitude for **48** and **49** compared to **1** and **2**, resulting in roughly equal ratios **1**:**2** and **48**:**49**.

The formation of **48** and **49** is consistent with the 8π/6π-electrocyclization cascade of either of the (*Z*,*Z*,*Z*,*Z*)- and (*E*,*Z*,*Z*,*E*)-isomers, **5b** and **5c** (Scheme 11). We have not observed this 'over-isomerization' previously with similar tetraenes, for example, **44**.[13,37] X-ray structures have indicated a lack of planarity of the polyene backbone of structures similar to **5**, for example, **44**, presumably due to 1,3-steric interactions between the methyl groups.[37] Firstly, such interactions for the reactive (*E*,*Z*,*Z*,*Z*)-isomer of **5** may be partly relieved in conformations like **8** and **9** thus facilitating the subsequent cascade of electrocyclizations (Scheme 1). Secondly, it should lead to a decrease in the



Scheme 11. Mechanistic rationale for the formation of isomers **48** and **49**.

conjugation of the C8–C9 double bond with the electron deficient *p*-nitrophenyl ring. The more electron-rich C8–C9 double bond is expected to be more prone to isomerizations with the cationic palladium moiety versus the C14–C15 double bond.[39] Hence, we favor that **48** and **49** may be formed predominately via the (*E*,*Z*,*Z*,*E*)-isomer **5c**. In support of this was the observation that subjection of the (*E*,*E*,*E*,*E*)-isomer **5a** to the Pd(II) conditions provided 23% of a 1.9:1 mixture of **48** and **49** and minor amounts of **1** and **2** (8%) (entry 7).

3. Conclusion

We have developed short and efficient synthesis of the metabolites (±)-aureothin (**3**), (±)-*N*-acetyl-aureothamine (**4**) and (±)-spectinabilin (**5**) by using several palladium-catalyzed reactions to assemble the congested polyene structures (23, 17, and 18% overall yield, respectively, from ethyl pyrone **14**). In addition, the key boronic ester **24** was synthesized via ruthenium-catalyzed cross metathesis of alkene **17**. Alternative routes to (±)-**3**, (±)-**4** and (±)-**5** via hydroboration or a modified Julia coupling proved ineffective. The successful biomimetic conversion of spectinabilin (**5**) to SNF4435C (**1**) and SNF4435D (**2**) shows that our biogenetic hypothesis connecting these natural products is chemically viable. The isolation of the isomers **48** and **49** was demonstrated to be a side effect of the Pd(II) conditions employed for the *E*/*Z*-isomerizations. Due to the lower efficiency of the biomimetic conversion and the general complexity of the product mixtures, we can only speculate that Nature uses efficient enzyme-mediated *E*/*Z*-isomerizations of **5**, which the subsequent cyclization cascade may benefit from as well.[40]

4. Experimental

4.1. General experimental

Unless otherwise stated, all reactions were carried out under nitrogen. Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried by passing through activated alumina columns. *N*,*N*-dimethylformamide (DMF) was dried over 3 Å molecular sieves. Pentanes of bp 30–40 °C were used exclusively. All reagents were purchased at the highest commercial quality and used without further purification. NMR spectra were recorded at 200, 400 or 500 MHz (^{1}H NMR), and calibrated to the residual solvent peak. The following abbreviations are used for NMR data: s, singlet; d, doublet; t, triplet; qn, quintet; m, multiplet; br, broad; app, apparent. Coupling constants are rounded to nearest 0.5 Hz. The following abbreviations are used for IR data: s, strong; m, medium; w, weak; br, broad. Room temperature (rt) is 22 °C. Column chromatography was carried out using Sorbsil C60 (40–63 mm, 230–240 mesh) silica gel. Preparative thin-layer chromatography was performed on Whatman precoated silica gel $60_{F\text{-}254}$ glass-supported plates with 1.0 mm thickness. Reactions were monitored by thin-layer chromatography (TLC) analysis. Spots were visualized by exposure to ultraviolet (UV) light (254 nm), or by staining with a 5% solution of phosphomolybdenic acid (PMA) in ethanol or basic aq potassium permangante ($KMnO_4$) and then heating. Crystallization solvents are in parenthesis. Melting points are uncorrected. All compounds synthesized were determined to be >95% pure by ^{1}H NMR. Compounds **14**,[41] **23**,[27] **26**,[29] **28**,[37] **32**[37] were prepared according to literature procedures.

4.1.1. (±)-2-Methoxy-3,5-dimethyl-6-(1-(phenylselenyl)-ethyl)-4*H*-pyran-4-one (15). To a solution of THF (20 mL) containing γ-pyrone **14**[41] (1.50 g, 8.23 mmol) at −78 °C

was added slowly a solution of KHMDS (19.8 mL, 0.5 M in toluene, 9.90 mmol) with stirring. The resulting solution was allowed to stir for 30 min at −78 °C after which time the reaction had developed a bright orange-red color. A solution of phenyl selenium bromide (2.34 g, 9.9 mmol) in THF (5 mL) was then added dropwise, and the reaction mixture was allowed to warm to rt over the course of 1 h. Satd aq NH_4Cl (30 mL) was added, and the aqueous layer was extracted with EtOAc three times. The combined organics were washed with brine and dried over $MgSO_4$, and the solvent was removed by evaporation in vacuo. The residue was subjected to column chromatography (pentanes/EtOAc, gradient elution) to give **15** as a white solid (2.28 g, 82%). Mp 103–105 °C (CH_2Cl_2/pentanes); R_f=0.4 (1:1 pentanes/EtOAc); IR (KBr) 1660 (s), 1618 (m), 1592 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.63 (s, 3H), 1.72 (t, J=7.0 Hz, 1H), 1.83 (s, 3H), 3.81 (s, 3H), 4.41 (q, J=7.0 Hz, 1H), 7.21–7.26 (m, 2H), 7.31–7.37 (m, 1H), 7.47–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.6, 18.4, 36.1, 55.1, 99.2, 117.8, 127.3, 129.1 (3C), 136.8 (2C), 157.1, 161.7, 180.5; HRMS (ESI) *m/e* calcd for $C_{16}H_{19}O_3{}^{80}Se$ (MH^+) 339.0499, found 339.0489.

4.1.2. 2-Methoxy-3,5-dimethyl-6-vinyl-4*H*-pyran-4-one (16). To a solution of phenylselenyl pyrone **15** (4.22 g, 12.5 mmol) in MeOH (90 mL) and H_2O (57 mL) was added a catalytic quantity of $NaHCO_3$ followed by $NaIO_4$ (5.35 g, 25.0 mmol) at rt. The resulting mixture was stirred for 1 h at rt. The methanol was removed by evaporation in vacuo, and the aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and evaporated to dryness to yield a light yellow solid. The resulting crude alkene **16** was carried on to the next step without further purification. A small amount was purified for characterization purposes by column chromatography (CH_2Cl_2/EtOAc, gradient elution) to yield **16** as a white solid. Mp 95–98 °C (CH_2Cl_2/pentanes); R_f=0.6 (1:1 pentanes/EtOAc); IR (KBr) 1657 (s), 1601 (m), 1572 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.86 (s, 3H), 2.03 (s, 3H), 4.02 (s, 3H), 5.53 (d, J=11.0 Hz, 1H), 5.93 (d, J=17.0 Hz, 1H), 6.71 (dd, J=11.0, 17.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 55.3, 99.7, 119.0, 119.4, 126.6, 151.3, 161.8, 181.0; HRMS (ESI) *m/e* calcd for $C_{10}H_{13}O_3$ (MH^+) 181.0865, found 181.0865.

4.1.3. 6-Methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-carbaldehyde (13).[21,24] To a solution of crude alkene **16** (see above) in THF–H_2O (1/1 v/v, 180 mL) was added $NaIO_4$ (5.35 g, 25.0 mmol) followed by the slow addition of OsO_4 (1.9 mL, 4% w/w in H_2O, 0.31 mmol). The resulting mixture was stirred for 1 h at rt. The THF was removed by evaporation in vacuo, and the remaining aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and evaporated to dryness in vacuo. The crude aldehyde was purified by crystallization from CH_2Cl_2-pentanes to yield **13** (1.76 g, 77% for two steps) as a white, crystalline solid. Mp 143–145 °C (CH_2Cl_2/pentanes); R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1694 (s), 1648 (s), 1590 (s), 1174 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.90 (s, 3H), 2.35 (s, 3H), 4.09 (s, 3H), 10.1 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 7.1, 8.3, 55.8, 102.4, 130.3, 147.3, 162.3, 179.9, 182.9; HRMS (ESI) *m/e* calcd for $C_9H_{11}O_4$ (MH^+) 183.0657, found 183.0660.

4.1.4. (±)-2-Methoxy-3,5-dimethyl-6-(4-methylene-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (17). A solution of $In(acac)_3$ (229 mg, 0.555 mmol) and $Pd(PPh_3)_4$ (321 mg, 0.278 mmol) in toluene (20 mL) was stirred for 10 min at rt. To the resulting yellow suspension was added a solution of aldehyde **13** (1.01 g, 5.54 mmol) in toluene (40 mL) and **18** (1.50 mL, 7.22 mmol). The reaction mixture heated at reflux for 5 h. The mixture was cooled to rt, and evaporated to dryness in vacuo. The residue was filtered through a pad of silica gel eluting with 1:1 CH_2Cl_2/EtOAc to afford (±)-**17** as a white solid, that was further purified by crystallization from CH_2Cl_2 with pentanes (1.21 g, 92%). Mp 115–117 °C (CH_2Cl_2/pentanes); R_f=0.3 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1606 (s), 1458 (s), 1322 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.71–2.98 (m, 2H), 3.93 (s, 3H), 4.42 (br d, J=13.0 Hz, 1H), 4.54 (br d, J=13.0 Hz, 1H), 5.02 (qn, J=2.0 Hz, 1H), 5.10 (qn, J=2.0 Hz, 1H), 5.18 (dd, J=6.5, 7.5 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8, 9.3, 35.9, 55.2, 71.7, 74.8, 99.7, 105.1, 119.7, 146.4, 155.0, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{13}H_{17}O_4$ (MH^+) 237.1127, found 237.1131.

4.1.5. (±)-(*E*)- and (±)-(*Z*)-2-(4-((1,3-Dioxolan-2-yl)-methylene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (21). To a solution of catalyst **20** (17 mg, 0.02 mmol) and pyrone (±)-**17** (95 mg, 0.40 mmol) in CH_2Cl_2 (2 mL) was added over a period of 3 h a solution of 2-vinyl-1,3-dioxolane (**19**) (120 μL, 1.20 mmol) in CH_2Cl_2 (3 mL) at reflux. The resulting solution was heated for a further 2 h at reflux, and then cooled to rt. The solvent was removed by evaporation in vacuo, and the residue was subjected to column chromatography (1:1 pentanes/EtOAc → EtOAc) to afford a 1:1.2 *E*/*Z* mixture of **21** (81 mg, 65%) as a viscous oil. R_f=0.35 (1:1 CH_2Cl_2/EtOAc); IR (film) 2930 (s), 1672 (s), 1664 (s), 1584 (br, s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.82 (s, 2×3H), 2.00 (s, 2×3H), 2.77–3.08 (m, 2×2H), 3.83–4.05 (m, 2×4H), 3.92 (s, 2×3H), 4.46 (d, J=13.5 Hz, 1H), 4.57 (d, J=14.5 Hz, 1H), 4.58 (d, J=13.5 Hz, 1H), 4.72 (d, J=14.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9 (2C), 9.4 (2C), 32.4, 36.3, 55.4 (2C), 64.9 (4C), 69.1, 71.9, 73.8, 75.1; HRMS (ESI) *m/e* calcd for $C_{16}H_{21}O_6$ (MH^+) 309.1338, found 309.1335.

4.1.6. (*E*)- and (*Z*)-2-(5-(6-Methoxy-3,5-dimethyl-4-oxo-4*H*-pyran-2-yl)-dihydrofuran-3(2*H*)-ylidene)acetaldehyde (22). To a solution of acetal **21** (432 mg, 1.40 mmol) in acetone (25 mL) was added water (200 μL) and *p*-toluenesulfonic acid (40 mg, 0.21 mmol). The resulting solution was stirred for 1 h. Satd aq $NaHCO_3$ (5 mL) was added, and the acetone was removed in vacuo. The aqueous phase was extracted with CH_2Cl_2 twice. The combined organic layers were washed with brine and dried over $MgSO_4$. Removal of the solvent in vacuo yielded pure **22** (366 mg, 99%) as 1:1.2 *E*/*Z* mixture and as an unstable oil, which required no further purification. R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (film) 1665 (s), 1593 (s), 1266 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 1.84 (s, 3H), 2.96–3.51 (m, 2×2H), 3.88 (s, 3H), 3.90 (s, 3H), 4.63 (d, J=17.0 Hz, 1H), 4.78 (d, J=17.0 Hz, 1H), 4.87 (d, J=17.5 Hz, 1H), 5.09 (d, J=17.5 Hz, 1H), 5.23 (t, J=6.5 Hz, 1H), 5.32 (t, J=7.0 Hz, 1H), 6.09–6.15 (m, 1H), 6.26–6.32 (m, 1H), 9.70 (d, J=4.5 Hz, 1H), 9.85 (d, J=6.5 Hz, 1H);

^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8 (2C), 9.4 (2C), 33.5, 37.2, 55.2, 55.3, 71.2, 72.4, 73.3, 75.4, 100.1 (2C), 119.8, 120.2, 120.5 (2C), 153.5 (2C), 162.0 (2C), 162.9, 163.2, 180.3 (2C), 189.3, 190.1; HRMS (ESI) *m/e* calcd for $C_{14}H_{17}O_5$ (MH^+) 265.1076, found 265.1079.

4.1.7. (±)-(*E*)- and (±)-(*Z*)-2-Methoxy-3,5-dimethyl-6-(4-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methylene)-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (24). To a solution of alkene **17** (869 mg, 3.68 mmol) and alkenyl boronic ester **23**[27] (1.24 g, 7.36 mmol) in CH_2Cl_2 (5 mL) was added catalyst **20** (156 mg, 0.184 mmol). The resulting was heated at reflux for 3 h, cooled to rt and evaporated to dryness in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, gradient elution) to afford **24** (1.31 g, 98%) as a 1:1.2 *E*/*Z* mixture and as an oil. R_f=0.35 (4:1 CH_2Cl_2/EtOAc); IR (film) 3054 (m), 2982 (s), 1665 (s), 1595 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.22 (s, 2×3H), 1.23 (s, 2×6H), 1.25 (s, 2×3H), 1.82 (s, 3H), 1.83 (s, 3H), 2.00 (s, 3H), 2.01 (s, 3H), 2.77–3.22 (m, 2×2H), 3.89 (s, 3H), 3.90 (s, 3H), 4.45 (br d, J=14.5 Hz, 1H), 4.58 (br d, J=14.5 Hz, 1H), 4.58 (br d, J=15.5 Hz, 1H), 4.79 (d, J=15.5 Hz, 1H), 5.13–5.25 (m, 2H), 5.33 (qn, J=2.0 Hz, 1H), 5.45 (qn, J=2.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.7 (2C), 9.2, 9.3, 24.5, 24.6 (2C), 24.6, 24.7 (4C), 35.8, 38.8, 55.0, 55.1, 72.0, 73.4, 73.7, 75.3, 83.0 (2C), 83.1 (2C), 95.6 (2C), 99.5 (2C), 119.5, 119.7, 154.9, 155.1, 161.9 (2C), 162.6, 163.2, 180.4, 180.5; HRMS (ESI) *m/e* calcd for $C_{19}H_{28}BO_6$ (MH^+) 363.1979, found 363.1975.

4.1.8. (*E*)- and (*Z*)-2-(4-(Iodomethylene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (11). To boronic ester **24** (362 mg, 1.0 mmol) in THF (2.5 mL) was added NaOH (1.0 mL, 3.0 M in H_2O, 3.00 mmol). The solution was stirred vigorously at rt for 10 min. The mixture was titrated with iodine (7.0 mL, 0.2 M in THF, 1.40 mmol) at such rate that only towards the end of addition was the mixture allowed to develop a persistent red color (~2 h). Satd aq sodium thiosulfate (0.5 mL) and water (4 mL) were added. The aqueous phase was extracted with CH_2Cl_2 twice and the combined organics were dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography (10:1→1:1 CH_2Cl_2/EtOAc) to afford **11** (169 mg, 47%) as a 1.2:1 *E*/*Z* mixture followed by recovered **24** (51 mg, 14%) both as clear oils. Data for **11**: R_f=0.3 (5:1 CH_2Cl_2/EtOAc); IR (film) 3054 (w), 2957 (w), 1664 (s), 1590 (s), 1467 (s), 1265 (s) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.82 (s, 3H), 1.83 (s, 3H), 1.98 (s, 3H), 2.01 (s, 3H), 2.71–3.03 (m, 2×2H), 3.22 (s, 2×3H), 4.29–4.57 (m, 2×2H), 5.26 (dd, J=6.5, 7.5 Hz, 1H), 5.34 (dd, J=6.0, 7.5 Hz, 1H), 6.10–6.17 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 6.8 (2C), 9.4 (2C), 37.9, 40.3, 55.4 (2C), 67.5, 68.2, 71.7, 74.1, 76.0, 76.1, 99.9 (2C), 119.9, 120.4, 149.8, 150.7, 154.1, 154.5, 162.0 (2C), 180.4 (2C); HRMS (ESI) *m/e* calcd for $C_{13}H_{16}IO_4$ (MH^+) 363.0093, found 363.0098.

4.1.9. 1-((1*E*,3*E*)-2,4-Dimethylhexa-1,3-dien-5-ynyl)-4-nitrobenzene (27). To a solution of LHMDS (6.0 mL, 1.0 M in THF, 6.00 mmol) in THF (25 mL) was added dropwise $TMSCHN_2$ (3.0 mL, 2.0 M in Et_2O, 6.00 mmol) at −78 °C. The resulting was stirred for 30 min, and then a solution of aldehyde **28**[36] (1.16 g, 5.00 mmol) in THF (20 mL) was added dropwise at −78 °C. The resulting mixture was stirred for 1 h at −78 °C, and allowed to warm slowly to rt. Satd aq NH_4Cl (10 mL) was added. The aqueous phase was extracted twice with CH_2Cl_2, and the combined organics were washed with brine and dried over $MgSO_4$. The solvent was removed in vacuo, and the residue was subjected to column chromatography (50:1 pentanes/EtOAc) to furnish **27** (802 mg, 71%) as a yellow paste. R_f=0.6 (9:1 pentanes/EtOAc); IR (KBr) 2283 (m), 1594 (m), 1514 (m), 1342 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 2.1 (s, 6H), 2.99 (s, 1H), 6.50 (s, 1H), 7.33 (s, 1H), 7.45 (d, J=8.5 Hz, 2H), 8.31 (d, J=8.5 Hz, 2H); ^{13}C NMR (125.7 MHz, $CDCl_3$) δ_C 19.2, 19.9, 77.0, 87.8, 119.8, 123.9 (2C), 130.0 (2C), 134.0, 138.7, 141.4, 144.5, 146.5; HRMS (CI(NH_3)) calcd for $C_{14}H_{17}N_2O_2$ (MNH_4^+) 245.1290, found 245.1286.

4.1.10. 1-((1*E*,3*E*)-2,4-Dimethylhepta-1,3-dien-5-ynyl)-4-nitrobenzene (25). To a stirred solution of alkyne **27** (773 mg, 3.40 mmol), in THF (20 mL), was added LHMDS (4.1 mL, 1.0 M solution in THF, 4.1 mmol) dropwise at rt. MeI (1.70 mL, 27.3 mmol) was added after 5 min. Water (10 mL) was added after another 10 min. The organic layer was separated, and the aqueous layer extracted with CH_2Cl_2 twice. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Purification of the crude oil using column chromatography (50:1 pentanes/EtOAc) gave **25** as a yellow solid (707 mg, 86%). Mp 54–55 °C (CH_2Cl_2/pentanes); R_f=0.55 (9:1 pentanes/EtOAc); IR (KBr) 1587 (s), 1522 (m), 1337 (s) cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 2.03 (s, 3H), 2.08 (s, 6H), 6.31 (s, 1H), 6.43 (s, 1H), 7.43 (d, J=8.5 Hz, 2H), 8.21 (d, J=8.5 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 4.8, 19.4, 20.3, 84.0, 86.0, 121.5, 123.9 (2C), 129.1, 130.0 (2C), 138.7, 139.1, 144.8, 146.4; HRMS (CI(NH_3)) calcd for $C_{15}H_{16}NO_2$ (MH^+) 242.1181, found 242.1178.

4.1.11. (*E*)-2-Methyl-3-(4-nitrophenyl)allyl methanesulfonate (33). To a solution of alcohol **32**[37] (2.55 g, 13.2 mmol) in CH_2Cl_2 (50 mL) was added Et_3N (2.76 mL, 19.8 mmol) at 0 °C, followed by the dropwise addition of MsCl (1.22 mL, 15.8 mmol) at −10 °C. The resulting solution was stirred at −10 to −15 °C for 1 h, then satd aq NH_4Cl (10 mL) was added. The organic phase was washed with water and brine, and dried over $MgSO_4$. The solvent was removed by evaporation in vacuo to yield a crude yellow-orange oil, that was purified by passing through a plug of silica gel eluting with 2:1 pentanes/EtOAc to yield **33** (3.48 g, 97%) as a unstable yellow solid. R_f=0.35 (2:1 pentanes/EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.97 (s, 3H), 3.08 (s, 3H), 4.78 (s, 2H), 6.68 (s, 1H), 7.43 (d, J=8.5 Hz, 2H), 8.20 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 15.4, 37.9, 74.4, 123.6 (2C), 128.2, 129.6 (2C), 134.7, 142.9, 146.6; HRMS (ESI) *m/e* calcd for $C_{11}H_{14}NO_5S$ (MH^+) 272.0593, found 272.0588.

4.1.12. (*E*)-2-(2-Methyl-3-(4-nitrophenyl)allylthio)benzo[*d*]thiazole (35). To a solution of 2-mercaptobenzothiazole (1.76 g, 10.5 mmol) in DMF (10 mL) was added sodium hydride (420 mg, 60 w/w % in oil, 10.5 mmol) slowly at 0 °C. The resulting suspension was stirred for 20 min at 0 °C. A solution of mesylate **33** (950 mg, 3.50 mmol) in DMF (5 mL) was added at 0 °C, and the mixture was allowed to warm to rt

then stirred for 2 h. Satd aq $NaHCO_3$ (10 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (20:1 pentanes/EtOAc) to afford **35** (1.07 g, 89%) as a light yellow solid. Mp 114–116 °C (CH_2Cl_2/pentanes); R_f=0.1 (20:1 pentanes/EtOAc); IR (KBr) 1593 (m), 1507 (s), 1425 (s), 1338 (s) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ_H 2.06 (s, 3H), 4.20 (s, 2H), 6.70 (s, 1H), 7.28–7.48 (m, 4H), 7.77 (d, J=8.0 Hz, 1H), 7.90 (d, J=8.0 Hz, 1H), 8.17 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ_C 17.3, 43.1, 121.0, 121.6, 123.4 (2C), 124.4, 126.1, 127.7, 129.4 (2C), 135.3, 137.1, 143.9, 146.2, 153.0, 165.8; HRMS (CI(NH_3)) *m/e* calcd for $C_{17}H_{15}N_2O_2S_2$ (MH^+) 343.0575, found 343.0567.

4.1.13. (*E*)-2-(2-Methyl-3-(4-nitrophenyl)allylsulfonyl)-benzo[*d*]thiazole (34). To a solution of sulfide **35** (599 mg, 1.75 mmol) in THF–EtOH (2/1, 30 mL) was added at 0 °C a solution of ammonium heptamolybdate tetrahydrate (433 mg, 0.35 mmol) in H_2O_2 (1.5 mL, 33% w/w, 17.5 mmol) over a period of 5 min. The resulting solution was allowed to warm to rt, and it was stirred for 20 h. A solution of Na_2SO_3 (2 g) in H_2O (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3×30 mL). The combined organics were washed with brine and dried over $MgSO_4$, and then the solvent was removed by evaporation in vacuo. The residue was subjected to column chromatography (7:1 pentanes/EtOAc, then CH_2Cl_2) to give **34** (544 mg, 83%) as a white solid. Mp 115–117 °C (CH_2Cl_2/pentanes); R_f=0.6 (CH_2Cl_2); IR (KBr) 1595 (m), 1511 (s), 1337 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 2.11 (s, 3H), 4.37 (s, 2H), 6.42 (s, 1H), 7.19 (d, J=8.5 Hz, 2H), 7.62 (app t, J=7.0 Hz, 1H), 7.67 (app t, J=7.0 Hz, 1H), 8.01 (d, J=8.0 Hz, 1H), 8.13 (d, J=8.5 Hz, 2H), 8.25 (d, J=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 19.0, 65.0, 122.3, 123.5 (2C), 125.5, 127.9, 128.3, 128.7, 129.5 (2C), 133.9, 136.9, 142.7, 146.6, 152.6, 165.2; HRMS (CI(NH_3)) *m/e* calcd for $C_{17}H_{15}N_2O_4S_2$ (MH^+) 375.0473, found 375.0475.

4.1.14. (±)-Aureonone (31).[21] To a solution of alkene **17** (165 mg, 0.70 mmol) in THF–H_2O (1/1, 6 mL) was added $NaIO_4$ (299 mg, 1.40 mmol) followed by OsO_4 (0.22 mL, 4% w/w in H_2O, 0.018 mmol) at rt. The resulting solution was stirred for 15 h, and the THF was removed by evaporation in vacuo, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over Na_2SO_4, and evaporated to dryness. The residue was subjected to column chromatography (3:1 CH_2Cl_2/EtOAc) to yield **31** (136 mg, 82%) as a white solid. Mp 119–121 °C (CH_2Cl_2/pentanes); R_f=0.25 (2:1 CH_2Cl_2/EtOAc); IR (KBr) 2927 (w), 1755 (s), 1666 (s), 1593 (s), 1328 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.05 (s, 3H), 2.71 (dd, J=6.0, 18.0 Hz, 1H), 2.87 (dd, J=8.0, 18.0 Hz, 1H), 3.89 (s, 3H), 4.05 (d, J=17.0 Hz, 1H), 4.16 (d, J=17.0 Hz, 1H), 5.54 (dd, J=6.0, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 39.2, 55.4, 70.6, 73.0, 100.4, 120.9, 153.3, 161.9, 190.2, 212.3; HRMS (ESI) *m/e* calcd for $C_{12}H_{15}O_5$ (MH^+) 239.0919, found 239.0919. The IR, ^1H and ^{13}C NMR spectral data were in excellent agreement with those previously published.[21]

4.1.15. 1-(2,2-Dibromovinyl)-4-nitrobenzene (37).[34] To a solution of PPh_3 (7.87 g, 30.0 mmol), Zn powder (1.96 g, 30.0 mmol) and pyridine (2.4 mL, 30 mmol) in CH_2Cl_2 (50 mL) was added portionwise solid CBr_4 (9.95 g, 30.0 mmol) at rt. The resulting suspension was stirred for 30 min. A solution of *p*-nitrobenzaldehyde (1.51 g, 10.0 mmol) in CH_2Cl_2 (25 mL) was added slowly at rt. The resulting reaction mixture was stirred for 2 h. Water (25 mL) was added. The organic phase was diluted with pentanes (~150 mL) with stirring and the resulting suspension was filtered through a pad of Celite®, and evaporated to dryness in vacuo. The residue was subjected to column chromatography (pentanes/EtOAc, gradient elution) to afford **37** (2.67 g, 87%) as an orange solid. Mp 101–103 °C (CH_2Cl_2/pentanes); R_f=0.75 (10:1 pentanes/EtOAc); IR (KBr) 1586 (s), 1512 (s), 1342 (s), 860 (s); ^1H NMR (200 MHz, $CDCl_3$) δ_H 7.55 (s, 1H), 7.69 (d, J=9.0 Hz, 2H), 8.21 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 94.0, 123.7 (2C), 129.1 (2C), 134.8, 141.4, 147.1; HRMS (ESI) *m/e* calcd for $C_8H_6^{79}Br_2NO_2$ (MH^+) 305.8765, found 305.8770. The ^1H and ^{13}C NMR spectral data are in good agreement with those previously published.[34]

4.1.16. (±)-2-((*E*)-4-((*Z*)-2-Bromo-3-(4-nitrophenyl)allylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one ((*E*)-40) and (±)-2-((*Z*)-4-((*Z*)-2-bromo-3-(4-nitrophenyl)allylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one ((*Z*)-40). To a solution of dibromide **37** (169 mg, 0.55 mmol), boronic ester **24** (181 mg, 0.50 mmol) and $Pd(PPh_3)_4$ (58 mg, 0.05 mmol) in THF–H_2O (3/1, 10 mL) was added slowly TlOEt (71 μL, 1.00 mmol) at rt. The resulting suspension was stirred for 75 min at rt. Brine (5 mL) and CH_2Cl_2 (20 mL) was added, and the separated aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product **40** was obtained as a 1:1.2 *E*/*Z* mixture as determined by ^1H NMR, which was subjected to column chromatography (pentanes/EtOAc, gradient elution) to afford (*E*)-**40** (69 mg, 30%) followed by (*Z*)-**40** (98 mg, 42%) as yellow solids. Data for (*E*)-**40**: Mp 117–119 °C (CH_2Cl_2/pentanes); R_f=0.5 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1607 (s), 1514 (s), 1343 (s); ^1H NMR (400 MHz, $CDCl_3$) δ_H 1.82 (s, 3H), 2.01 (s, 3H), 3.11–3.40 (m, 2H), 3.94 (s, 3H), 4.59 (br s, J=14.0 Hz, 1H), 4.71 (br d, J=14.0 Hz, 1H), 5.27 (dd, J=6.0, 7.5 Hz, 1H), 6.25 (br s, 1H), 6.93 (s, 1H), 7.76 (d, J=8.5 Hz, 2H), 8.19 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.5, 34.4, 55.4, 73.0, 75.4, 100.0, 120.2, 121.3, 123.3, 123.4 (2C), 129.3, 129.8 (2C), 141.9, 144.2, 146.9, 154.3, 162.1, 180.5; HRMS (Cl(NH_3)) *m/e* calcd for $C_{21}H_{21}^{79}BrNO_6$ (MH^+) 462.0552, found 462.0562. Data for (*Z*)-**40**: Mp 146–148 °C (CH_2Cl_2/pentanes); R_f=0.4 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1665 (s), 1603 (s), 1510 (s), 1345 (s); ^1H NMR (200 MHz, $CDCl_3$) δ_H 1.85 (s, 3H), 2.03 (s, 3H), 2.98 (br dd, J=6.0, 16.5 Hz, 1H), 3.14 (br dd, J=7.5, 16.5 Hz, 1H), 3.95 (s, 3H), 4.87 (br d, J=15.0 Hz, 1H), 5.05 (br d, J=15.0 Hz, 1H), 5.19 (dd, J=6.0, 7.5 Hz, 1H), 6.39 (br s, 1H), 6.83 (s, 1H), 7.77 (d, J=8.5 Hz, 2H), 8.23 (d, J=8.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 9.4, 38.0, 55.4, 70.1, 73.2, 100.1, 120.2, 122.6, 123.1, 123.5 (2C), 129.2, 129.8 (2C), 141.9, 144.8,

147.0, 154.5, 162.1, 180.5; HRMS ($Cl(NH_3)$) *m/e* calcd for $C_{21}H_{21}^{79}BrNO_6$ (MH^+) 462.0552, found 462.0555.

4.1.17. (±)-Aureothin (3).[4,21] To a solution of bromide (*Z*)-**40** (69.5 mg, 0.15 mmol) and $Pd(^tBu_3P)_2$ (1.5 mg, 3 μmol) in THF (3 mL) was added slowly Me_2Zn (150 μL, 0.30 mmol) at rt. The resulting was stirred for 30 min at rt, and then satd aq NH_4Cl (1 mL) was added carefully, followed by brine (1 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, 1:1) to afford (±)-aureothin (**3**) (57 mg, 95%) as a light sensitive crystalline, yellow solid. Mp 173–175 °C (CH_2Cl_2/pentanes); R_f=0.45 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1666 (s), 1586 (s), 1510 (m), 1332 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.95 (br dd, *J*=6.0, 16.0 Hz, 1H), 3.05 (br dd, *J*=6.0, 16.0 Hz, 1H), 3.93 (s, 3H), 4.74 (br d, *J*=14.0 Hz, 1H), 4.86 (br d, *J*=14.0 Hz, 1H), 5.13 (t, *J*=6.0 Hz, 1H), 6.19 (br s, 1H), 6.36 (s, 1H), 7.38 (d, *J*=8.5 Hz, 2H), 8.18 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.7, 38.2, 55.2, 70.1, 73.2, 99.9, 120.1, 123.5 (2C), 125.9, 128.3, 129.5 (2C), 138.6, 140.6, 144.2, 146.0, 154.6, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{22}H_{24}NO_6$ (MH^+) 398.1604, found 398.1600. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[21]

4.1.18. (±)-Aureothamine (41)[4] To a solution of (±)-aureothin (**3**) (80.5 mg, 0.20 mmol) in acetone–H_2O (5/1, 10 mL) was added Zn powder (165 mg, 2.52 mmol) and solid NH_4Cl (225 mg, 4.20 mmol) at rt. The bright yellow suspension was heated at reflux for 15 min. The resulting almost colorless mixture was cooled to rt and concentrated under reduced pressure. The aqueous mixture was extracted several times with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was filtered through a pad of silica gel eluting with 1:1 CH_2Cl_2/EtOAc to afford (±)-**41** (73.5 mg, 99%) as a white, crystalline solid. Mp 177–179 °C (CH_2Cl_2/pentanes); R_f=0.25 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 3454 (s), 3343 (s), 3227 (m), 1660 (s), 1582 (s), 1326 (s); ^{1}H NMR (200 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.87 (dd, *J*=6.0, 15.5 Hz, 1H), 3.04 (dd, *J*=7.5, 15.5 Hz, 1H), 3.93 (s, 3H), 4.73 (br d, *J*=14.0 Hz, 1H), 4.86 (br d, *J*=14.0 Hz, 1H), 5.12 (dd, *J*=6.0, 7.5 Hz, 1H), 6.14 (br s, 1H), 6.24 (s, 1H), 6.67 (d, *J*=8.5 Hz, 2H), 7.09 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.5, 38.2, 55.2, 70.1, 73.0, 99.8, 114.7 (2C), 119.7, 127.1, 127.8, 130.2 (2C), 130.8, 132.1, 136.4, 145.1, 155.2, 162.1, 180.6; HRMS (ESI) *m/e* calcd for $C_{22}H_{26}NO_4$ (MH^+) 368.1862, found 368.1863.

4.1.19. (±)-*N*-Acetyl-aureothamine (4).[6] To a solution of aureothamine (**41**) (35.5 mg, 97 μmol) in CH_2Cl_2 (1.5 mL) was added pyridine (16 μL, 0.20 mmol) at 0 °C. Acetyl chloride (11 μL, 0.15 mmol) was added slowly to the resulting solution. The mixture was stirred for 45 min at 0 °C. Satd aq NH_4Cl (2 mL) was added, and the aqueous phase was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$, and the solvent was removed in vacuo. The residue was subjected to column chromatography (CH_2Cl_2/EtOAc, 1:1) to afford (±)-**4** as a white solid (30.5 mg, 77%). Mp 175–177 °C (CH_2Cl_2/pentanes); R_f=0.2 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1683 (s), 1661 (s), 1572 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.17 (s, 3H), 2.90 (dd, *J*=6.5, 16.0 Hz, 1H), 3.04 (dd, *J*=7.5, 16.0 Hz, 1H), 3.94 (s, 3H), 4.73 (d, *J*=14.0 Hz, 1H), 4.85 (d, *J*=14.0 Hz, 1H), 5.13 (dd, *J*=6.5, 7.5 Hz, 1H), 6.15 (s, 1H), 6.28 (s, 1H), 7.20 (d, *J*=8.5 Hz, 2H), 7.52 (d, *J*=8.5 Hz, 2H), 7.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 17.5, 24.5, 38.2, 55.3, 70.1, 73.1, 99.9, 119.5 (2C), 119.8, 126.7, 129.6 (2C), 130.1, 133.2, 134.2, 136.8, 137.6, 155.2, 162.2, 168.5, 180.7; HRMS (ESI) *m/e* calcd for $C_{24}H_{28}NO_5$ (MH^+) 410.1967, found 410.1967. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[6]

4.1.20. 1-((1*E*,3*E*)-6,6-Dibromo-2,4-dimethylhexa-1,3,5-trienyl)-4-nitrobenzene (42). To a solution of PPh_3 (11.8 g, 45.0 mmol), Zn powder (2.94 g, 45.0 mmol) and pyridine (3.6 mL, 45.0 mmol) in CH_2Cl_2 (150 mL) was added portionwise solid CBr_4 (14.9 g, 45.0 mmol) at rt. The resulting was stirred for 30 min. A solution of aldehyde **28** (3.47 g, 15.0 mmol) in CH_2Cl_2 (50 mL) was added slowly. The resulting reaction mixture was stirred for 2 h then water (50 mL) was added. The organic phase was diluted with pentanes (~400 mL) with stirring and the resulting suspension was filtered through a pad of Celite®, and evaporated to dryness in vacuo. The residue was subjected to column chromatography (20:1→10:1 pentanes/EtOAc) to afford **42** (5.67 g, 98%) as a light sensitive yellow-orange solid. Mp 76–78 °C (CH_2Cl_2/pentanes); R_f=0.55 (9:1 pentanes/EtOAc); IR (KBr) 1590 (m), 1513 (m), 1340 (m); ^{1}H NMR (250 MHz, $CDCl_3$) δ_H 2.08 (3H, s), 2.13 (3H, s), 6.22 (1H, s), 6.50 (1H, s), 7.02 (1H, s), 7.44 (d, *J*=8.5 Hz, 2H), 8.22 (d, *J*=8.5 Hz, 2H); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ_C 18.1, 19.5, 85.5, 124.0, 129.6, 130.0, 134.3, 137.8, 138.0, 141.4, 144.6, 146.5; HRMS ($Cl(NH_3)$) *m/e* calcd for $C_{14}H_{17}^{79}Br_2N_2O_2$ (MNH_4^+) 402.9657, found 402.9655.

4.1.21. (±)-2-((*Z*)-4-((2*Z*,4*E*,6*E*)-2-Bromo-4,6-dimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (43) and (±)-2-((*E*)-4-((2*Z*,4*E*,6*E*)-2-bromo-4,6-dimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-6-methoxy-3,5-dimethyl-4*H*-pyran-4-one (43). To a solution of dibromide **42** (852 mg, 2.20 mmol), boronic ester **24** (724 mg, 2.00 mmol) and $Pd(PPh_3)_4$ (231 mg, 0.20 mmol) in THF–H_2O (3/1, 40 mL) was added slowly TlOEt (283 μL, 4.00 mmol) at rt. The resulting suspension was stirred for 30 min at rt. Brine (20 mL) and CH_2Cl_2 (40 mL) was added, and the separated aqueous layer was extracted twice with CH_2Cl_2. The combined organics were dried over $MgSO_4$ and the solvent was removed in vacuo. The crude product **43** was obtained as a 1:1.2 *E*/*Z* mixture as determined by ^{1}H NMR. The crude product was subjected to column chromatography (2:1→1:1 pentanes/EtOAc) to afford (*E*)-**43** (315 mg, 29%) as a stiff red foam followed by (*Z*)-**43** (380 mg, 35%) as an yellow solid, both as light sensitive compounds. Data for (*E*)-**43**: R_f=0.25 (1:1 pentanes/EtOAc); IR (KBr) 1665 (s), 1594 (s), 1512 (s), 1339 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.83 (s, 3H), 2.01 (s, 3H), 2.07 (s, 3H), 2.17 (s, 3H), 3.10

(dd, J=5.0, 17.0 Hz, 1H), 3.24 (dd, J=7.5, 17.0 Hz, 1H), 3.94 (s, 3H), 4.58 (d, J=13.5 Hz, 1H), 4.65 (d, J=13.5 Hz, 1H), 5.25 (dd, J=5.0, 7.5 Hz, 1H), 6.11 (s, 1H), 6.28 (s, 1H), 6.44 (s, 1H), 6.50 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 8.18 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.4, 19.2, 18.6, 34.2, 55.4, 72.8, 75.2, 99.8, 118.1, 120.0, 122.0, 123.5 (2C), 129.0, 129.5 (2C), 134.2, 135.7, 137.5, 138.7, 141.4, 144.3, 145.9, 154.7, 162.0, 180.5; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}^{79}BrNO_6$ (MH^+) 542.1178, found 542.1181. Data for (*Z*)-**43**: Mp 101–103 °C (CH_2Cl_2/pentanes); R_f=0.15 (1:1 pentanes/EtOAc); IR (KBr) 1665 (s), 1594 (s), 1512 (s), 1339 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.02 (s, 3H), 2.08 (s, 3H), 2.17 (s, 3H), 2.91 (dd, J=5.0, 16.0 Hz, 1H), 3.08 (dd, J=7.5, 16.0 Hz, 1H), 3.95 (s, 3H), 4.80 (d, J=15.0 Hz, 1H), 4.96 (d, J=15.0 Hz, 1H), 5.16 (dd, J=5.0, 7.5 Hz, 1H), 6.24 (s, 1H), 6.28 (s, 1H), 6.34 (s, 1H), 6.51 (s, 1H), 7.44 (d, J=9.0 Hz, 2H), 8.19 (d, J=9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 18.6, 19.2, 37.8, 55.4, 70.1, 73.1, 99.9, 117.9, 119.9, 123.2, 123.5 (2C), 129.1, 129.6 (2C), 134.2, 135.6, 137.5, 138.7, 141.9, 144.3, 146.0, 154.9, 162.1, 180.5; HRMS (ESI) *m/e* calcd for $C_{27}H_{29}^{79}BrNO_6$ (MH^+) 542.1178, found 542.1177.

4.1.22. (±)-Spectinabilin (5).[7] To a solution of bromide (*Z*)-**43** (1.01 g, 1.86 mmol) and Pd(^{t}Bu$_3$P)$_2$ (19 mg, 37.2 μmol) in THF (40 mL) was added slowly Me_2Zn (1.87 mL, 2.0 M in PhMe, 3.74 mmol) at rt. The resulting was stirred for 45 min at rt. Satd aq NH_4Cl (10 mL) was added carefully, followed by brine (10 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc) to afford (±)-**5** (795 mg, 89%) as a light sensitive yellow solid. Mp 133–135 °C (CH_2Cl_2/pentanes); R_f=0.55 (1:1 CH_2Cl_2/EtOAc); IR (KBr) 1667 (s), 1601 (s), 1517 (s), 1338 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.85 (s, 3H), 2.00 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.09 (s, 3H), 2.89 (dd, J=6.0, 15.5 Hz, 1H), 3.02 (dd, J=7.5, 15.5 Hz, 1H), 3.94 (s, 3H), 4.71 (d, J=14.0 Hz, 1H), 4.81 (d, J=14.0 Hz, 1H), 5.12 (dd, J=6.0, 7.5 Hz, 1H), 5.83 (s, 1H), 5.96 (s, 1H), 6.08 (s, 1H), 6.46 (s, 1H), 7.42 (d, J=9.0 Hz, 2H), 8.18 (d, J=9.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.4, 17.8, 19.4, 19.6, 38.2, 55.2, 70.0, 73.1, 99.8, 119.9, 123.5 (2C), 126.8, 128.1, 129.5 (2C), 133.9, 134.3, 135.2, 135.6, 137.7, 139.3, 144.6, 145.8, 155.0, 162.0, 180.6; HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2241. The IR, ^{1}H and ^{13}C NMR spectral data are in excellent agreement with those previously published.[7]

4.1.23. (±)-2-Methoxy-3,5-dimethyl-6-((*E*)-4-((2*E*,4*E*,6*E*)-2,4,6-trimethyl-7-(4-nitrophenyl)hepta-2,4,6-trienylidene)-tetrahydrofuran-2-yl)-4*H*-pyran-4-one (5a). To a solution of bromide (*E*)-**43** (195 mg, 0.36 mmol) and Pd(^{t}Bu$_3$P)$_2$ (3.5 mg, 7.2 μmol) in THF (7.5 mL) was added slowly Me_2Zn (360 μL, 2.0 M in PhMe, 0.72 mmol) at rt. The resulting was stirred for 20 min at rt. Satd aq NH_4Cl (3 mL) was added carefully, followed by brine (3 mL). The mixture was extracted twice with CH_2Cl_2, and the combined organics were dried over $MgSO_4$ and evaporated to dryness in vacuo. The residue was subjected to column chromatography (silica gel, 2:1 CH_2Cl_2/EtOAc) to afford (±)-**5a** (153 mg, 89%) as a light sensitive orange foam. R_f=0.55 (1:1 CH_2Cl_2/EtOAc); IR (film) 1666 (s), 1595 (s), 1514 (s), 1340 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.84 (s, 3H), 2.02 (s, 3H), 2.04 (s, 3H), 2.07 (s, 3H), 2.08 (s, 3H), 2.98 (dd, J=6.0, 16.5 Hz, 1H), 3.16 (dd, J=7.5, 16.5 Hz, 1H), 3.94 (s, 3H), 4.53 (d, J=13.0 Hz, 1H), 4.63 (d, J=13.0 Hz, 1H), 5.22 (dd, J=6.0, 7.5 Hz, 1H), 5.94 (s, 1H), 5.97 (s, 1H), 5.98 (s, 1H), 6.46 (s, 1H), 7.42 (d, J=8.5 Hz, 2H), 8.19 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.9, 9.4, 18.2, 19.5, 19.6, 34.3, 55.3, 73.8, 75.7, 99.8, 119.8, 123.5 (2C), 125.4, 128.1, 129.5 (2C), 133.9, 134.4, 135.6, 135.7, 137.0, 139.4, 144.6, 145.8, 155.0, 162.1, 180.6; HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2228.

4.1.24. (±)-SNF4435C (1), (±)-SNF4435D (2), and isomers 48 and 49 from (±)-5. To (±)-spectinabilin (**5**) (311 mg, 0.65 mmol) was added $PdCl_2(MeCN)_2$ (42 mg, 0.163 mmol) and then dry DMF (10 mL). The resulting red-brown solution was heated in the dark at 70 °C for 23 h. At the end of the reaction, a precipitate of palladium black had formed and the solution had a pale yellowish color. After cooling to rt the reaction mixture was evaporated to dryness in vacuo. The residue was directly subjected to column chromatography (2:1 pentanes/EtOAc) to afford a slightly impure mixture of **1**, **2**, **48** and **49** (160 mg). The mixture was subjected to preparative TLC (1:1 hexanes/Et_2O, multiple elutions) to afford a 2.1:1 mixture of **48** and **49** (56 mg, 18%) as a yellowish stiff foam, followed by a 2.5:1 mixture of **1** and **2** (68.5 mg, 22%) as a yellowish stiff foam. (±)-SNF4435C (**1**) and (±)-SNF4435D (**2**) could be separated by preparative TLC (3:1 pentanes/EtOAc, multiple elutions) to provide **1** and **2** as pale yellow solids.

Data for mixture of **48** and **49**: R_f=0.2 (2:1 pentanes/EtOAc); IR (KBr) 2954 (m), 2856 (m), 1667 (s), 1601 (s), 1519 (s), 1346 (s); HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2236. Data for **48**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.26 (s, 3H), 1.64 (s, 3H), 1.69 (s, 3H), 1.76 (s, 3H), 1.80 (s, 3H), 2.05 (dd, J=10.0, 14.0 Hz, 1H), 2.46 (dd, J=6.5, 14.0 Hz, 1H), 2.74 (s, 1H), 3.56 (s, 1H), 3.91 (s, 3H), 4.02 (d, J=9.0 Hz, 1H), 4.06 (d, J=9.0 Hz, 1H), 4.14 (dd, J=6.5, 10.0 Hz, 1H), 5.20 (s, 1H), 5.61 (s, 1H), 7.61 (d, J=8.5 Hz, 2H), 8.81 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.8, 9.0, 22.2, 22.9, 30.7, 32.0, 42.3, 49.1, 52.6, 55.2, 63.3, 75.0, 81.5, 99.9, 119.5, 122.3, 123.3 (2C), 124.0, 129.5 (2C), 130.7, 130.8, 145.1 (2C), 154.7, 162.0, 180.4. Data for **49**: ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.22 (s, 3H), 1.75 (s, 3H), 1.77 (s, 3H), 1.86 (s, 3H), 1.91–1.94 (m, 1H), 1.92 (s, 3H), 2.57 (dd, J=6.5, 13.0 Hz, 1H), 2.72 (s, 1H), 3.42 (s, 3H), 3.61 (s, 1H), 3.78 (d, J=9.0 Hz, 1H), 4.04 (d, J=9.0 Hz, 1H), 4.85 (dd, J=6.5, 10.0 Hz, 1H), 5.00 (s, 1H), 5.73 (s, 1H), 7.49 (d, J=8.5 Hz, 2H), 8.81 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 6.7, 9.4, 22.2, 22.3, 30.5, 32.3, 43.2, 51.9, 54.6, 54.9, 58.6, 75.5, 80.6, 99.8, 119.6, 123.1 (3C), 124.4, 130.6 (2C), 130.9, 131.4, 143.6, 147.0, 154.9, 162.0, 180.4.

Data for mixture of (±)-**1** and (±)-**2**: HRMS (ESI) *m/e* calcd for $C_{28}H_{32}NO_6$ (MH^+) 478.2230, found 478.2238. Data for (±)-SNF4435C (**1**): R_f=0.16 (2:1 pentanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (s, 3H), 1.72 (s, 3H), 1.74 (s, 3H), 1.84 (s, 3H), 1.89 (s, 3H), 2.43

(d, J=8.5 Hz, 2H), 2.84 (s, 1H), 3.64 (s, 1H), 3.96 (s, 3H), 3.96 (d, J=10.0 Hz, 1H), 4.32 (d, J=10.0 Hz, 1H), 4.76 (t, J=8.5 Hz, 1H), 4.94 (s, 1H), 5.58 (s, 1H), 7.54 (d, J=9.0 Hz, 2H), 8.20 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.9, 9.4, 22.2, 23.0, 30.4, 42.9, 46.3, 51.1, 51.8, 55.5, 63.6, 70.5, 73.5, 100.2, 119.6, 122.0, 123.6 (2C), 123.8, 129.1 (2C), 130.4, 131.0, 145.1, 146.9, 155.0, 162.0, 180.5. Data for (±)-SNF4435D (**2**): R_f=0.15 (2:1 pentanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.30 (s, 3H), 1.73 (s, 3H), 1.79 (s, 3H), 1.84 (s, 3H), 1.97 (s, 3H), 2.28 (dd, J=9.5, 13.0 Hz, 1H), 2.48 (dd, J=7.0, 13.0 Hz, 1H), 2.73 (s, 1H), 3.53 (s, 3H), 3.74 (s, 1H), 3.83 (d, J=9.0 Hz, 1H), 4.18 (d, J=9.0 Hz, 1H), 4.89 (s, 1H), 4.93 (dd, J=7.0, 9.5 Hz, 1H), 5.70 (s, 1H), 7.47 (d, J=9.0 Hz, 2H), 8.15 (d, J=9.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 6.8, 9.4, 22.1, 22.5, 30.7, 43.0, 45.4, 51.1, 54.8, 55.2, 61.0, 70.6, 72.5, 99.9, 119.7, 121.9, 123.2 (2C), 124.4, 129.9 (2C), 131.2, 131.3, 144.0, 146.9, 154.9, 161.9, 180.5. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** in $CDCl_3$ are in excellent agreement with those previously reported.[3] The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** in DMSO-d_6 are also in excellent agreement with those previously reported.[2b] Minor errors in the reported data for (−)-**1** (^{13}C NMR) and (+)-**2** (^{1}H and ^{13}C NMR) in $CDCl_3$ by Parker and co-workers are evident by comparison to their own included copies of spectra, thus making slight differences from ours.[16]

4.1.25. (±)-SNF4435C (1), (±)-SNF4435D (2), 48 and 49 from (±)-5a. To (±)-**5a** (115 mg, 0.24 mmol) was added $PdCl_2(MeCN)_2$ (15.5 mg, 0.06 mmol) and then dry DMF (3 mL). The resulting red-brown solution was heated in the dark at 70 °C for 23 h. Towards the end a precipitate of palladium black had formed and the solution had a pale yellowish color. After cooling to rt the reaction mixture was evaporated to dryness in vacuo. The residue was subjected to preparative TLC (3:1→2:1 pentanes/EtOAc, multiple elutions) to afford a 1.9:1 mixture of **48** and **49** (26 mg, 23%) as a yellowish foam, followed by a 2:1 mixture of (±)-**1** and (±)-**2** (9 mg, 8%) as a yellow foam. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** were identical to those above.

4.1.26. (±)-SNF4435C (1) and (±)-SNF4435D (2) from (±)-5. To (±)-spectinabilin (**5**) (100 mg, 0.21 mmol) was added dry DMF (3 mL). The resulting yellow solution was heated at 70 °C for 72 h in the dark. The resulting yellow-orange solution was evaporated to dryness in vacuo. The residue was subjected to preparative TLC (3:1 pentanes/EtOAc, multiple elutions) twice to afford (±)-**1** (18 mg, 18%) and (±)-**2** (5 mg, 5%) as yellow foams. The spectral data (^{1}H and ^{13}C NMR) for (±)-**1** and (±)-**2** were identical to those above.

Acknowledgements

We thank Roche for funding to Mikkel F. Jacobsen and EPSRC for funding to John E. Moses. We thank Dr. B. Odell for NMR assistance. We are grateful for an authentic sample of (−)-spectinabilin (**5**) donated by Dr. M. Isaka, National Center for Genetic Engineering and Biotechnology, Klong Luang, Pathumthani 12120, Thailand.

References and notes

1. (a) Tchabanenko, K.; Adlington, R. M.; Cowley, A. R.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 585–588. (b) Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, *6*, 3617–3619. (c) Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661–663. (d) Moses, J. E.; Commeiras, L.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2003**, *5*, 2987–2988. (e) Baldwin, J. E.; Claridge, T. D. W.; Culshaw, A. J.; Heupel, F. A.; Lee, V.; Spring, D. R.; Whitehead, R. C. *Chem. Eur. J.* **1999**, *5*, 3154–3161. (f) Schwaebisch, D.; Tchabanenko, K.; Adlington, R. M.; Cowley, A. M.; Baldwin, J. E. *Chem. Commun.* **2004**, 2552–2553.
2. (a) Kurosawa, K.; Takahashi, K.; Tsuda, E. *J. Antibiot.* **2001**, *54*, 541–547. (b) Takahashi, K.; Tsuda, E.; Kurosawa, K. *J. Antibiot.* **2001**, *54*, 548–553.
3. Kazuhiko, K.; Kousaku, T.; Kyouko, M.; Masayuki, O.; Naohiro, W.; Kanji, H. Japanese Patent WO9743434, 1997.
4. Hirata, Y.; Nakata, H.; Yamada, K.; Okuhara, K.; Naito, T. *Tetrahedron* **1961**, *14*, 252–274.
5. (a) Oishi, H.; Hosogawa, T.; Okutomi, T.; Suzuki, K.; Ando, K. *Agric. Biol. Chem.* **1969**, *33*, 1790–1791. (b) Schwartz, J. L.; Tishler, M.; Arison, B. H.; Shafer, H. M.; Omura, S. *J. Antibiot.* **1976**, *29*, 236–241. (c) Maeda, K. *J. Antibiot.* **1953**, *6*, 137–139.
6. Taniguchi, M.; Watanabe, M.; Nagai, K.; Suzumura, K.-I.; Suzuki, K.-I.; Tanaka, A. *J. Antibiot.* **2000**, *53*, 844–847.
7. Kakinuma, K.; Hanson, C. A.; Rinehart, K. L., Jr. *Tetrahedron* **1976**, *32*, 217–222.
8. Isaka, M.; Jaturapat, A.; Kramyu, J.; Tanticharoen, M.; Thebtaranonth, Y. *Antimicrob. Agents Chemother.* **2002**, *46*, 1112–1113.
9. Nair, M. G.; Chandra, A.; Thorogod, D. L. *Pest. Manag. Sci.* **1995**, *43*, 361–365.
10. He, J.; Hertweck, C. *J. Am. Chem. Soc.* **2004**, *126*, 3694–3695.
11. He, J.; Müller, M.; Hertweck, C. *J. Am. Chem. Soc.* **2004**, *126*, 16742–16743.
12. He, J.; Hertweck, C. *Chem. Biol.* **2003**, *10*, 1225–1232.
13. Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Cowley, A. R. *Org. Lett.* **2002**, *4*, 3731–3734.
14. Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, 2473–2476.
15. Beaudry, C. M.; Trauner, D. *Org. Lett.* **2002**, *4*, 2221–2224.
16. (a) Parker, K. A.; Lim, Y.-H. *J. Am. Chem. Soc.* **2004**, *126*, 15968–15969. (b) Parker, K. A.; Lim, Y.-H. *Org. Lett.* **2004**, *6*, 161–164.
17. In 1997 the Snow Brand Milk Products Co., Ltd submitted a Japanese language patent application, which contained a claimed chemical synthesis (cat. I_2, $CHCl_3$, 4.5 h, rt) of SNF4435C (**1**) and SNF4435D (**2**) from spectinabilin (**5**) in 40 and 4%, respectively [*Chem. Abstr.*, *128*, 47383].[3] In our hands we have been unable to repeat this result with at best only less than 5% conversion to **1** and **2** being found within a multitude of other products. Curiously this patent application was not referred to in the 2001 *J. Antibiot.* articles published by the same group.[2]
18. Banfield, J. E.; Black, D. St. C.; Johns, S. R.; Willing, R. I. *Aust. J. Chem.* **1982**, *35*, 2247–2256.

19. (a) Nicolaou, K. C.; Petasis, N. A.; Uenishi, J.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5557–5558. (b) Nicolaou, K. C.; Zipkin, R. E.; Petasis, N. A. *J. Am. Chem. Soc.* **1982**, *104*, 5558–5560. (c) Nicolaou, K. C.; Petasis, N. A.; Zipkin, R. E. *J. Am. Chem. Soc.* **1982**, *104*, 5560–5562.
20. Thomas, B. E., IV,; Evanseck, J. D.; Houk, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 4165–4169.
21. Ishibashi, Y.; Ohba, S.; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 3643–3649.
22. Jacobsen, M. F.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Lett.* **2005**, *7*, 641–644.
23. Suzuki, E.; Hamajima, R.; Inoue, S. *Synth. Commun.* **1975**, 192–193.
24. Rappo, R.; Allen, D. S., Jr.,; Lemieux, U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478–479.
25. Trost, B. M.; Bonk, P. J. *J. Am. Chem. Soc.* **1985**, *107*, 1778–1781.
26. Trost, B. M.; Sharma, S.; Schmidt, T. *J. Am. Chem. Soc.* **1992**, *114*, 7903–7904.
27. (a) Morrill, C.; Grubbs, R. H. *J. Org. Chem.* **2003**, *68*, 6031–6034. (b) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58–71.
28. A model study (using **17** Ph not Pyr, and **23** tetraphenyl not tetramethyl) did not significantly improve this *E*/*Z* selectivity (Wegner, H. A.; Morandi, S.).
29. Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481–2484.
30. Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107–108.
31. Patrick, M.; Gennet, D.; Rassat, A. *Tetrahedron Lett.* **1999**, *40*, 8575–8578.
32. Ohira, S. *Synth. Commun.* **1989**, *19*, 561–564.
33. Hilpert, H.; Wirz, B. *Tetrahedron* **2001**, *57*, 681–694.
34. Shastin, A. V.; Korotchenko, V. N.; Nenajdenko, V. G.; Balenkova, E. S. *Synthesis* **2001**, *14*, 2081–2085.
35. (a) Rousch, W. R.; Riva, R. *J. Org. Chem.* **1988**, *53*, 710–712. (b) Rousch, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708–8721.
36. Shi, J.-C.; Zeng, X.; Negishi, E.-I. *Org. Lett.* **2003**, *11*, 1825–1828.
37. Moses, J. E.; Baldwin, J. E.; Brückner, S.; Eade, S. J.; Adlington, R. M. *Org. Biomol. Chem.* **2003**, *1*, 3670–3684.
38. Moses, J. E.; Baldwin, J. E.; Marquez, R.; Adlington, R. M.; Claridge, T. D. W.; Odell, B. *Org. Lett.* **2003**, *5*, 661–663.
39. Yu, J.; Gaunt, M. J.; Spencer, J. B. *J. Org. Chem.* **2002**, *67*, 4627–4629.
40. For an example of enzymatic *E*/*Z*-isomerization in Nature, the conversion of tetraene all-*trans*-retinol to 11-*cis*-retinol in the retinoid cycle, see: Kuksa, V.; Imanishi, Y.; Batten, M.; Palczewski, K.; Moise, A. R. *Vision Res.* **2003**, *43*, 2959–2981.
41. Hatakeyama, S.; Ochi, N.; Takano, S. *Chem. Pharm. Bull.* **1993**, *41*, 1358–1361.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1690–1698
Tetrahedron

Effect of ionic liquid organizing ability and amine structure on the rate and mechanism of base induced elimination of 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes

Francesca D'Anna,* Vincenzo Frenna, Vitalba Pace and Renato Noto*

Dipartimento di Chimica Organica "E. Paternò", Università degli Studi di Palermo, Viale delle Scienze-Parco d'Orleans II, 90128 Palermo, Italy

Received 16 September 2005; revised 4 November 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—The kinetics of the elimination reaction of 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes into the corresponding 1,1-dibromo-2,2-bis(phenyl-substituted)ethenes induced by amines were studied in three room temperature ionic liquids ([BMIM][BF_4], [BMIM][PF_6], [BdMIM][BF_4]). In order to have information about reagent–ionic liquid interactions, the reaction was carried out over the temperature range (293.1–313.1 K). To study the effect of the amine on the rate and occurrence of the elimination reaction, several primary, secondary and tertiary amines with different structure (cyclic and acyclic), basicity and steric requirements were used. The data collected show that the reaction occurs faster in ionic liquids than in other conventional solvents. Furthermore, ionic liquids seem to be able to induce, for the studied reaction, a shift of mechanism from $E1_{cb}$ (in MeOH) versus E2 (in ionic liquid).

1. Introduction

There is growing interest in the utility and application of the room temperature ionic liquids (RTILs). Ionic liquids have been proposed as environmentally benign solvents for their non-detectable vapor pressure, their non-flammability and for easy recyclability.[1] ILs promise several advantages in organic synthesis both making the process more efficient and reducing use of raw materials.[2] Several organic reactions have been performed with success and for some of these the quantitative aspects in ILs have also been much investigated.[3] The ILs, with respect to conventional organic solvents, can provide a very different microenvironment and this can significantly influence the outcome of a reaction. At least two factors must be considered in determining how IL and solute influence one another. The former concerns the fact that ILs are systems having some degree of organization and this could be strongly affected by guest molecules. The latter is related to organizing ability of ILs, these, owing to π–π interactions, can help the substrate to maximize the stabilizing interactions. Therefore, we believed it interesting to investigate kinetically the effect that ILs have on classical organic reactions such as β-elimination. This is one of the most studied reactions in organic chemistry. It is well known that both the electronic and steric properties of β-substituent (generally an aryl-substituted ring) are able to affect the reactivity and, in some cases, the mechanism of base promoted elimination. We chose as substrates the 1,1,1-tribromo-2,2-bis(phenyl-substituted)ethanes (**1**) as the alkoxide-induced β-elimination has been studied by some of us (Fig. 1).[4]

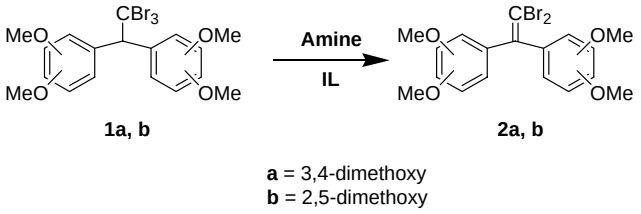


Figure 1.

The data collected allowed us to hypothesize that the reaction of **1** to the corresponding 1,1-dibromo-2,2-bis(phenyl-substituted)ethenes (**2**) occurs through an irreversible $E1_{cb}$ mechanism. The E2 mechanism seemed unlikely. The analyzed substrates differ for steric requirements (**1a**,**b**) of aryl groups. Their reactivity changes drastically with the conformation. This seemed stimulating for quantitative studies because the IL, owing to π–π interactions, could constrain **1** to assume a planar conformation, that should maximize the electronic effects exerted by aromatic rings on the route of reaction. To avoid strong interactions between charged bases, as alkoxide ions,

Keywords: Ionic liquid; Kinetic; Elimination mechanism.
* Corresponding authors. Tel.: +39 091596919; fax: +39 091596825; e-mail addresses: fdanna@unipa.it; rnoto@unipa.it

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.061

and imidazolium cation, we chose to use neutral amine bases. These are, in conventional organic solvents, largely used while, in ILs, they have been less investigated both as nucleophiles and bases. Several primary, secondary and tertiary amines with different structure (cyclic or acyclic), basicity and steric requirements were chosen as base for inducing elimination of **1a**. The pseudo first-order kinetics of amine-promoted elimination reaction were studied following the appearance of **2** spectrophotometrically. The reaction was performed in solution of 1-butyl-3-methylimidazolium tetrafluoroborate ([BMIM][BF_4]) at various concentrations (from 0.008 up to 0.0304 M) of amine over the temperature range (293.1–313.1 K). Several recent studies demonstrated that changes in the nature of cation part or the counterion could bring about notable variations in the reaction mechanism;[5] for this reason the piperidine-promoted elimination reaction was also studied in 1-butyl-3-methylimidazolium hexafluorophosphate ([BMIM][PF_6]) and in 1-butyl-2,3-dimethylimidazolium tetrafluoroborate ([BdMIM][BF_4]). The [BMIM][PF_6] was chosen to investigate the effect of the anion. As a matter of fact, the presumably unlike cation–anion of different size interactions between BMIM and two anions (a larger PF_6^- and a smaller BF_4^-) could in turn affect the interaction between the activated complex and solvent. The [BdMIM][BF_4] was chosen to evaluate the effect of hydrogen bond donor ability of imidazolium cation.

2. Results and discussion

First, we verified that **1a** did not spontaneously give the elimination product **2a** in IL within 10 days (i.e., if a reaction occurs $k_{obs} \approx 10^{-8}\ s^{-1}$). Then, we analyzed the behavior of **1a**, in [BMIM][BF_4], in the presence of amines. The results are reported in Table 1.

Table 1

Amine	pK_{BH^+} in H_2O[a]	nr/er[b]
Primary amines		
Butylamine	10.68	nr
Cyclohexylamine	10.66	nr
Secondary amines		
N-Butyl-*N*-methylamine	[c]	nr
Pyrrolidine	11.27	er
Piperidine	11.12	er
Hexamethyleneimine	10.89	er
Heptamethyleneimine	10.78	er
Morpholine	8.33	nr
2,2,6,6-Tetramethylpiperidine	11.07	nr
Tertiary amines		
Triethylamine	10.75	nr
N-Methylpyrrolidine	10.46	nr
N-Methylpiperidine	10.08	nr

[a] See Ref. 6.
[b] nr=no elimination reaction was detected; er=elimination reaction was detected.
[c] The pK_{BH^+} value should be in the range 10.64 (*N*,*N*-dimethylamine)–11.25 (*N*,*N*-dibutylamine).

As can be seen from Table 1, the primary and tertiary amines, independent of their basicity and alkyl groups structure, were unable to induce the elimination reaction. The secondary amines were more variable. The acyclic *N*-butyl-*N*-methylamine was unreactive as was the highly hindered 2,2,6,6-tetramethylpiperidine and the scarcely basic morpholine (pK_{BH^+}=8.33). We are aware of the fact that the amines basicity, measured in water, could not be adequate to describe the effective strength in IL. Indeed, the occurrence of peculiar interactions IL–amine should determine a different basicity order in IL and water. In this light, dramatically different behaviors can be surely related to deeply unlike IL–amine interactions. Nevertheless, structurally similar amines (i.e., secondary cyclic) should interact with IL in a comparable manner and the aqueous pK_{BH^+} values constitute a good starting point for analyzing the reactivity trend.

For reactive amines a quantitative study was undertaken. To make a comparison with conventional organic solvents, a kinetic measurement of the elimination reaction of **1a** in dioxane (the cosolvent used for reaction in IL solution, see Section 4) in the presence of pyrrolidine (7.5×10^{-3} M) as a model amine was carried out. The elimination reaction was very slow ($k_{obs}<5.5\times10^{-7}\ s^{-1}$). In IL solution, the above reaction was faster and the complete course of the absorbance as a function of the time is shown in Figure 2.

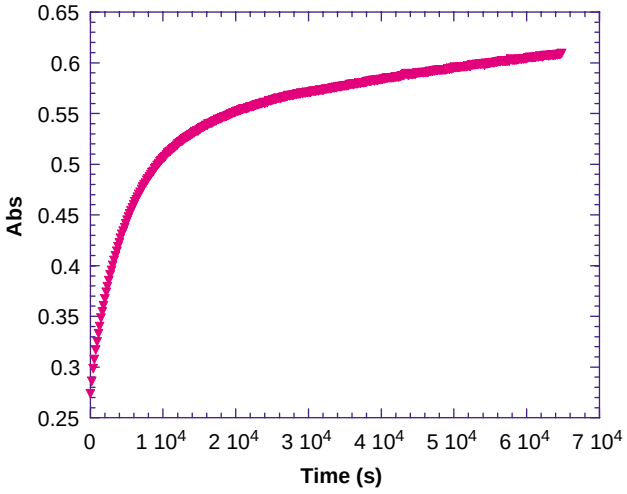


Figure 2. Experimental plot of Abs versus time for the elimination reaction of **1a** in the presence of pyrrolidine (0.0304 M) in [BMIM][BF_4] at 298.1 K and λ=280 nm.

It can be seen that the curve does not show a typical trend of a simple kinetic process. It seems that at least two kinetically relevant steps are responsible for the observed trend. In fact, first- or higher-order kinetic equations do not fit the experimental trace. From a careful analysis of the system we found that the absorbance of the IL–pyrrolidine mixture, for each of studied ILs, changed as function of the time. Furthermore a slow variation in the UV–vis spectrum of IL, induced by some of the used amines, was observed. For example, in Fig. 3, the spectra of IL in the presence of heptamethyleneimine, collected over a time range (48 h), are reported.

Data previously obtained by us seem to exclude that the observed variation could be a consequence of an acid–base equilibrium between the acidic imidazolium ion and the amine. Indeed, in this case, the observed variation of UV–vis spectrum is fast.[7]

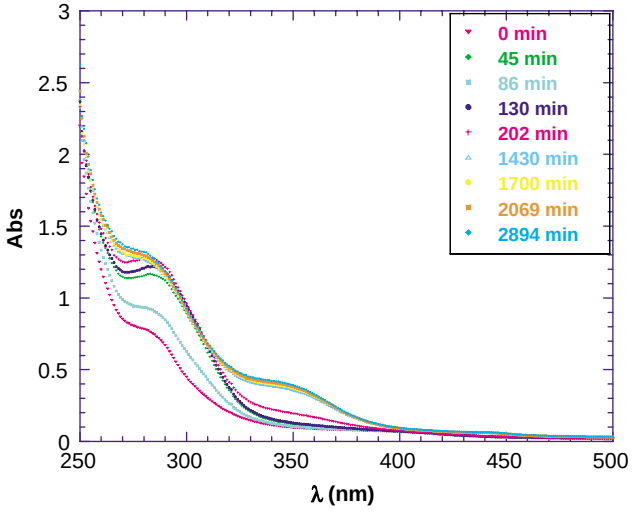


Figure 3. UV–vis spectra of [BMIM][BF_4] in the presence of heptamethyleneimine 0.0304 M collected in 48 h.

The variation in UV–vis spectrum cannot be accounted as well for the occurrence of an amino demethylation of imidazolium cation. Indeed, this reaction occurs with scarce yields to 398 K.[8] To confirm of this, the IL–amine mixture, after some days from mixing, was extracted with diethylether. The extract, analyzed by HPLC and GC–MS, did not show the presence of methylamine or other reaction products.

The IL–amine interaction was also studied by ^{1}H NMR spectroscopy recording the spectra of a mixture IL–heptamethyleneimine during a time range. Firstly, we analyzed the effect of dioxane addition to IL and a significant variation of the NMR spectrum was observed. For example, the signal due to the H-2 proton was split in a couple of signals of different intensity, the more shielded signal had the lesser intensity and was broad. The same splitting, but with opposite relative intensity and shape of signals, was observed for adding of a solution of amine in dioxane (see Fig. 4)

However, as can be observed, every signal is affected by amine solution addition and after 5 min, all the signals result enlarged and lose the multiplicity.

The signals splitting can be easy explained considering that two different ion-pairs are present in the IL–amine mixture.

This hypothesis perfectly agrees with both the formation of ion-pairs in imidazolium-based ionic liquids,[9] and with the observed variations induced by trace amounts of water in the ^{1}H NMR spectrum of [BMIM][BF_4].[10] However, the shape of signals changes slowly in the time. For example, the signals at 7.34 and 7.29 ppm due to H-4 and H-5, respectively, (see Fig. 5 spectrum **A**) change. In fact, in a first time (60 min, see Fig. 5 spectrum **B**) they seem to collapse, later (180 min, see Fig. 5 spectrum **C**) they return as two distinct signals.

The spectrum acquired after 8 days show distinct signals for the heterocyclic hydrogen atoms but broad signals for aliphatic ones (see Fig. 5, spectrum **D**).

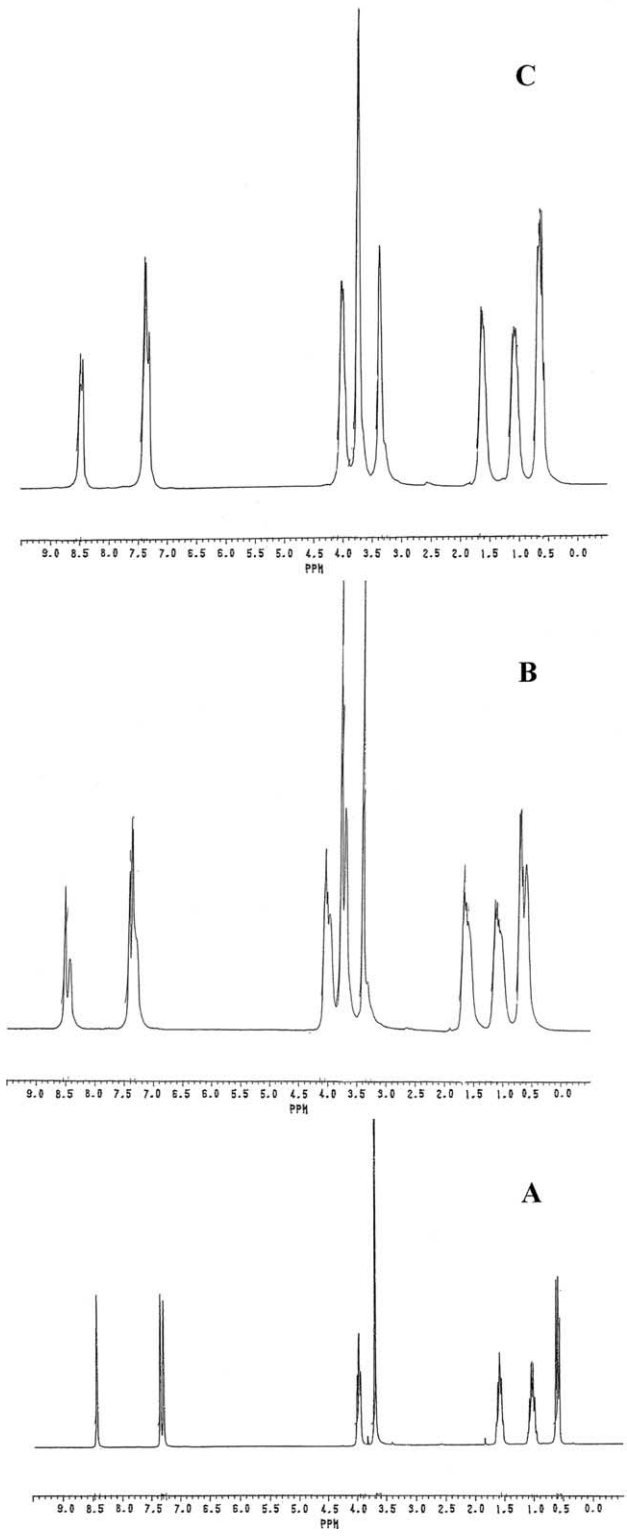


Figure 4. ^{1}H NMR spectra of: (A) neat [BMIM][BF_4]; (B) [BMIM][BF_4] in the presence of 50 μL of 1,4-dioxane; (C) [BMIM][BF_4] in the presence of a dioxane solution of heptamethyleneimine (0.0304 M) at $t=0$ min.

The above picture could be a consequence of a little and slow reorganization of molecules of IL; the different and variable interactions between two imidazolium rings could explain the variation in NMR and UV–vis spectra. To verify if the reorganization process is operative only for

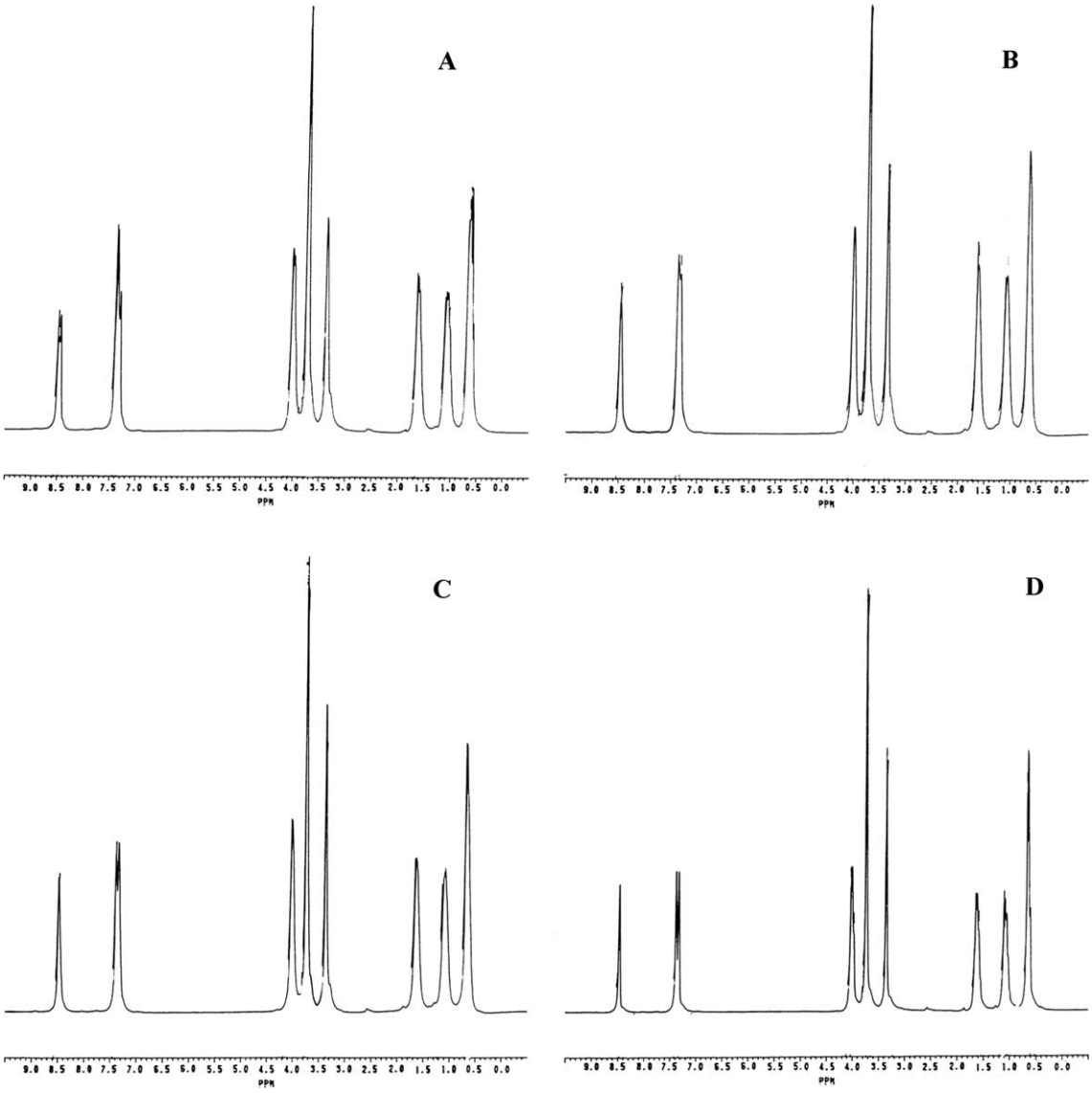


Figure 5. ^{1}H NMR spectra of: (A) [BMIM][BF_4] in the presence of a dioxane solution of heptamethyleneimine (0.0304 M) at $t=0$ min; (B) at $t=1$ h; (C) at $t=3$ h; (D) at $t=8$ days.

amines for which a variation in UV–vis spectrum was observed, we collected NMR spectra of an IL–piperidine mixture in a range of time. A very similar behavior was observed. However, it must be remarked that no signal due to transformation products of IL and amines was detected. Furthermore, the ratios among integrals relative to different signals were constant in the time. It is noteworthy that both variations in UV–vis and ^{1}H NMR spectra can not be related to a deficiency in homogeneity of IL–amine mixtures. Indeed, these were perfectly clear.

2.1. Kinetic data

In order to avoid invalidating the kinetic data by variations in UV–vis spectrum of the IL–amine mixture, the kinetic runs were registered using a sample of IL containing the same amine concentration of the kinetic run as reference. In this manner, excellent pseudo first-order curves were obtained (Fig. 6).

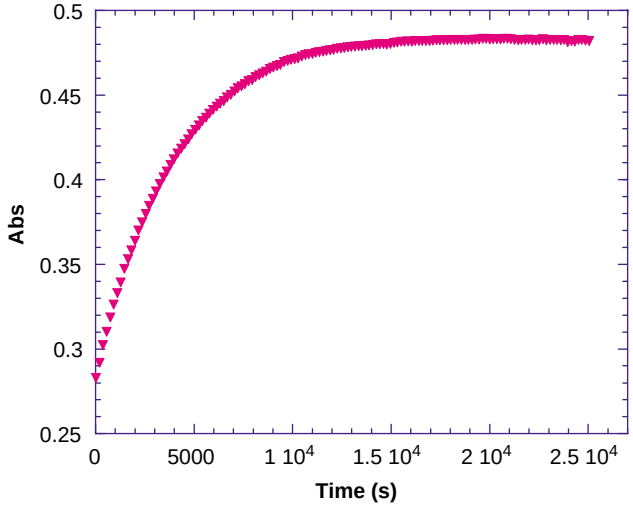


Figure 6. Experimental plot of Abs versus time for the elimination reaction of **1a** in the presence of pyrrolidine (0.0304 M) in [BMIM][BF_4] at 298.1 K and $\lambda=280$ nm recorded by using the [BMIM][BF_4]–amine mixture as reference.

To verify that the effect of the IL–amine mixture on the studied reaction was not a function of IL reorganization time, a kinetic run was carried out adding the substrate solution to an equilibrate (after 3 h from mixing) of IL–amine mixture. The observed kinetic constant was equal to that collected with a typical methodology (see Section 4).

The kinetic data for the elimination reaction of **1a** to **2a** induced by different IL–amine mixtures are reported in Table 2 (data collected at different amine concentration are available in Supplementary data: Table 4).

The secondary cyclic amines namely pyrrolidine, piperidine, hexamethyleneimine and heptamethyleneimine (five, six, seven and eight membered rings, respectively) were able to induce the elimination reaction. Similar results were previously reported by Yadav et al.[11] The geometry of amine seems to be one of the determinant factors for their reactivity. Indeed, for example, the opposite behavior of butylamine (unable to induce the elimination in **1a**) and heptamethyleneimine, bases with comparable pK_{BH^+} values (10.68 and 10.78, respectively), could be attributed to their different conformational freedom. This, higher for the butylamine than for the hexamethyleneimine, should disturb the ionic liquid organization with the consequent loss of its activating effect. However, for amines having comparable geometry and flexibility, large differences in basicity, as for piperidine and morpholine ($pK_{BH^+}=11.12$ and 8.33, respectively) are, of course, responsible of the unlike behavior. Also, the steric hindrance can change the reactivity as in the case of piperidine and 2,2,6,6-tetramethylpiperidine that have barely different basicity ($pK_{BH^+}=11.12$ and 11.07, respectively), the same geometry and flexibility but very different reactivity.

The above data show that the elimination reaction, in IL solution, is very sensitive to the amine structure (i.e., flexibility and steric hindrance). In contrast, the base strength plays a minor part. Then, it is possible to think, on the grounds of literature reports,[12] that the mechanism proceeding by an $E1_{cb}$ (in MeOH)[4] will be moved in the E2 direction in IL solution. Indeed, the E2 mechanism involving a highly crowded activated complex should be more affected than the $E1_{cb}$ mechanism by steric effects. Changes in reaction mechanism going from conventional organic solvents to IL are well documented. For example, in a nucleophilic displacement reaction, a change in mechanism was proposed on the grounds of a different nucleophilicity order observed going from conventional solvents to IL.[13]

For reactive amines, an excellent linear dependence of k_{obs} (collected values are reported in Supplementary data: Table 4) on amine concentration was found according to Eq. 1.

$$k_{obs} = a + (k_{II})_{amine}[Amine] \quad (1)$$

Significant 'negative' intercept values were calculated for [BMIM][BF_4]. They were related to an acid–base interaction between the acidic imidazolium ion and the amine as previously reported.[7]

The k_{II} values show that reactivity of **1a** decreases on going from pyrrolidine to piperidine to hexamethyleneimine to heptamethyleneimine in the order 22.7:3.1:2.7:1. The ability of amines to induce the elimination seems to be a function of their flexibility (i.e., higher flexibility, lower reactivity), due to the ring dimension, rather than of nitrogen basicity. Indeed, this changes in the order 3.1:2.2:1.3:1 on going from pyrrolidine to piperidine to heptamethyleneimine.

It is noteworthy that pyrrolidine induced elimination of **1a** ($k_{II}=9.16\times10^{-3}\ M^{-1}\ s^{-1}$) is faster than the methoxide/methanol reaction ($k_{II}=8.3\times10^{-3}\ M^{-1}\ s^{-1}$) despite the difference in basicity between the two considered bases, and that [BMIM][BF_4] and methanol have comparable polarity. Indeed, the E_{NR} values for [BMIM][BF_4] and methanol are 217.2 and 217.7, respectively.[14] This is surely indicative that the IL has an activating effect on the reaction that only the polarity is not able to explain. Probably, this effect could be a consequence both of the electrostatic interactions (bromine–imidazolium ion) and π–π interactions. The positive effect of electrostatic interactions can be explained by the E2 mechanism where an assistance to bromine departure by IL cation owing to its donor hydrogen bond ability is important. Also, Chiappe et al. studying the bromination of alkynes in ILs, accounted the possibility that

Table 2. Calculated second order rate constants and third order rate constants at 298.1 K for the elimination reaction of **1a** and **1b**, in ionic liquids solution, in the presence of amines[a,b]

IL	Substrate	Amine	k_{II} ($M^{-1}\ s^{-1}$)	k_{III} ($M^{-2}\ s^{-1}$)	i	n	R
[BMIM][BF_4]	**1a**	Pyrrolidine	0.00916 (0.00038)		-4.88×10^{-5} (8.48×10^{-6})	7	0.996
		Piperidine	0.00124 (0.00010)		-3.33×10^{-6} (2.28×10^{-6})	7	0.983
		Hexamethyleneimine	0.00109 (2.20×10^{-5})		-5.21×10^{-6} (4.87×10^{-7})	7	0.999
		Heptamethyleneimine	0.000404 (2.71×10^{-5})		1.42×10^{-6} (6.00×10^{-7})	7	0.989
[BMIM][PF_6]	**1a**	Piperidine	0.000851 (1.65×10^{-5})		2.21×10^{-6} (3.54×10^{-7})	7	0.999
[BdMIM][BF_4]	**1a**	Piperidine		0.0633 (0.014)		6	0.996
[BMIM][BF_4]	**1b**	Piperidine	0.000372 (3.02×10^{-5})		-1.11×10^{-6} (6.31×10^{-7})	7	0.987

[a] The values of k_{obs}, from which the k^{II} and k_{III} values were obtained, were reproducible within ±3%.
[b] Standard deviations are given in parenthesis.

the imidazolium cation could assist the bromine–bromine bond breaking, in the 1:1 π complex, to give a bromirenium bromide intermediate.[15] On the other hand, π–π interactions are able to increase the coplanarity between aromatic rings then favoring the conjugation and stabilizing the transition state. The relevance of π–π interactions in IL media has been previously reported by Atwood et al. according to the hypothesis that the high solubility of aromatic compounds in ILs could be related to some kind of clathrate formation.[16]

It is noteworthy that the imidazolium cation acidity, as well as, its hydrogen bond ability could negatively affect the reaction owing to a decrease in free amine concentration. However, the data collected show that the activating assistance to bromine departure seems to be predominant.

In order to study the effect of a different structure of IL cation or anion, the piperidine induced elimination of **1a** was also carried out in [BMIM][PF_6] and in [BdMIM][BF_4].

The reaction was faster (1.45 times) in [BMIM][BF_4] than in [BMIM][PF_6]. A similar reactivity trend in these ionic liquids was recently observed. Chi attributed this trend to a lower solubility of nucleophile in hexafluorophosphate than in tetrafluoroborate.[17] Welton claimed that changing the anion affected the halide nucleophilicity.[18] Recently we, studying an heterocyclic rearrangement, explained the higher reactivity in [BMIM][BF_4] than in [BMIM][PF_6], as a consequence of a different 'packing' of two ionic liquids. This determines a different catalytic effect.[7] Probably the same explanation could be used for the data reported herein, as the present elimination reaction seems more influenced by steric or stereoelectronic factors rather than by basicity of amines.

A more interesting behavior was found in [BdMIM][BF_4] solution; in fact, in this case the observed kinetic rate constant shows a dependence on second order amine concentration, that is, $k_{obs}=(k_{III})_{amine}$[Amine].[2] The observed trend could be a further support to the occurrence of the E2 mechanism. Indeed, the lesser donor hydrogen bond ability of the [BdMIM][BF_4] that hampers the assistance to bromine departure, causes the intervention of a second amine molecule to favor product formation. The effect of imidazolium cation in BMIM and BdMIM due to different hydrogen bond donor ability is well documented. Welton et al. reported a decrease in nucleophilicity of chloride anion, going from BdMIM to BMIM, owing to its stabilization via hydrogen bonding.[19] Also the *endo*-selectivity for Diels–Alder reaction between methyl acrylate and cyclopentadiene, in IL, was influenced by hydrogen bond ability of the cations.[20] At last, conversions and reaction rates of Tsuji–Trost allylic substitution, in BMIM and BdMIM, were explained considering the different nature of cations used.[21]

Previously, it was reported that the elimination of 1,1,1-trihalo-2,2-bis(phenyl-substituted)ethanes was affected by steric effects. In fact, the *ortho*-substituted derivatives were found to be less reactive than the corresponding unsubstituted derivatives as a consequence of the hindrance to conjugation between aromatic ring and π-electrons of the forming double bond.[4b] As ionic liquids are organizing media, we verified if they were able to decrease the entity of steric effects. So we carried out the piperidine induced elimination of **1b** in [BMIM][BF_4]. Effectively, the kinetic results show that the **1b** reactivity in IL is less affected by steric effects and prevalently determined by electronic effects. In fact, the reactivity ratio $(k_{II})_{1a}/(k_{II})_{1b}$ is only 3.3 in IL compared to 600 calculated for methanol solution;[22] this high value was attributed to the fact that steric effects were, in determining the different reactivities, more important than electronic ones. Indeed, the latter should equally act in both substrates. So the result obtained for reaction of **1b** in IL–piperidine mixture can be interpreted as due to a decrease in steric effects. The IL, by means of π–π interactions, constrains the aryl rings in **1b** to a coplanar conformation despite the *ortho*-methoxy groups.

2.2. Activation parameters

It is well known that, for kinetics carried out in ILs, in some cases, a significant curvature in Arrhenius or Eyring plots can be observed as a consequence of structural changes in the solvent.[23] So for a careful analysis of the temperature effect, the elimination reaction was carried out at five temperatures going from 293.1 K up to 313.1 K. For each amine and IL, an excellent linear correlation of log (k_{obs}/T) versus $1/T$ was obtained. This indicates that, in the analyzed range, the above upsetting effect is not operative. So the calculated activation parameters are only dependent on the elimination process. The activation parameter values are reported in Table 3, for an useful comparison the values for methoxide/methanol induced elimination are also reported (data collected at different temperatures are available in Supplementary data: Table 5).

The enthalpy values range from 47.4 kJ/mol up to 64.7 kJ/mol, whereas the entropy values range from −180 J/K mol up to −119 J/K mol. The collected values show that, with respect

Table 3. Activation parameters for the elimination reaction of **1a** and **1b**, in ionic liquids solution, in the presence of amines[a]

IL	Substrate	Base	$\Delta H^{\neq}$ (kJ/mol)	$\Delta S^{\neq}$ (kJ/mol)
MeOH	**1a**	MeO^-	71.9[b]	−72[b]
[BMIM][BF_4]	**1a**	Pyrrolidine	54.9 (3.2)	−135 (10)
		Piperidine	47.4 (2.2)	−180 (7)
		Hexamethyleneimine	59.0 (2.8)	−138 (9)
		Heptamethyleneimine	52.1 (4.9)	−165 (16)
[BMIM][PF_6]	**1a**	Piperidine	60.5 (2.4)	−132 (8)
[BdMIM][BF_4]	**1a**	Piperidine	64.7 (4.6)	−119 (15)
[BMIM][BF_4]	**1b**	Piperidine	36.7 (2.8)	−220 (9)

[a] Standard deviations are given in parenthesis.
[b] See Ref.4a.

to that induced by methoxide, the elimination induced by amines is enthalpy favored but entropy disfavored. These differences could be due to the fact that in methanol, compared to the IL, stronger interactions and more extensive solvation of initial state with respect to the transition state are operative. This causes a larger enthalpic contribution but a less unfavorable entropic one.

In IL, the particularly unfavorable entropic contribution is according to both the E2 mechanism and not relevant differences in solvation between initial state and transition state.

The activation parameter values trend for elimination induced by piperidine in [BMIM][BF_4], [BdMIM][BF_4] and [BMIM][PF_6] can be explained considering that different cation–anion interactions are operative. Welton claimed that a charge-separated activated complex from neutral starting materials can induce a disruption of the ionic liquid structure leading to a less negative entropy value.[24] The main contributions to this effect could be due to the degree of cation–anion interaction and to hydrogen-bond acceptor and donor ability of ionic liquid. It is noteworthy that the outcome of the reaction depends on the balance of the above factors that can also act in opposite directions.

In the studied reaction the above effects could be a consequence of the interaction between the anion and the ammonium acid proton in the activated complex. A careful analysis of entropy values seems to indicate that only the β solvent parameter is unable to explain the observed trend. The [BMIM][BF_4] having the higher β value shows the more negative $\Delta S^{\neq}$ value. Thus the strong interaction cation–anion should be responsible of the scarce disruption of ionic liquid structure. This can only be a partial explanation, as [BdMIM][BF_4], having similar β value, shows a less negative entropy value. Furthermore, [BMIM][PF_6] having the lowest β value shows an intermediate entropy value. Also the other solvent parameters do not explain the variation of activation parameters as a function of IL. This could be a consequence of the fact that the solvent parameters for ILs are probably inadequate. Indeed, it is well known that it is questionable whether the empirically derived measurements of solvent properties could be exclusively referred to room temperature ionic liquids or whether they are also affected by the nature of the tested compounds.[25] However, the entropy increase, going from an IL to another, could be attributed to an easier disruption of ionic liquid structure owing to weaker electrostatic interactions between cation–anion pairs, according to that previously reported by Welton et al.[17]

The above discussion is also supported by enthalpy values, that are higher for [BMIM][PF_6] and [BdMIM][BF_4] than [BMIM][BF_4].

Activation parameter values for **1b** show that the piperidine induced elimination is enthalpy but not entropy favored with respect to **1a**. The decrease in enthalpy could be related to a gain in energy due to an increase, going from initial state to transition state, in conjugation between the aromatic rings and π-electrons of the forming double bond, which favors the reaction of **1b**.

The same factor could cause the highly negative entropic contribution as a forcedly ordered activated complex, entropically hampered, is needed.

3. Conclusions

The data collected herein confirm the idea that ionic liquids represent an intriguing solvent system that can not be only described by means of the usual solvent parameters. Indeed, most of the obtained results seem to be a consequence of the order as well as the organizing ability of these systems. For example, the addition of a small quantity of amine solution induces a reorganization of ionic liquid structure as detected by NMR experiments. In addition, the structure rather than amine basicity determines the occurrence of the reaction. This seems to indicate that ionic liquids induce, for the studied reaction, a shift of mechanism from $E1_{cb}$ (in MeOH) versus E2 (in ionic liquid). However, it is probable that in ionic liquid deep changes in amine structure could correspond to significant variations in amine basicity, so the observed reactivity could reflect the basicity in ionic liquids. Unfortunately the lack of basicity data in ionic liquid does not allow to verify this hypothesis. The activating effect of ionic liquid on elimination of **1a** could be a consequence both of the electrostatic interactions (bromine–imidazolium ion) and π–π interactions.

The data collected show that the reaction rate is influenced by dimension and charge distribution in ionic liquid anion as well as by the hydrogen bond ability of cation that could assist the bromine departure. Finally, in the case of **1b**, the organizing ability of ionic liquids is able to minimize the unfavorable steric effects, operative in conventional organic solvents.

4. Experimental

4.1. Materials

1,1,1-Tribromo-2,2-bis(3,4-dimethoxyphenyl)ethane (**1a**) and the corresponding 1,1-dibromo-2,2-bis(3,4-dimethoxyphenyl)ethene (**2a**) were prepared according to a procedure reported.[26]

4.1.1. 1,1,1-Tribromo-2,2-bis(2,5-dimethoxyphenyl)-ethane (1b). To a stirred solution of 1,4-dimethoxybenzene (4.25 g, 0.03 mol) and bromal (1.68 g, 0.006 mol) in glacial acetic acid (20 mL), 98% sulfuric acid (7.5 mL) was added dropwise, while the temperature was maintained below 30 °C. After standing at room temperature overnight, the mixture was poured on to crushed ice and the precipitate was filtered, neutralized and dried. The product was purified by chromatography over silica gel employing a mixture of light petroleum–ethyl acetate (10/1) and crystallized from ethanol (yield 1.93 g). White crystals, mp: 118–120 °C.

IR (Nujol) ν_{max} 1059, 1284 cm^{-1}. ^1H NMR δ_H (250 MHz; $CDCl_3$): 3.76 (s, 6H, 2OCH_3); 3.83 (s, 6H, 2OCH_3); 5.40 (s, 1H); 6.70–6.83 (m, 4H, Ar); 7.10 (d, 2H, J=2.7 Hz, Ar); ^{13}C NMR δ_C (250 MHz; $CDCl_3$): 48.3; 52.9; 55.6; 56.2; 112.1; 112.3; 115.9; 130.3; 151.3; 153.3. Anal. Calcd for

$C_{18}H_{19}Br_3O_4$: C, 40.10; H, 3.55; Br, 44.47%. Found: C, 40.15; H, 3.48; Br, 44.70%.

4.1.2. 1,1-Dibromo-2,2-bis(2,5-dimethoxyphenyl)ethene (2b). 1,1,1-Tribromo-2,2-bis(2,5-dimethoxyphenyl)ethane (2.14 g, 0.004 mol) (**1b**) was dehydrobrominated by heating under reflux with a solution of CH_3ONa (0.43 g, 0.008 mol) in dry CH_3OH (10 mL). The crude dehydrohalogenated was purified by chromathography over silica gel employing a mixture of light petroleum–ethyl acetate (15/1) and crystallized from ethanol (yield 1.0 g). White crystals, mp: 115–116 °C.

IR (Nujol) ν_{max} 1053, 1309, 1583 cm^{-1}. ^1H NMR δ_H (250 MHz; $CDCl_3$): 3.72 (s, 6H, 2OC*H*$_3$); 3.77 (s, 6H, 2OC*H*$_3$); 6.77–6.87 (m, 4H); 7.05 (s, 2H); ^{13}C NMR δ_C (250 MHz; $CDCl_3$): 55.7; 56.5; 112.7; 112.9; 116.7; 130.1; 140.3; 151.3; 153.4. Anal. Calcd for $C_{18}H_{18}Br_2O_4$: C, 47.19; H, 3.96; Br, 34.88%. Found: C, 47.40; H, 3.85; Br, 34.79%.

All other products were commercial. [BMIM][BF_4], [BdMIM][BF_4] and [BMIM][PF_6] were purchased from Solvent innovation, were dried on a vacuum line at 60 °C at least for 2 h and stored in a dryer under argon and over calcium chloride. 1,4-Dioxane (for fluorescence) was purchased from Fluka and was used without further purification. Amines (Aldrich) were freshly distilled before use. UV–vis spectra and kinetic measurements were carried out by using a Beckman DU 800 spectrophotometer equipped with a peltier temperature controller, able to keep the temperature within 0.1 K. NMR spectra were collected on a Bruker AC-E Series 250 spectrometer.

4.2. Measurements and calculations

In NMR measurements 500 μL of IL were added to a 5 mm NMR tube, under argon. 75 μL of 1,4-dioxane or 75 μL of amine solution were added to IL, by a syringe. A stem coaxial capillary tube, loaded with DMSO-d_6, was inserted into the 5 mm NMR tube and this solvent was used as external lock.

All UV–vis spectra of IL–amine solutions were recorded against air.

Kinetic runs were carried out over the temperature range 293.1–313.1 K. The sample for a typical kinetic run was prepared by injecting into a quartz cuvette (optical path 0.2 cm) 500 μL of IL, 50 μL of a solution of **1** in 1,4-dioxane, and then 25 μL of a concentrated solution of amine in 1,4-dioxane, previously thermostated. The concentration of **1** was constant and equal to 0.00019 M, and the amine concentration ranging from 0.008 up to 0.0304 M. To avoid that the reorganization process of IL, induced by amine solution, affected the kinetic run, all measurements were carried out by using as reference a sample prepared injecting into a quarz cuvette 500 μL of IL, 50 μL of 1,4-dioxane and then 25 μL of a concentrated solution of amine in 1,4-dioxane. In this manner, the net absorbance at $\lambda=280$ nm for **1a** and at $\lambda=270$ nm for **1b** was plotted versus time and showed a simple exponential dependence. The reactions were all studied over 6 half-lives or more. In all cases the correlation coefficient was higher than 0.9998.

To evaluate the possibility of reusing ILs, we tried a fast and simple treatment of the solvent used. Thus, 5 mL of the used [BMIM][BF_4] was extracted four times with 3 mL of Et_2O. The IL layer was kept under vacuum at 60 °C for 2 h and reused. The apparent first-order rate constants then obtained were reproducible within ±15% with respect to values determined in fresh IL.

All kinetic data were analyzed by means of the KALEIDAGRAPH 3.0.1 software.

Acknowledgements

We thank MIUR (PRIN 2004): 'Non-aromatic heterocycles in stereo-controlled processes' and University of Palermo for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.11.061.

References and notes

1. (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071–2083. (b) Holbrey, J. D.; Seddon, K. R. *J. Chem. Soc., Dalton Trans.* **1999**, 2133–2139. (c) Earle, M. J.; Seddon, K. R. *Pure Appl. Chem.* **2000**, *72*, 1391–1398. (d) Wasserscheid, P.; Keim, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772–3789. (e) Rogers, R. D.; Seddon, K. R. *Ionic Liquids: Industrial Applications to Green Chemistry*; ACS Symposium Series 818; American Chemical Society: Washington, DC, 2002. (f) *Ionic Liquids in Synthesis*; Wasserscheid, P., Welton, T., Eds.; Wiley-VCH: Weinheim, 2003. (g) Rogers, R. D.; Seddon, K. R. *Ionic Liquids as Green Solvents. Progress and Prospects*; ACS Symposium Series 855; American Chemical Society: Washington, DC, 2003. (h) Wilkes, J. S. *J. Mol. Catal. A: Chem.* **2004**, *214*, 11–17. (i) Picquet, M.; Poinsot, D.; Stutzmann, S.; Tkatchenko, I.; Tommasi, I.; Wasserscheid, P.; Zimmermann, J. *Top. Catal.* **2004**, *29*, 139–143.
2. (a) Laali, K. K.; Borodkin, G. I. *J. Chem. Soc., Perkin Trans. 2* **2002**, 953–957. (b) Lagrost, C.; Carrié, D.; Vaultier, M.; Hapiot, P. *J. Phys. Chem. A* **2003**, *107*, 745–752. (c) Wishart, J. F.; Neta, P. *J. Phys. Chem. A* **2003**, *107*, 745–752. (d) Debreul, J. F.; Bazureau, J. P. *Tetrahedron Lett.* **2004**, *41*, 7351–7355. (e) Conte, V.; Floris, B.; Galloni, P. *Green Chem.* **2005**, *7*, 262–266. (f) Klein, H.; Jackstell, R.; Beller, M. *Chem. Commun.* **2005**, *17*, 2283–2285. (g) Xiao, J. C.; Shreeve, J. M. *J. Org. Chem.* **2005**, *70*, 3072–3078. (h) Siddiqui, S. A.; Narkhede, U. C.; Palimkar, S. S. *Tetrahedron* **2005**, *61*, 3539–3546.
3. (a) McLean, A. J.; Muldoon, M. J.; Gordon, C. M.; Dunkin, I. R. *Chem. Commun.* **2002**, 1880–1881. (b) Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Am. Chem. Soc.* **2002**, *124*, 10278–10279. (c) Skzypczak, A.; Neta, P. *J. Phys. Chem. A* **2003**, *107*, 7800–7803. (d) Kim, D. W.; Hong, H. K.; Seo, J. W.; Kim, H. S.; Kim, H. K.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2004**, *69*, 3186–3189. (e) Chiappe, C.; Pieraccini, D.

J. Org. Chem. **2004**, *69*, 6059–6064. (f) Dal, E.; Lancaster, N. L. *Org. Biomol. Chem.* **2005**, *3*, 682–686.
4. (a) Fontana, G.; Frenna, V.; Gruttadauria, M.; Natoli, M. C.; Noto, R. *J. Phys. Org. Chem.* **1998**, *11*, 54–58. (b) Fontana, G.; Frenna, V.; Lamartina, L.; Natoli, M. C.; Noto, R. *J. Phys. Org. Chem.* **2002**, *15*, 108–114.
5. (a) Earle, M. J.; Katdare, S. P.; Seddon, K. R. *Org. Lett.* **2004**, *6*, 707–710. (b) Chiappe, C.; Pieraccini, D. *Arkivoc* **2002**, *xi*, 249–255. (c) Shen, H. Y.; Yudeh, Z. M. A.; Ching, C. B.; Xia, Q. H. *J. Mol. Catal. A: Chem.* **2004**, *212*, 301–308.
6. (a) Frenna, V.; Vivona, N.; Consiglio, G.; Spinelli, D. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1865–1868. (b) Hall, H. K., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 5441–5444. (c) Lide, D. R. *CRC Handbook of Chemistry and Physics*, 80th ed.; CRC: London, 1999–2000.
7. D'Anna, F.; Frenna, V.; Noto, R.; Pace, V.; Spinelli, D. *J. Org. Chem.* **2005**, *70*, 2828–2831.
8. Glenn, A. G.; Jones, P. B. *Tetrahedron Lett.* **2004**, *45*, 6967–6969.
9. (a) Avent, A. G.; Chaloner, A. P.; Day, M. P.; Seddon, K. R.; Welton, T. *J. Chem. Soc., Dalton Trans.* **1994**, 3405–3413. (b) Bonhôte, P.; Dias, A.-P.; Papageorgiou, N.; Kalymnasundraram, K.; Grätzel, M. *Inorg. Chem.* **1996**, *35*, 1168–1178. (c) Tubbs, J. D.; Hoffmann, M. M. *J. Sol. Chem.* **2004**, *33*, 381–394.
10. Mele, A.; Tran, C. D.; De Paoli Lacerda, S. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4364–4366.
11. Yadav, J. S.; Reddy, B. V. S.; Basak, A. K.; Navsaiah, A. V. *Tetrahedron Lett.* **2003**, *44*, 2217–2220.
12. Smith, M. B.; March, J. *March's Advanced Organic Chemistry: Reactions, Mechanisms and Structure* 5th ed.; Wiley-Interscience, Wiley: New York, 2001; pp 1317–1320.
13. Chiappe, C.; Pieraccini, D.; Sullo, P. *J. Org. Chem.* **2003**, *68*, 6710–6715.
14. Carmichael, A. J.; Seddon, K. R. *J. Phys. Org. Chem.* **2000**, *13*, 591–595.
15. Chiappe, C.; Conte, V.; Pieraccini, D. *Eur. J. Org. Chem.* **2002**, 2831–2837.
16. (a) Atwood, J. L. In Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Liquid Clathrates, Inclusion Compounds; Academic: London, 1984; Vol. 1. (b) Holbrey, J. D.; Reichert, W. M.; Nieuwenhuyzen, M.; Sheppard, O.; Hardacre, C.; Rogers, R. D. *Chem. Commun.* **2003**, 476–477. (c) Deetlefs, M.; Hardacre, C.; Nieuwenhuyzen, M.; Sheppard, O.; Soper, A. K. *J. Phys. Chem. B* **2005**, *109*, 1593–1598.
17. Kim, D. W.; Song, C. E.; Chi, D. Y. *J. Org. Chem.* **2003**, *68*, 4281–4285.
18. Lancaster, N. L.; Welton, T. *J. Org. Chem.* **2004**, *69*, 5986–5992.
19. Lancaster, N. L.; Salter, P. A.; Welton, T.; Young, G. B. *J. Org. Chem.* **2002**, *67*, 8855–8861.
20. Aggarwal, A.; Lancaster, N. L.; Sethi, A. R.; Welton, T. *Green Chem.* **2002**, *4*, 517–520.
21. (a) Chen, W. P.; Xu, L. J.; Chatterton, C.; Xiao, J. L. *Chem. Commun.* **1999**, 1247–1248. (b) Ross, J.; Chen, W. P.; Xu, L. J.; Xiao, J. L. *Organometallics* **2001**, *20*, 138–142.
22. The $(k_{II})_{1b}$ value (4.51×10^{-5} M^{-1} s^{-1}) in methanol solution, at 313.1 K, was determined in this work.
23. Gordon, C. M.; McLean, A. J.; Muldoon, M. J.; Dunkin, I. R. In *Ionic Liquids as Green Solvents. Progress and Prospects*; Rogers, R. D., Seddon, K. R., Eds.; ACS Symposium Series 855; American Chemical Society: Washington, DC, 2003; pp 357–369.
24. Crowhurst, L.; Lancaster, N. L.; Arlandis, J. M.; Welton, T. *J. Am. Chem. Soc.* **2004**, *126*, 11549–11555.
25. Armstrong, D. W.; He, L.; Liu, Y.-S. *Anal. Chem.* **1999**, *71*, 3873–3876.
26. Arcoleo, A.; Paternostro, M. P. *Ann. Chim. (Rome)* **1968**, *58*, 290–297.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1699–1707

Efficient sulfonation of 1-phenylsulfonyl-1*H*-pyrroles and 1-phenylsulfonyl-1*H*-indoles using chlorosulfonic acid in acetonitrile

Tomasz Janosik,[a,*] Hamid Shirani,[a] Niklas Wahlström,[a] Ilham Malky,[a] Birgitta Stensland[b] and Jan Bergman[a,c,*]

[a]*Unit for Organic Chemistry, CNT, Department of Biosciences at Novum, Karolinska Institute, Novum Research Park, SE-141 57, Huddinge, Sweden*
[b]*Preformulation and Biopharmaceutics, Solid State Analysis AstraZeneca PAR & D/SBBG B341:3, SE-151 85 Södertälje, Sweden*
[c]*Södertörn University College, SE-141 04 Huddinge, Sweden*

Received 1 September 2005; revised 3 November 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—The sulfonation of various 1-phenylsulfonyl-1*H*-pyrroles and 1-phenylsulfonyl-1*H*-indoles using chlorosulfonic acid in acetonitrile has been studied, leading to the development of a clean and operationally simple protocol allowing direct synthesis of the corresponding 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chlorides and 1-phenylsulfonyl-1*H*-indole-3-sulfonyl chlorides, respectively, both of which may be easily converted to various sulfonamide derivatives by treatment with nitrogen nucleophiles. Efficient and selective removal of the phenylsulfonyl- or tosyl groups in the sulfonamide series may be achieved under mild conditions.

1. Introduction

Sulfonation of aromatic compounds is a process of great industrial importance due to the availability and low cost of the reagents (i.e., H_2SO_4, $HOSO_2Cl$, SO_3, or its pyridine complex), the relatively simple technology required for these types of transformations, and perhaps most importantly, the broad applicability of the resulting products, for instance sulfonic acids and sulfonyl chlorides. Consequently, sulfonation reactions have been studied extensively over the years, leading to the syntheses of a multitude of various aromatic sulfonyl derivatives.[1,2] The mechanistic aspects of sulfonation and related reactions have also been investigated in considerable detail.[2] Despite the fact that efficient procedures for the sulfonation of a number of different heterocycles are known,[3] only a few examples of sulfonation reactions involving pyrroles or indoles have been described. Both indole and pyrrole are electron rich heterocyles, which dimerize or polymerize readily under acidic conditions, thereby severely limiting the choice of reagents and substrates. For example, treatment of various indoles possessing alkyl substituents with pyridinium-1-sulfonate in refluxing pyridine gave the expected pyridinium indole-3-sulfonates in good yields.[4] Moreover, four different indole-3-sulfonyl chlorides (**1**) have been obtained by sulfonation of the corresponding nitroindoles with chlorosulfonic acid in anhydrous chloroform in the presence of sodium sulfate.[5] The latter example demonstrates that the presence of strong electron-withdrawing substituents is necessary in order to access the desired products if the process is performed in acidic media. Similar structural requirements are valid for pyrroles, as a series of ethyl pyrrole-2-carboxylates having various substituents at the pyrrole nitrogen, for example, **2**, were prepared by sulfonation in neat chlorosulfonic acid.[6] In contrast to previous claims that pyrrole undergoes sulfonation with sulfur trioxide pyridine complex to afford pyridinium 1*H*-pyrrole-2-sulfonate,[7] it was recently shown that this reaction gives instead the corresponding C-3-sulfonated product. Thus, sulfonation of pyrrole with sulfur trioxide pyridine complex followed by treatment with Na_2CO_3 gave the salt **3**, which could in turn be converted to the sulfonyl chloride **4** upon treatment with PCl_5. The position of the substitution in **3** was elucidated from NOESY data, and further corroborated by an X-ray crystallographic study of a bicyclic sulfonamide derived from **4** (Fig. 1).[8]

Keywords: Pyrroles; Indoles; Sulfonation; Chlorosulfonic acid.
* Corresponding authors. Tel.: +46 8 6089206; fax: +46 8 6081501; e-mail addresses: toja@cnt.ki.se; jabe@cnt.ki.se

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.062

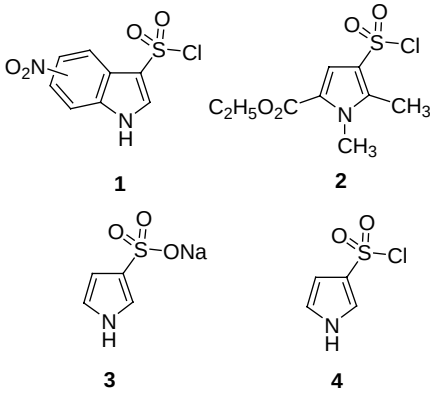


Figure 1.

Indoles possessing sulfone- or sulfonamide functionalities at C-3 have attracted considerable interest in medicinal chemistry. Thus, for example, L-737,126 (**5**) has been investigated as a inhibitor of HIV-1 reverse trancriptase,[9] while a series of closely related sulfones have been shown to possess activity against resistant HIV-1 mutants.[10] Very recently, short peptide derivatives of L-737,126 (**5**) have been demonstrated to exhibit in vitro activity against HIV-1 wild type and mutants possessing non-nucleoside reverse transcriptase inhibitor resistance.[11] The platelet-activating factor antagonist **6** was prepared via an indole-3-sulfonyl chloride, which was obtained from the corresponding *N*-protected indole involving bromination at C-3, followed by halogen–lithium exchange, treatment of the organometallic intermediate with SO_2, and subsequent chlorination with NCS (Fig. 2).[12]

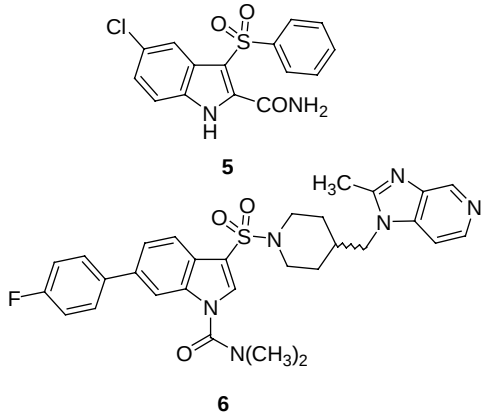
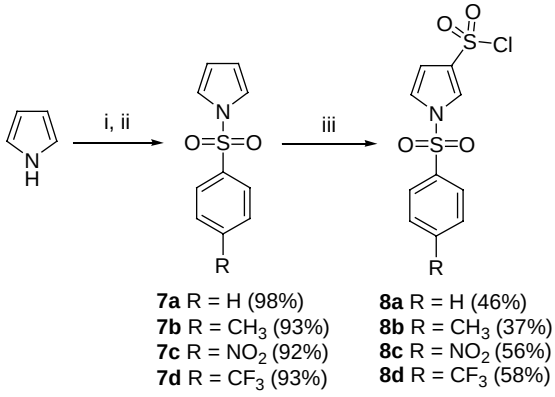


Figure 2.

2. Results and discussion

In order to evaluate the scope and limitations of chlorosulfonation of electron deficient indoles and pyrroles, a series of phenylsulfonyl-protected substrates were selected. Both 1-phenylsulfonyl-1*H*-indoles and 1-phenylsulfonyl-1*H*-pyrroles can be readily prepared, are stable towards acidic media, and the N-protecting group can be removed conveniently under various conditions.[13] Surprisingly enough, the reactivity of 1-phenylsulfonyl-1*H*-indoles and 1-phenylsulfonyl-1*H*-pyrroles towards sulfonating agents has never been studied. Since our initial experiments performed on the 1-phenylsulfonyl-1*H*-pyrroles **7a–b**[14a] in neat chlorosulfonic acid employing a procedure previously used for chlorosulfonation of some related electron deficient pyrroles[6] led to severe decomposition of the starting materials, the reactions were instead conducted in the presence of acetonitrile as the solvent. Using this reagent–solvent combination, clean conversion of **7a–b** to the desired 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chlorides **8a–b** took place (Scheme 1). Although the yields of **8a** and **8b** (46 and 37%, respectively) were only moderate, this route is very attractive because of the operational simplicity and the high purity even of the crude products. All side products are conveniently removed during aqueous workup. An excess of chorosulfonic acid must be used in order to effect efficient conversion to the desired sulfonyl chlorides, since it is known that treatment of, for example, benzene with equimolar amounts of chlorosulfonic acid gives benzenesulfonic acid, which is then in turn converted to benzenesulfonyl chloride upon treatment with an excess of the sulfonating agent in an equilibrium process.[15] Next, we turned our attention to even more electron deficient pyrroles such as **7c–d**. The standard procedures for the N-protection of pyrrole using phenylsulfonyl chlorides, which are usually conducted in the presence of strong inorganic bases such as NaOH[16] or KOH,[17] did not prove to be applicable for the synthesis of **7c–d** due to rapid decomposition of the products upon exposure to the strongly basic conditions (complex tarry mixtures were obtained). The alternative methods relying on treatment of pyrrole with potassium in refluxing THF, and subsequent introduction of 4-nitrobenzenesulfonyl chloride,[14a] or the reaction of 4-nitrobenzenesulfonamide with 2,5-dimethoxytetrahydrofuran,[14b] have been reported to give 1-(4-nitrophenyl)sulfonyl-1*H*-pyrrole (**7c**) in yields of only 26 and 46%, respectively. On the other hand, treatment of pyrrole with butyllithium in THF, followed by introduction of the appropriate sulfonyl chlorides, enabled clean and high-yielding syntheses of the known pyrroles **7a–c**,[14a] as well as the new compound **7d**. As anticipated, the pyrroles **7c–d** gave even better results during sulfonation, affording the corresponding sulfonyl chlorides **8c–d** in 56 and 58% yield, respectively, thus also supporting our expectation that the presence of strongly electron-withdrawing groups in the phenylsulfonyl part of the pyrroles **7** would provide higher yields of the sulfonyl chlorides **8**. In an additional experiment, the sulfonyl



Scheme 1. Reagents and conditions: (i) BuLi, THF, −78 °C to rt, 1 h; (ii) $RC_6H_4SO_2Cl$, −78 °C to rt, 15–20 h; (iii) $HOSO_2Cl$, CH_3CN, rt, 70–75.5 h.

chloride **8c** could also be obtained in comparable yield when **7c** and chlorosulfonic acid were heated at reflux in acetonitrile for 1.5 h, but the product contained a few percent of impurities (not identified), and the procedure performed at rt is therefore the method of choice. An X-ray crystallographic study of **8a** confirmed the expected functionalization at C-3 (Fig. 3),[18] which is in analogy with, for example, the regioselective C-3 acylation of 1-phenylsulfonyl-1*H*-pyrroles mediated by $AlCl_3$.[16b,19] Thus, the position of sulfonation is the same when using our procedure, as during sulfonation of pyrrole itself with sulfur trioxide pyridine complex in pyridine.[8] It is also interesting to note that the crystal structure of **8a** displays very similar geometry around the *N*-phenylsulfonyl unit as noted previously in several 1-phenylsulfonyl-1*H*-pyrroles and -indoles.[20]

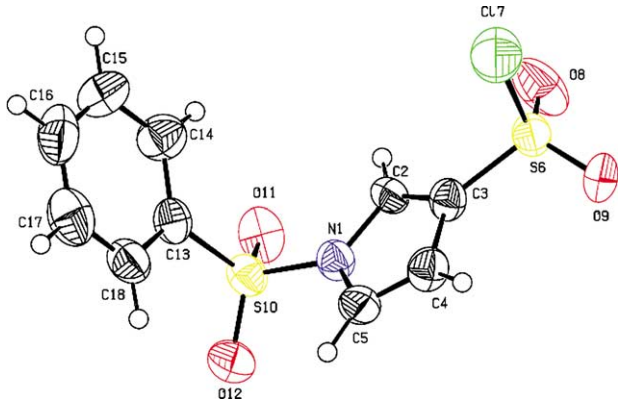
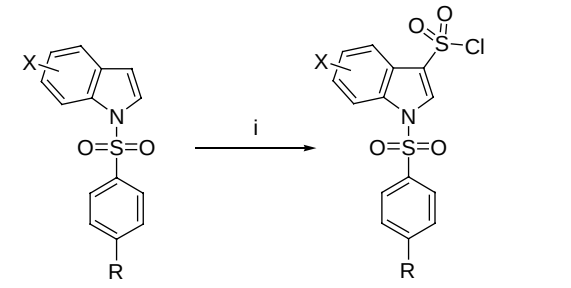


Figure 3. The molecular structure of compound **8a**, showing the atom labelling used in the crystal structure refinement.[18]



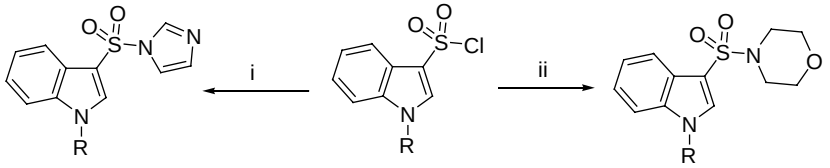
9a R = H, X = H
9b R = CH_3, X = H
9c R = H, X = 6-Br
9d R = H, X = 6-Cl
9e R = H, X = 5-F

10a R = H, X = H (79%)
10b R = CH_3, X = H (72%)
10c R = H, X = 6-Br (88%)
10d R = H, X = 6-Cl (89%)
10e R = H, X = 5-F (100%)

Scheme 2. Reagents and conditions: (i) $HOSO_2Cl$, CH_3CN, 0 °C to rt (for **10a–b**) or rt (for **10c–e**), 66–75.5 h.

Based on the observations made during the studies on the reactivity of 1-phenylsulfonyl-1*H*-pyrroles towards chlorosulfonic acid in acetonitrile, we wished to extend the scope of our method to indoles. A series of 1-phenylsulfonyl-1*H*-indoles was therefore subjected to similar reaction conditions. For instance, the readily available 1-phenylsulfonyl-1*H*-indole (**9a**)[16a,21] and 1-(*p*-toluenesulfonyl)-1*H*-indole (**9b**)[16a] underwent clean conversion to the sulfonyl chlorides **10a** and **10b**, respectively, upon treatment with 3 equiv of chlorosulfonic acid in acetonitrile (Scheme 2). The yields of these transformations were, just as expected, considerably higher than in the pyrrole series because the indoles **9a–b** are less electron rich heterocycles than the corresponding pyrroles, and are therefore also less likely to participate in side-reactions. Acceptable results can also be obtained by performing the reactions for shorter periods of time (48 h), which generally only leads to somewhat lower yields. Further deactivation of the indole nucleus leads, in similarity to the reactivity trend observed in the pyrrole series, to even more efficient chlorosulfonation, as illustrated by the syntheses of the halogenated indole-3-sulfonyl chlorides **10c–e** upon exposure of the indoles **9c**,[22] **9e**,[23] and 6-chloro-1-phenylsulfonyl-1*H*-indole (**9d**) to approximately 4 equiv of chlorosulfonic acid. On the other hand, the considerably more electron rich 5-methoxy-1-phenylsulfonyl-1*H*-indole[24] gave only a very low yield (~5%) of 5-methoxy-1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride in impure form under similar conditions, even when the reaction was initially performed at 0 °C, followed by slow warming to rt overnight. Attempted sulfonation of the somewhat more deactivated 5-methoxy-1-(4-nitrophenyl)sulfonyl-1*H*-indole[25] gave similar results. Obviously, the presence of electron releasing groups on the six-membered ring of the indole leads to extensive side reactions, and very little of the desired 3-sulfonated products are formed.

With substantial amounts of sulfonyl chlorides **8a–d** and **10a–e** in hand, studies of the reactivity and synthetic applicability of these compounds were initiated. For that purpose, indole-3-sulfonyl chlorides **10a–b** were chosen as the substrates and subjected to reactions with selected nitrogen nucleophiles (Scheme 3). Both compounds **10a–b** were cleanly converted to the imidazole derivatives **11a–b** upon treatment with imidazole in CH_2Cl_2. Likewise, exposure of **10a** to an excess of morpholine gave the sulfonamide **12** in excellent yield. As anticipated, cleavage of the phenylsulfonyl group of **12** was carried out conveniently and selectively employing potassium carbonate in aqueous methanol, providing the sulfonamide **13**.

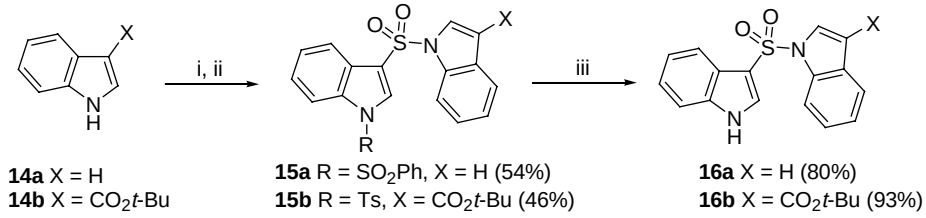


11a R = SO_2Ph (91%)
11b R = Ts (74%)

10a R = SO_2Ph
10b R = Ts

12 R = SO_2Ph (93%)
13 R = H (92%)

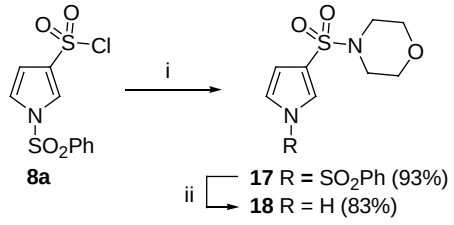
Scheme 3. Reagents and conditions: (i) imidazole, CH_2Cl_2, rt; (ii) morpholine, CH_2Cl_2, rt; (iii) K_2CO_3, MeOH, H_2O, rt.



Scheme 4. Reagents and conditions: (i) LDA, THF, −78 °C; (ii) **10a** (for **14a**), or **10b** (for **14b**), −78 °C to rt; (iii) K_2CO_3, MeOH, H_2O, rt (for **15a**), or K_2CO_3, MeOH, THF, H_2O, rt (for **15b**).

The sulfonyl chlorides **10a–b** were also used in reactions with *N*-metalated derivatives of the indoles **14a** and **14b**[26] (readily available by treatment of indole-3-carboxylic acid with oxalyl chloride, followed by exposure of the intermediate acid chloride to potassium *tert*-butoxide in *t*-BuOH), affording the new sulfur-containing systems **15a** and **15b**, respectively (Scheme 4). The use of LDA proved to be crucial in this application, as attempts involving indole and potassium *tert*-butoxide or BuLi gave inferior yields of the desired product **15a**, along with compound **16a**, resulting from base-induced cleavage of the protecting group. Again, selective cleavage of the phenylsulfonyl- or *p*-toluenesulfonyl protecting groups was achieved by treatment with potassium carbonate rendering compounds **16a–b**. Under these mild conditions, the sulfonyl linkage between the indole units remained untouched, presumably as a result of the different steric and electronic properties of the two sulfone functionalities. A member belonging to this class, namely 3-(1*H*-indole-1-sulfonyl)-7-nitro-1*H*-indole, has been prepared recently by treatment of indole with sodium hydride, followed by introduction of 7-nitro-1*H*-indole-3-sulfonyl chloride,[5] as an intermediate en route to new compounds displaying affinity for the 5-HT_6-receptor.[27] Attempts to use the sulfonyl chlorides **10a–b** in reactions with indolyl magnesium halides or *C*-metalated indoles under a variety of different conditions failed to produce the corresponding diindolyl sulfones.

In analogy to the indole-3-sulfonyl chlorides, the pyrrole-3-sulfonyl chloride **8a** could be efficiently converted to the sulfonamide **17**, which was in turn deprotected rendering **18** (Scheme 5), thus demonstrating the applicability of this chemistry to the pyrrole series.



Scheme 5. Reagents and conditions: (i) morpholine, CH_2Cl_2, rt; (ii) K_2CO_3, MeOH, H_2O, rt.

In conclusion, a practical procedure for sulfonation of 1-arylsulfonyl-1*H*-pyrroles and 1-arylsulfonyl-1*H*-indoles with chlorosulfonic acid in acetonitrile has been developed. Initial experiments probing the reactivity of the 1-arylsulfonyl-1*H*-indole-3-sulfonyl chlorides and the corresponding pyrrole derivatives clearly indicate that a wide variety of sulfonamides may be generated by reactions with suitable nitrogen nucleophiles, providing practical routes to new heterocyclic systems with potential for pharmacological applications, and that selective cleavage of the phenylsulfonyl or *p*-toluenesulfonyl protecting groups takes place under mild conditions, which tolerate the presence of sensitive functional groups.

3. Experimental

3.1. General experimental procedures

NMR data were recorded at 300.1 MHz for ^1H, and 75.5 MHz for ^{13}C, respectively. IR spectra were acquired on a FT-IR instrument. High-resolution mass spectra were recorded by Nilsson, University of Lund, Sweden. The elemental analyses were performed by Kolbe Mikroanalytisches Laboratorium, Mülheim an der Ruhr, Germany. Melting points were taken on a capillary apparatus in open capillary tubes. All reactions were performed under nitrogen atmosphere. Acetonitrile (analytical grade) was stored over activated molecular sieves (4 Å). Pyrrole was freshly distilled prior to use. THF was distilled from sodium and benzophenone.

3.1.1. 1-Phenylsulfonyl-1*H*-pyrrole (7a). BuLi (1.6 M in hexanes, 32.6 mL, 52.2 mmol) was added to a solution pyrrole (3.48 mL, 50 mmol) in anhydrous THF (100 mL) at −78 °C during 20 min. After complete addition, the mixture was stirred at −78 °C for 10 min, and was thereafter allowed to reach rt over 1 h. After cooling to −78 °C, a solution of benzenesulfonyl chloride (6.41 mL, 50 mmol) in anhydrous THF (12 mL) was added over 20 min at −78 °C. The resulting mixture was allowed to slowly reach rt overnight (~18.5 h), was thereafter poured into water (~200 mL) containing brine (~20 mL), and extracted with CH_2Cl_2 (100 mL) and (3×50 mL). The combined organic extracts were washed with water (100 mL), followed by a mixture of water (50 mL) and brine (50 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo gave pure 1-phenylsulfonyl-1*H*-pyrrole (**7a**) (10.17 g, 98%) as an off-white solid. If necessary, this material can be crystallized from *i*-PrOH. Colourless plates, mp (*i*-PrOH) 88–89 °C [lit.[14a] mp (MeOH) 89–89.5 °C].

3.1.2. 1-(4-Methyl-phenylsulfonyl)-1*H*-pyrrole (7b). This compound was prepared according to the procedure above using *p*-toluenesulfonyl chloride (9.53 g, 50 mmol) dissolved in anhydrous THF (15 mL). Yield: 10.25 g (93%). If necessary, this compound can be crystallized

from *i*-PrOH. Colourless plates, mp (*i*-PrOH) 103–103.5 °C [lit.[14a] mp (MeOH) 104.5 °C].

3.1.3. 1-(4-Nitro-phenylsulfonyl)-1*H*-pyrrole (7c). BuLi (1.6 M in hexanes, 16.3 mL, 26.1 mmol) was added to a solution pyrrole (1.74 mL, 25 mmol) in anhydrous THF (50 mL) at −78 °C during 20 min. After complete addition, the mixture was stirred at −78 °C for 10 min, and was thereafter allowed to reach rt over 1 h. It was thereafter cooled to −78 °C, and a solution of 4-nitrobenzenesulfonyl chloride (5.54 g, 50 mmol) in anhydrous THF (15 mL) was added over 20 min at −78 °C. The resulting mixture was allowed to slowly reach rt overnight (∼15 h), was thereafter poured into water (∼200 mL) containing brine (∼20 mL), and extracted with CH_2Cl_2 (4×50 mL). The combined organic extracts were washed with water (50 mL), followed by a mixture of water (50 mL) and brine (50 mL), and dried over $MgSO_4$. Evaporation of the solvents gave a brownish crystalline residue, which was dissolved in CH_2Cl_2 (∼50 mL) and the solution was passed through a plug of silica gel, which was washed with several small portions of CH_2Cl_2. The combined filtrate and washings were concentrated in vacuo to give pure **7c** (5.80 g, 92%) as a yellowish/orange crystalline solid. Crystallization of this product from *i*-PrOH gave analytically pure material as golden plates, mp (*i*-PrOH) 140.5–141.5 °C [lit.[14a] mp (MeOH) 142–142.5 °C]; IR (neat) 1525, 1375, 1346, 1191, 1169, 1061, 865, 855, 740, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (d, J=8.7 Hz, 2H), 8.02 (d, J=8.7 Hz, 2H), 7.16 (dd, J=2.0, 2.0 Hz, 2H), 6.35 (dd, J=2.0, 2.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 150.8, 144.6, 128.3, 124.8, 121.2, 115.1.

3.1.4. 1-(4-Trifluoromethyl-phenylsulfonyl)-1*H*-pyrrole (7d). A solution of BuLi (1.6 M in hexanes, 8.2 mL, 13.1 mmol) was added to a solution pyrrole (0.87 mL, 12.5 mmol) in anhydrous THF (25 mL) at −78 °C during 10 min. After complete addition, the mixture was stirred at −78 °C for 10 min, and was thereafter allowed to reach rt over 1 h. It was thereafter cooled to −78 °C, and a solution of 4-(trifluoromethyl)benzenesulfonyl chloride (3.04 g, 12.4 mmol) in anhydrous THF (6 mL) was added over 15 min at −78 °C. The resulting mixture was allowed to slowly reach rt overnight (∼20 h), was thereafter poured into water (∼100 mL) containing brine (∼20 mL), and extracted with CH_2Cl_2 (4×30 mL). The combined organic extracts were washed with water (50 mL), followed by a mixture of water (50 mL) and brine (50 mL), and dried over $MgSO_4$. Evaporation of the solvents in vacuo gave pure **7d** (3.19 g, 93%) as an off-white crystalline solid. Crystallization from *i*-PrOH gave an analytically pure sample as colourless crystals, mp (*i*-PrOH) 92–93.5 °C; IR (neat) 1376, 1317, 1170, 1146, 1109, 1058, 1031, 1018, 731, 715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (d, J=8.6 Hz, 2H), 7.76 (d, J=8.6 Hz, 2H), 7.17 (dd, J=2.1, 2.1 Hz, 2H), 6.34 (dd, J=2.1, 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 142.7, 135.6 (q, J_{C-F}=33.2 Hz), 127.5, 126.8 (q, J_{C-F}=3.7 Hz), 123.1 (q, J_{C-F}=273.1 Hz), 121.1, 114.6. Anal. Calcd for $C_{11}H_8NO_2SF_3$: C, 48.00; H, 2.93; N, 5.09. Found: C, 47.98; H, 2.84; N, 5.02.

3.1.5. 6-Bromo-1-phenylsulfonyl-1*H*-indole (9c).[22] This compound was prepared using a modification[21,24a] of the procedure described by Illi.[16a] To a suspension of finely powdered NaOH (3.13 g, 78 mmol) in CH_2Cl_2 (50 mL) cooled to 0 °C were added 6-bromoindole (4.90 g, 25 mmol) in one portion, followed by tetrabutylammonium hydrogensulfate (220 mg, 0.65 mmol). To this mixture was thereafter added benzenesulfonyl chloride (4.0 mL, 31 mmol) dropwise at 0 °C during ∼25 min. The resulting mixture was stirred at 0 °C for 1 h, the cooling bath was then removed, and stirring was continued for another 2 h at rt. The mixture was filtered through Celite, the pad was washed with several small portions of CH_2Cl_2, and the combined filtrate and washings were concentrated in vacuo. The residue was crystallized from MeOH, which gave **9c** (5.47 g) as colourless crystals. A second crop (1.66 g) was obtained after slow concentration of the mother liquor. The residual mother liquors were concentrated and subjected to column chromatography [CH_2Cl_2–*n*-hexane (2/3)] to give more **9c** (1.04 g) as a colourless crystalline solid. Overall, 8.17 g (97%) of **9c** was obtained. Mp (MeOH) 100–101 °C; IR (neat) 1367, 1174, 1134, 1125, 1093, 991, 890, 804, 753, 723, 711 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.19 (br, 1H), 7.89–7.87 (m, 2H), 7.59–7.32 (m, 6H), 6.62 (d, J=3.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.2, 135.7, 134.3, 129.8, 129.6, 127.0, 127.0, 126.9, 122.7, 118.5, 116.8, 109.2.

3.1.6. 6-Chloro-1-phenylsulfonyl-1*H*-indole (9d). This material was prepared using a modification[21,24a] of the procedure described by Illi.[16a] To a suspension of finely powdered NaOH (1.25 g, 31 mmol) in CH_2Cl_2 (20 mL) cooled to 0 °C was added 6-chloroindole (1.52 g, 10 mmol) in one portion, followed by tetrabutylammonium hydrogensulfate (88 mg, 0.26 mmol). To this mixture was thereafter added benzenesulfonyl chloride (1.4 mL, 11 mmol) dropwise at 0 °C during ∼20 min. The resulting mixture was stirred at 0 °C for 1 h, the cooling bath was then removed, and stirring was continued for another 2 h at rt. The mixture was filtered through Celite, the pad was washed with several small portions of CH_2Cl_2, and the combined filtrate and washings were concentrated in vacuo. The residue was crystallized from MeOH, which gave **9d** (2.10 g) as colourless crystals. The mother liquor was concentrated and subjected to column chromatography [CH_2Cl_2–*n*-hexane (2/3)] to give more **9d** (0.70 g) as a colourless crystalline solid. Overall, 2.80 g (96%) of **9d** was obtained. Mp (MeOH) 98–99.5 °C; IR (neat) 1363, 1170, 1129, 1093, 897, 865, 806, 752, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.03 (br, 1H), 7.90–7.87 (m, 2H), 7.59–7.41 (m, 5H), 7.22–7.19 (m, 1H), 6.63 (d, J=3.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 138.2, 135.4, 134.3, 130.9, 129.6, 129.4, 127.1, 127.0, 124.3, 122.4, 113.9, 109.1. Anal. Calcd for $C_{14}H_{10}NO_2SCl$: C, 57.63; H, 3.45; N, 4.80. Found: C, 57.60; H, 3.42; N, 4.75.

3.1.7. 1-Phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chloride (8a). To a solution of 1-phenylsulfonyl-1*H*-pyrrole (**7a**) (2.07 g, 10 mmol) in dry CH_3CN (12.5 mL) was carefully added chlorosulfonic acid (4.0 mL, 60 mmol) at rt. An exothermic reaction ensued, and the resulting solution was stirred at rt for 72 h. The mixture was thereafter poured on ice/water (∼100 g), and extracted with $CHCl_3$ (3×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3×50 mL) [addition of small amounts of brine (∼20 mL) was sometimes necessary to prevent formation of emulsions], brine (50 mL), and dried over

$MgSO_4$. Removal of the solvents in vacuo gave pure **9a** (1.41 g, 46%) as a colourless crystalline solid. An analytically pure sample was obtained as colourless crystals by crystallization from CH_3CN, mp (CH_3CN) 131.5–132.5 °C; IR (neat) 1378, 1363, 1188, 1176, 1149, 1084, 1050, 816, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98–7.95 (m, 2H), 7.89–7.88 (m, 1H), 7.77–7.71 (m, 1H), 7.64–7.59 (m, 2H), 7.26 (dd, $J=3.4$, 2.3 Hz, 1H), 6.73 (dd, $J=3.4$, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 137.2, 135.7, 132.2, 130.3, 127.8, 124.4, 122.5, 111.1. HRMS (EI) *m/z* calcd for $C_{10}H_8NO_4S_2^{35}Cl$: 304.9583 [M^+], found 304.9580. Anal. Calcd for $C_{10}H_8NO_4S_2Cl$: C, 39.28; H, 2.64; N, 4.58. Found: C, 39.27; H, 2.57; N, 4.49.

3.1.8. 1-(4-Methyl-phenylsulfonyl)-1*H*-pyrrole-3-sulfonyl chloride (8b). This compound was prepared according to the procedure above, using 1-(4-methylphenyl)sulfonyl-1*H*-pyrrole (2.21 g, 10 mmol). Yield: 1.17 g (37%). Colourless crystals, mp (CH_3CN) 146.5–148 °C; IR (neat) 1382, 1367, 1191, 1171, 1155, 1084, 1081, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.87–7.83 (m, 3H), 7.40 (d, $J=8.1$ Hz, 2H), 7.23 (dd, $J=3.5$, 2.4 Hz, 1H), 6.71 (dd, $J=3.5$, 1.7 Hz, 1H), 2.46 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.3, 134.2, 132.0, 131.0, 127.9, 124.3, 122.4, 111.0, 22.0. HRMS (EI) *m/z* calcd for $C_{11}H_{10}NO_4S_2^{35}Cl$: 318.9740 [$M^+$], found 318.9729. Anal. Calcd for $C_{11}H_{10}NO_4S_2Cl$: C, 41.31; H, 3.15; N, 4.38. Found: C, 41.43; H, 3.11; N, 4.36.

3.1.9. 1-(4-Nitro-phenylsulfonyl)-1*H*-pyrrole-3-sulfonyl chloride (8c). To a suspension of 1-(4-nitrophenyl)sulfonyl-1*H*-pyrrole (**7c**) (0.63 g, 2.5 mmol) in anhydrous CH_3CN (5 mL) was added chorosulfonic acid (2.0 mL, 30 mmol) carefully at rt. An exothermic reaction ensued. The mixture was stirred at rt for 70 h, was thereafter poured on ice/water (~50 g), and was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3×25 mL) [addition of small amounts of brine (~20 mL) was sometimes necessary to prevent formation of emulsions], brine (50 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo gave pure **8c** (0.49 g, 56%) as a colourless crystalline solid. An analytically pure sample was obtained as fine crystals with a yellowish tinge by crystallization from CH_3CN, mp (CH_3CN) 169.5–171 °C; IR (neat) 1525, 1396, 1367, 1347, 1185, 1150, 1050, 854, 740, 733 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.46 (d, $J=9.0$ Hz, 2H), 8.17 (d, $J=9.0$ Hz, 2H), 7.90–7.89 (m, 1H), 7.28 (dd, $J=3.5$, 2.4 Hz, 1H), 6.79 (dd, $J=3.5$, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 151.7, 142.6, 133.3, 129.3, 125.6, 124.3, 122.6, 112.0. HRMS (EI) *m/z* calcd for $C_{10}H_7N_2O_6S_2^{35}Cl$: 349.9434 [$M^+$], found 349.9438. Anal. Calcd for $C_{10}H_7N_2O_6S_2Cl$: C, 34.24; H, 2.01; N, 7.99. Found: C, 34.30; H, 1.98; N, 8.00.

3.1.10. 1-(4-Trifluoromethyl-phenylsulfonyl)-1*H*-pyrrole-3-sulfonyl chloride (8d). This compound was prepared according to the procedure above, using 1-(4-trifluoromethylphenyl)sulfonyl-1*H*-pyrrole (**7d**) (0.69 g, 2.5 mmol). Reaction time: 75.5 h. Yield: 0.54 g (58%). Colourless crystals, mp (CH_3CN) 144–145 °C; IR (neat) 1389, 1374, 1322, 1182, 1163, 1153, 1133, 1110, 1051, 1011, 713 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.10 (d, $J=8.3$ Hz, 2H), 7.89 (dd, $J=2.4$, 1.7 Hz, 1H), 7.89 (d, $J=8.3$ Hz, 2H), 7.27 (dd, $J=3.5$, 2.4 Hz, 1H), 6.77 (dd, $J=3.5$, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 140.7, 137.3 (q, $J_{C-F}=33.6$ Hz), 132.9, 128.4, 127.6 (q, $J_{C-F}=3.6$ Hz), 124.3, 123.1 (q, $J_{C-F}=273.5$ Hz), 122.6, 111.7. HRMS (EI) *m/z* calcd for $C_{11}H_7NO_4S_2^{35}ClF_3$: 372.9457 [$M^+$], found 372.9463. Anal. Calcd for $C_{11}H_7NO_4S_2ClF_3$: C, 35.35; H, 1.89; N, 3.75. Found: C, 35.49; H, 1.98; N, 3.71.

3.1.11. 1-Phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (10a). To a solution of 1-phenylsulfonyl-1*H*-indole (**9a**)[21] (5.14 g, 20 mmol) in dry CH_3CN (25 mL) was carefully added chorosulfonic acid (4.0 mL, 60 mmol) at 0 °C. The solution was allowed to reach rt over ~4 h, and was thereafter stirred at rt for 68 h. The resulting mixture was poured into ice/water (~100 g), and extracted with $CHCl_3$ (100 mL and 2×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×50 mL) [addition of small amounts of brine (~20 mL) was sometimes necessary to prevent formation of emulsions], brine (50 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo gave pure **10a** (5.65 g, 79%) as a pinkish crystalline solid. An analytically pure sample was obtained as colourless crystals by crystallization from CH_3CN, mp (CH_3CN) 144–145 °C; IR (neat) 1366, 1185, 1171, 1152, 1142, 1112, 1089, 942, 756, 729, 702 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.05–7.96 (m, 4H), 7.70–7.65 (m, 1H), 7.60–7.44 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 136.9, 135.5, 134.5, 131.2, 130.2, 127.6, 127.3, 125.8, 125.2, 123.9, 120.6, 114.0. HRMS (EI) *m/z* calcd for $C_{14}H_{10}NO_4S_2^{35}Cl$: 354.9740 [$M^+$], found 354.9734. Anal. Calcd for $C_{14}H_{10}NO_4S_2Cl$: C, 47.26; H, 2.83; N, 3.94. Found: C, 47.26; H, 2.86; N, 3.99.

3.1.12. 1-(4-Methyl-phenylsulfonyl)-1*H*-indole-3-sulfonyl chloride (10b). This material was prepared as above, starting from 1-(4-methylphenyl)sulfonyl-1*H*-indole (**9b**)[16a] (5.42 g, 20 mmol). Reaction time: 66 h. Yield: 5.34 g (72%). Pinkish crystals, mp (CH_3CN) 160–161 °C; IR (neat) 1376, 1367, 1174, 1149, 1136, 1107, 1087, 939, 765, 758, 709 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.38 (s, 1H), 8.04–8.01 (m, 1H), 7.98–7.95 (m, 1H), 7.89 (d, $J=8.5$ Hz, 2H), 7.54–7.43 (m, 2H), 7.35 (d, $J=8.5$ Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1, 134.5, 133.9, 131.2, 130.8, 127.7, 127.2, 125.7, 125.0, 123.9, 120.5, 114.0, 21.9. HRMS (EI) *m/z* calcd for $C_{15}H_{12}NO_4S_2^{35}Cl$: 368.9896 [$M^+$], found 368.9897. Anal. Calcd for $C_{15}H_{12}NO_4S_2Cl$: C, 48.71; H, 3.27; N, 3.79. Found: C, 48.57; H, 3.21; N, 3.91.

3.1.13. 6-Bromo-1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (10c). To a solution of 6-bromo-1-phenylsulfonyl-1*H*-indole (**9c**) (1.04 g, 3.1 mmol) in dry CH_3CN (8 mL) was carefully added chlorosulfonic acid (0.83 mL, 12.5 mmol) at rt. An exothermic reaction ensued, and the resulting solution was stirred at rt for 75.5 h. The mixture was thereafter poured on ice/water (~100 g), and extracted with $CHCl_3$ (50 mL, and 2×50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3×50 mL), brine (50 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo gave pure **10c** (1.18 g, 88%) as a crystalline solid with a pinkish tinge. An analytically pure sample was obtained as pinkish crystals by crystallization from CH_3CN, mp (CH_3CN) 187.5–189 °C; IR (neat) 1379, 1166, 1142, 1119, 1086, 942, 740, 721 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.33 (s, 1H), 8.22

(d, J=1.3 Hz, 1H), 8.02–7.99 (m, 2H), 7.83 (d, J=8.6 Hz, 1H), 7.75–7.70 (m, 1H), 7.64–7.58 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 136.8, 135.8, 135.2, 131.4, 130.4, 129.4, 127.7, 125.3, 122.8, 121.8, 121.3, 117.1. HRMS (EI) m/z calcd for $C_{14}H_9NO_4S_2^{79}Br^{35}Cl$: 432.8845 [$M^+$], found 432.8832. Anal. Calcd for $C_{14}H_9NO_4S_2BrCl$: C, 38.68; H, 2.09; N, 3.22. Found: C, 38.66; H, 1.95; N, 3.26.

3.1.14. 6-Chloro-1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (10d). This compound was prepared according to the procedure above, starting from 6-chloro-1-phenylsulfonyl-1*H*-indole (**9d**) (904 mg, 3.1 mmol). Reaction time: 68 h. Yield: 1.08 g (89%). Colourless crystals, mp (CH_3CN) 180–181 °C; IR (neat) 1390, 1379, 1186, 1166, 1144, 1122, 1087, 953, 945, 814, 749, 722 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H), 8.05–8.00 (m, 3H), 7.88 (d, J=8.6 Hz, 1H), 7.75–7.70 (m, 1H), 7.64–7.58 (m, 2H), 7.45 (dd, J=8.6, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 136.7, 135.8, 134.9, 133.7, 131.5, 130.4, 127.7, 126.7, 125.3, 122.4, 121.5, 114.2. HRMS (EI) m/z calcd for $C_{14}H_9NO_4S_2^{35}Cl_2$: 388.9350 [$M^+$], found 388.9338. Anal. Calcd for $C_{14}H_9NO_4S_2Cl_2$: C, 43.09; H, 2.32; N, 3.59. Found: C, 43.17; H, 2.27; N, 3.62.

3.1.15. 5-Fluoro-1-phenylsulfonyl-1*H*-indole-3-sulfonyl chloride (10e). This compound was prepared according to the procedure above, starting from 5-fluoro-1-phenylsulfonyl-1*H*-indole (**9e**)[23] (0.853 g, 3.1 mmol). Reaction time: 72 h. Yield: 1.16 g (100%). Colourless crystals, mp (CH_3CN) 171–172 °C; IR (neat) 1386, 1174, 1167, 1159, 1108, 1086, 972, 862, 857, 849, 816, 723 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 8.01–7.97 (m, 3H), 7.73–7.68 (m, 1H), 7.64–7.56 (m, 3H), 7.28–7.21 (m, 1H). HRMS (EI) m/z calcd for $C_{14}H_9NO_4S_2^{35}ClF$: 372.9646 [M^+], found 372.9626. Anal. Calcd for $C_{14}H_9NO_4S_2ClF$: C, 44.98; H, 2.43; N, 3.75. Found: C, 44.90; H, 2.38; N, 3.71.

3.1.16. 3-(Imidazole-1-sulfonyl)-1-phenylsulfonyl-1*H*-indole (11a). To a solution of **10a** (1.78 g, 5.0 mmol) in CH_2Cl_2 (50 mL) was added imidazole (0.73 g, 10.7 mmol). The resulting mixture was stirred at rt for 21 h, and was thereafter diluted with CH_2Cl_2 (50 mL), washed with water (3×50 mL), followed by brine (25 mL), and dried over $MgSO_4$. Removal of the solvent in vacuo gave a colourless residue, which was triturated with warm *i*-PrOH. The precipitate was collected by filtration (while warm), washed with *i*-PrOH, and dried to provide **11a** (1.76 g, 91%) as a white crystalline solid, mp (*i*-PrOH) 187–188 °C; IR (neat) 1376, 1149, 1140, 1089, 1035, 942, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.11 (s, 1H), 7.99–7.96 (m, 3H), 7.82–7.80 (m, 1H), 7.67–7.57 (m, 1H), 7.58–7.53 (m, 2H), 7.48–7.35 (m, 3H), 7.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 137.0, 136.6, 135.5, 134.9, 132.1, 131.5, 130.2, 127.6, 127.2, 125.8, 124.3, 120.0, 119.0, 117.5, 114.2. MS (ESI+) m/z 388 [$M+H]^+$. Anal. Calcd for $C_{17}H_{13}N_3O_4S_2$: C, 52.70; H, 3.38; N, 10.85. Found: C, 52.68; H, 3.50; N, 10.86.

3.1.17. 3-(Imidazole-1-sulfonyl)-1-(4-methyl-phenylsulfonyl)-1*H*-indole (11b). This material was prepared according to the same procedure as for **11a**, using **10b** (0.93 g, 2.5 mmol), and imidazole (0.37 g, 5.4 mmol) in CH_2Cl_2 (25 mL). Workup as above, followed by trituration of the crude product with warm *i*-PrOH gave pure **11b** (0.74 g, 74%) as a white crystalline solid, mp (*i*-PrOH) 206.5–208 °C; IR (neat) 1383, 1166, 1152, 1136, 1090, 1053, 942, 735, 715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.39 (s, 1H), 8.11 (s, 1H), 7.98 (d, J=7.9 Hz, 1H), 7.88–7.80 (m, 3H), 7.49–7.33 (m, 5H), 7.08 (s, 1H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 147.1, 136.6, 134.8, 133.9, 132.1, 131.5, 130.8, 127.6, 127.0, 125.7, 124.3, 120.0, 118.7, 117.5, 114.2, 21.9. MS (ESI+) m/z 402 [$M+H]^+$. Anal. Calcd for $C_{18}H_{15}N_3O_4S_2$: C, 53.85; H, 3.77; N, 10.47. Found: C, 53.76; H, 3.77; N, 10.36.

3.1.18. 3-(Morpholine-4-sulfonyl)-1-phenylsulfonyl-1*H*-indole (12). To a solution of **10a** (1.78 g, 5.0 mmol) in CH_2Cl_2 (50 mL) was added morpholine (0.92 mL, 10.5 mmol) at rt. The resulting mixture was stirred at rt for 24 h, and was thereafter washed with a mixture of water (25 mL) and brine (25 mL). The aqueous layer was extracted with CH_2Cl_2 (25 mL), and the combined organic layers were washed sequentially with 1 M aqueous HCl (25 mL), water (25 mL), brine (25 mL), followed by drying over $MgSO_4$. Removal of the solvent in vacuo gave pure **12** (1.89 g, 93%) as colourless foam. Crystallization from ethanol gave an analytically pure sample as colourless crystals, mp (EtOH) 150–151 °C; IR (neat) 1355, 1158, 1138, 1071, 935, 765, 727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 8.13 (s, 1H), 8.04–8.00 (m, 1H), 7.98–7.94 (m, 2H), 7.90–7.86 (m, 1H), 7.66–7.61 (m, 1H), 7.55–7.50 (m, 2H), 7.47–7.42 (m, 1H), 7.39–7.33 (m, 1H), 3.76–3.73 (m, 4H), 3.12–3.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 137.3, 135.1, 135.0, 130.7, 130.0, 127.3, 126.5, 126.2, 125.1, 121.3, 117.5, 113.9, 66.2, 46.0. HRMS (FAB+) m/z calcd for $C_{18}H_{19}N_2O_5S_2$: 407.0735 [$M+H]^+$, found 407.0734.

3.1.19. 3-(Morpholine-4-sulfonyl)-1*H*-indole (13). A mixture of **12** (0.81 g, 2.0 mmol) and K_2CO_3 (1.11 g, 8.0 mmol) in methanol (16 mL) and water (4 mL) was stirred at rt for 19 h. The pH was adjusted to ~5 by addition of acetic acid, and the mixture was thereafter concentrated at reduced pressure. The residue was partitioned between EtOAc (50 mL) and water (50 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (2×25 mL), brine (25 mL), and dried over $MgSO_4$. Evaporation of the solvents in vacuo gave pure **13** (490 mg, 92%) as a colourless foam. Crystallization from benzene gave an analytically pure sample as colourless crystals, mp (benzene) 177.5–178.5 °C; IR (neat) 3302, 1314, 1257, 1140, 1129, 1110, 1066, 936, 924, 753, 711 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.04 (br s, 1H), 7.97–7.94 (m, 1H), 7.71 (d, J=3.0 Hz, 1H), 7.49–7.46 (m, 1H), 7.35–7.25 (m, 2H), 3.77–3.74 (m, 4H), 3.10–3.07 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 136.2, 130.0, 124.5, 124.3, 122.7, 120.4, 112.3, 110.7, 66.3, 46.1. HRMS (FAB+) m/z calcd for $C_{12}H_{15}N_2O_3S$: 267.0803 [$M+H]^+$, found 267.0797.

3.1.20. *tert*-Butyl 1*H*-indole-3-carboxylate (14b).[26] Oxalyl chloride (4.87 mL, 55.8 mmol) was added to a suspension of indole-3-carboxylic acid (3.0 g, 18.6 mmol) in anhydrous CH_2Cl_2 (150 mL), followed by a catalytic amount of anhydrous DMF (four drops). The suspension was stirred at rt for 3 h. Removal of the solvent in vacuo gave the crude acid chloride a yellow solid. To this material was added slightly warmed anhydrous *t*-BuOH (25 mL), followed by potassium *tert*-butoxide (3.40 g, 30.3 mmol).

The resulting viscous mixture was stirred for 90 min, and was thereafter partitioned between Et_2O (200 mL), saturated aqueous NH_4Cl (100 mL), and brine (50 mL). The layers were separated, and the aqueous phase was extracted with additional Et_2O (100 mL). The combined organic extracts were washed with 2 M NaOH (100 mL), water (100 mL), and brine (100 mL), followed by drying over Na_2SO_4. Removal of the solvents in vacuo gave an oily residue, which was subjected to column chromatography [EtOAc–CH_2Cl_2 (4/1)] to provide **14b** (3.10 g, 77%) as a light tan viscous oil, IR (neat) 3287, 2971, 1663, 1530, 1365, 1148, 1120, 1044, 1026, 776, 741 cm^{-1}; ^1H NMR (DMSO-d_6) δ 11.83 (s, 1H), 7.99–7.97 (m, 2H), 7.48–7.44 (m, 1H), 7.21–7.13 (m, 2H), 1.56 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 164.0, 136.4, 125.5, 122.1, 121.0, 120.5, 112.2, 108.2, 78.8, 28.2.

3.1.21. 3-(1*H*-Indole-1-sulfonyl)-1-phenylsulfonyl-1*H*-indole (15a). BuLi (2.5 M in hexanes, 3.8 mL, 10.6 mmol) was added at −78 °C to a solution of diisopropylamine (1.33 mL, 9.5 mmol) in THF (50 mL). After stirring at −78 °C for 20 min, indole (0.91 g, mmol) in THF (11 mL) was added at −78 °C during ~15 min. The mixture was stirred at −78 °C for 35 min, followed by addition of a solution of **10a** (2.89 g, 8.1 mmol) in THF (20 mL) during ~10 min at −78 °C. The resulting solution was allowed to slowly reach rt during 15 h. Saturated aqueous NH_4Cl (10 mL) was added, followed by water (50 mL). The resulting mixture was extracted with EtOAc (2×50 mL), and the combined organic layers were washed with water (2×50 mL), brine (50 mL), and dried over $MgSO_4$. Removal of the solvents in vacuo gave a residue, which was triturated with methanol (~30 mL). The precipitate was collected by filtration, washed with methanol, and dried to provide pure **15a** (1.83 g, 54%) as a slightly pinkish solid. An analytically pure sample was obtained by crystallization from toluene as colourless crystals, mp (toluene) 182–183.5 °C; IR (neat) 1444, 1385, 1374, 1174, 1155, 1134, 1111, 1088, 942, 745, 726 cm^{-1}; ^1H NMR (DMSO-d_6) δ 9.02 (s, 1H), 8.12–8.09 (m, 2H), 8.04 (d, J=8.3 Hz, 1H), 7.99 (d, J=3.7 Hz, 1H), 7.94 (d, J=8.2 Hz, 1H), 7.80 (d, J=7.4 Hz, 1H), 7.72–7.67 (m, 1H), 7.58–7.51 (m, 3H), 7.46–7.33 (m, 3H), 7.26–7.21 (m, 1H), 6.75 (d, J=3.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 135.6, 135.5, 133.7, 133.5, 132.6, 130.3, 130.1, 127.3, 127.0, 126.8, 125.2, 124.7, 123.5, 123.4, 121.5, 119.8, 117.8, 113.6, 113.1, 109.0. HRMS (FAB+) m/z calcd for $C_{22}H_{16}N_2O_4S_2$: 436.0551 [M^+], found 436.0543.

3.1.22. *tert*-Butyl 1-[1-(4-methyl-sulfonyl)-1*H*-indole-3-sulfonyl]-1*H*-indole-3-carboxylate (15b). The procedure above was used, employing *tert*-butyl indole-3-carboxylate (**14b**) (1.68 g, 7.7 mmol), and **10b** (3.0 g, 8.1 mmol) dissolved in THF (25 mL). After workup, removal of the solvents in vacuo gave a residue, which was triturated with EtOAc (~25 mL). The precipitate was collected by filtration, washed with EtOAc, and dried to provide **15b** (1.95 g, 46%) as a white crystalline solid, mp (EtOAc) 210–212 °C; IR (neat) 1700, 1378, 1169, 1141, 1129, 1110, 1066, 741 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.44 (s, 1H), 8.29 (s, 1H), 8.11–8.08 (m, 1H), 7.95–7.87 (m, 2H), 7.83–7.80 (m, 1H), 7.75–7.71 (m, 2H), 7.42–7.31 (m, 4H), 7.24–7.21 (m, 2H), 2.36 (s, 3H), 1.63 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 163.1, 146.8, 134.7, 134.6, 133.8, 131.9, 131.8, 130.6, 128.1, 127.4, 126.8, 125.5, 125.4, 124.5, 124.5, 122.6, 120.3, 118.6, 115.6, 114.0, 113.2, 81.6, 28.6, 21.9. Anal. Calcd for $C_{28}H_{26}N_2O_6S_2$: C, 61.07; H, 4.76; N, 5.09. Found: C, 61.16; H, 4.58; N, 4.81.

3.1.23. 3-(1*H*-Indole-1-sulfonyl)-1*H*-indole (16a). To a suspension of **15a** (0.48 g, 1.1 mmol) in MeOH (12 mL) and water (3 mL), was added K_2CO_3 (0.60 g, 4.3 mmol), and the resulting mixture was stirred at rt for 22 h. Acidification to pH ~5 with AcOH, followed by concentration at reduced pressure gave a residue, which was diluted with water (25 mL), and extracted with EtOAc (3×25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2×25 mL), brine (25 mL), and dried over $MgSO_4$. Removal of the solvent in vacuo gave a solid residue, which was subjected to column chromatography [EtOAc–*n*-heptane (3/7)] to provide **16a** (0.26 g, 80%) as a white crystalline solid, mp (*i*-PrOH) 193.5–195 °C; IR (neat) 3371, 1352, 1146, 1130, 1120, 1100, 742 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.39 (br s, 1H), 8.49 (s, 1H), 7.97–7.93 (m, 2H), 7.81–7.78 (m, 1H), 7.56–7.54 (m, 1H), 7.48–7.44 (m, 1H), 7.32–7.16 (m, 4H), 6.72 (dd, J=3.7, 0.7 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 136.2, 133.7, 132.7, 130.2, 127.0, 124.0, 123.5, 122.7, 122.5, 122.1, 121.3, 118.5, 113.0, 112.9, 110.5, 107.5. HRMS (FAB+) m/z calcd for $C_{16}H_{12}N_2O_2S$: 296.0619 [M^+], found 296.0625.

3.1.24. *tert*-Butyl 1-(1*H*-indole-3-sulfonyl)-1*H*-indole-3-carboxylate (16b). To a suspension of **15b** (0.60 g, 1.09 mmol) in a mixture of THF (12 mL), MeOH (12 mL), and water (3 mL), was added K_2CO_3 (1.80 g, 13.0 mmol), and the resulting mixture was stirred at rt for 30 min. It was thereafter acidified to pH ~5 with AcOH, and concentrated at reduced pressure. Workup as above for **15a** gave a residue, which was subjected to column chromatography [EtOAc–*n*-heptane (3/7)] to afford **16b** (0.40 g, 93%) as a white crystalline solid, mp (*i*-Pr_2O) 226 °C (dec); IR (neat) 3348, 1699, 1360, 1149, 1125, 1101, 1097, 965, 743 cm^{-1}; ^1H NMR (DMSO-d_6) δ 12.61 (br s, 1H), 8.68 (s, 1H), 8.39 (s, 1H), 8.04–7.96 (m, 2H), 7.83–7.78 (m, 1H), 7.52–7.49 (m, 1H), 7.39–7.23 (m, 4H), 1.55 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 162.3, 136.2, 134.1, 133.8, 131.7, 126.9, 125.0, 124.0, 123.8, 122.6, 122.5, 121.5, 118.1, 113.3, 113.2, 113.0, 109.2, 80.8, 27.9. HRMS (FAB+) m/z calcd for $C_{21}H_{20}N_2O_4S$: 396.1144 [M^+], found 396.1126.

3.1.25. 4-(1-Phenylsulfonyl-1*H*-pyrrole-3-sulfonyl)-morpholine (17). The same procedure as for **12** was used, employing 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chloride (**8a**) (1.53 g, 5.0 mmol), to give pure **17** (1.66 g, 93%) as a white foamy solid. This material softens gradually at temperatures over ~80 °C, and a definite mp could not be determined. IR (neat) 1374, 1344, 1173, 1148, 1115, 1071, 1054, 946, 932, 723 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.95–7.91 (m, 2H), 7.74–7.68 (m, 1H), 7.63 (dd, J=2.4, 1.7 Hz, 1H), 7.62–7.56 (m, 2H), 7.25 (dd, J=3.3, 2.4 Hz, 1H), 6.48 (dd, J=3.3, 1.7 Hz, 1H), 3.76–3.73 (m, 4H), 3.01–2.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 137.7, 135.2, 130.1, 127.5, 123.8, 123.4, 122.3, 112.2, 66.1, 46.0. HRMS (FAB+) m/z calcd for $C_{14}H_{18}N_2O_5S_2$: 357.0579 [$M+H]^+$, found 357.0578.

3.1.26. 4-(1*H*-Pyrrole-3-sulfonyl)-morpholine (18). The same procedure was used as for **13** was used, employing compound **17** (0.71 g, 2 mmol), to afford pure **18** (0.36 g, 83%) as colourless crystals, mp (*i*-PrOH/*i*-Pr_2O) 102.5–104 °C; IR (neat) 3321, 1313, 1258, 1134, 1105, 1066, 939, 924, 750, 724 cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.31 (br s, 1H), 7.25–7.23 (m, 1H), 6.86–6.84 (m, 1H), 6.44–6.41 (m, 1H), 3.77–3.74 (m, 4H), 2.99–2.96 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 122.6, 120.3, 116.7, 108.5, 66.1, 46.1. Anal. Calcd for $C_8H_{12}N_2O_3S$: C, 44.43; H, 5.59; N, 12.95. Found: C, 44.55; H, 5.65; N, 12.95.

3.1.27. Crystal data for 1-phenylsulfonyl-1*H*-pyrrole-3-sulfonyl chloride (8a). $C_{10}H_8NO_4Cl$, $M_r=305.76$, space group: monoclinic, $P2_1/c$ (No. 14). Unit-cell parameters: $a=13.597(1)$, $b=8.322(1)$, $c=11.496(1)$ Å, $\alpha=90$, $\beta=105.34(1)$, $\gamma=90°$, $V=1254.5(2)$ $Å^3$, $Z=4$. $D_x=1.619(1)$ g/cm^3, $F(000)=624$. μ(Mo Kα)=6.41 cm^{-1}. Crystal dimensions 0.06×0.29×0.29 mm. A total of 1054 independent reflections [$F^2>3\sigma(F^2)$] was refined on F^2 to give $R=0.0479$, $R_w=0.0934$ for 165 parameters $w=1/[\sigma^2F_o^2+(0.1000)F_o^2]$. $(\Delta/\sigma)_{max}=0.0002$, $(\Delta/\sigma)_{mean}=0.0000$, $\Delta\rho_{max}=1.16$ e $Å^{-3}$, $\Delta\rho_{min}=-1.73$ e $Å^{-3}$, $\Delta\rho_{mean}=0.32$ e $Å^{-3}$. The data was corrected for extinction effects.

References and notes

1. Nelson, K. L. In *Friedel-Crafts and Related Reactions*, Olah, G. A., Ed.; Wiley: New York, 1964; Vol. 3, pp 1355–1392.
2. Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley: New York, 1968.
3. For numerous examples, see Ref. 2, pp 137–180.
4. Smith, G. F.; Taylor, D. A. *Tetrahedron* **1973**, *29*, 669–672.
5. Mandur, A. H. M.; Buyanov, V. N.; Zhigachev, V. E.; Kurkovskaya, L. N.; Suvorov, N. N. *Khim. Geterotsikl. Soedin.* **1990**, 1341–1345.
6. Moranta, C.; Molins-Pujol, A. M.; Pujol, M. D.; Bonal, J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3285–3291.
7. (a) Terent'ev, A. P.; Yanovski, L. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1949**, *19*, 487–491. (b) Terentyev, A. P.; Yanovskaya, L. A.; Yashunsky, V. G. *J. Gen. Chem. USSR (Engl. Transl.)* **1950**, *20*, 539–542.
8. Mizuno, A.; Kan, Y.; Fukami, H.; Kamei, T.; Miyazaki, K.; Matsuki, S.; Oyama, Y. *Tetrahedron Lett.* **2000**, *41*, 6605–6609.
9. Williams, T. M.; Ciccarone, T. M.; MacTough, S. C.; Rooney, C. S.; Balani, S. K.; Condra, J. H.; Emini, E. A.; Goldman, M. E.; Greenlee, W. J.; Kaufman, L. R.; O'Brien, J. A.; Sardana, V. V.; Schleif, W. A.; Theoharides, A. D.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 1291–1294.
10. Silvestri, R.; De Martino, G.; La Regina, G.; Artico, M.; Massa, S.; Vargiu, L.; Mura, M.; Loi, A. G.; Marceddu, T.; La Colla, P. *J. Med. Chem.* **2003**, *46*, 2482–2493.
11. Silvestri, R.; Artico, M.; De Martino, G.; La Regina, G.; Loddo, R.; La Colla, M.; La Colla, P. *J. Med. Chem.* **2004**, *47*, 3892–3896.
12. (a) Curtin, M. L.; Davidsen, S. K.; Heyman, H. R.; Garland, R. B.; Sheppard, G. S.; Florjancic, A. S.; Xu, L.; Carrera, G. M., Jr.; Steinman, D. H.; Trautmann, J. A.; Albert, D. H.; Magoc, T. J.; Tapang, P.; Rhein, D. A.; Conway, R. G.; Luo, G.; Denissen, J. F.; Marsh, K. C.; Morgan, D. W.; Summers, J. B. *J. Med. Chem.* **1998**, *41*, 74–95. (b) Sheppard, G. S.; Davidsen, S. K.; Summers, J. B.; Carrera, G. M., Jr. U.S. Patent 5,654,305, 1997; *Chem. Abstr.* **1997**, *127*, 205591. (c) Sheppard, G. S.; Davidsen, S. K.; Summers, J. B.; Carrera, G. M., Jr. U.S. Patent 5,567,711, 1996; *Chem. Abstr.* **1996**, *125*, 328713.
13. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999; pp 615–617.
14. (a) Papadopoulos, E. P.; Haidar, N. F. *Tetrahedron Lett.* **1968**, 1721–1723. (b) Wasley, J. W.; Chan, K. *Synth. Commun.* **1973**, *3*, 303–304.
15. For a discussion, see Ref. 2, pp 39–41.
16. (a) Illi, V. O. *Synthesis* **1979**, 136. For an extension of this excellent procedure to the synthesis of 1-phenylsulfonyl-1*H*-pyrroles, see also: (b) Xu, R. X.; Anderson, H. J.; Gogan, N. J.; Loader, C. E.; McDonald, R. *Tetrahedron Lett.* **1981**, *22*, 4899–4900.
17. Zelikin, A.; Shastri, V. R.; Langer, R. *J. Org. Chem.* **1999**, *64*, 3379–3380.
18. The crystallographic data (excluding structure factors) for compound **8a** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 281814. 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].
19. See, for example: (a) Rokach, J.; Hamel, P.; Kakushima, M.; Smith, G. M. *Tetrahedron Lett.* **1981**, *22*, 4901–4904. (b) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214–3219.
20. Beddoes, R. L.; Dalton, L.; Joule, J. A.; Mills, O. S.; Street, J. D.; Watt, C. I. F. *J. Chem. Soc., Perkin Trans. 2* **1986**, 787–797.
21. Conway, S. C.; Gribble, G. W. *Heterocycles* **1990**, *30*, 627–633.
22. Although no spectral or physical data were given, this compound has previously been obtained in 92% yield by reaction of indole with NaH in DMF, followed by treatment with benzenesulfonyl chloride, see: Sasaki, T.; Igarashi, Y.; Ogawa, M.; Furumai, T. *J. Antibiot.* **2002**, *55*, 1009–1012.
23. 5-Fluoro-1-phenylsulfonyl-1*H*-indole was prepared according to the procedure of Illi (Ref. 16a) by replacing benzene with CH_2Cl_2 as the solvent, see: Davis, D. A. Ph.D. Thesis, Dartmouth College, Hanover, NH, 1990.
24. (a) Gribble, G. W.; Fletcher, G. L.; Ketcha, D. M.; Rajopadhye, M. *J. Org. Chem.* **1989**, *54*, 3264–3269. (b) Sundberg, R. J.; Parton, R. L. *J. Org. Chem.* **1976**, *41*, 163–165.
25. Janosik, T.; Bergman, J. Unpublished work.
26. (a) Ludwig, J.; Lehr, M. *Synth. Commun.* **2004**, *34*, 3691–3695. (b) Stanovnik, B.; Tišler, M.; Carlock, J. T. *Synthesis* **1976**, 754–755.
27. WO Patent Appl. 03/013510, 2003; *Chem. Abstr.* **2003**, *138*, 187788.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1708–1716
Tetrahedron

An efficient synthesis of highly substituted pyrroles from β-oxodithiocarboxylates

Paulson Mathew[†] and C. V. Asokan*

School of Chemical Sciences, Mahatma Gandhi University, Priyadarshini Hills, Kottayam 686560, India

Received 1 August 2005; revised 8 November 2005; accepted 24 November 2005

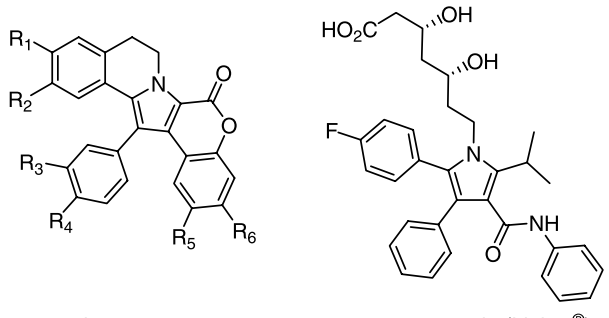
Available online 27 December 2005

Abstract—α-Oxoketene-*N*,*S*-acetals, prepared by the reaction of alkyl glycinate hydrochlorides with β-oxodithiocarboxylates followed by alkylation, underwent cyclization in presence of chloromethyleneiminium salt derived from $POCl_3$/DMF to afford alkyl-3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates in excellent yields. Alkyl-3-aryl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates were formed in moderate yields when the same *N*,*S*-acetals were treated with DBU.

1. Introduction

Pyrroles are heterocycles of great importance because of their presence in numerous natural products like heme, chlorophyll, vitamin B_{12}, and various cytochrome enzymes.[1] Some of the recently isolated pyrrole containing marine natural products have been found to exhibit considerable cytotoxicity and function as multi drug resistant (MDR) reversal agents.[2] Many of these biologically active compounds have emerged as chemotherapeutic agents. In addition, polysubstituted pyrroles are molecular frameworks having immense importance in material science.[3] The unique structural array and the unusual biological activity displayed by many pyrrole containing natural products have made them attractive synthetic targets. Classical methods like Knorr reaction, Paal–Knorr synthesis[4] and Hantzsh synthesis[5] are still widely in use for the synthesis of substituted pyrroles. Since these methods and more recent pyrrole syntheses[6] that showcase newer methodologies have limitations like functional group compatibility and regiospecificity, newer, simple and more convenient methods leading to highly substituted pyrroles are still desirable. In our recent communication, we have shown that α-oxoketene-*N*,*S*-acetals undergo cyclization in presence of Vilsmeier–Haack reagent to afford alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates in excellent yields. The utility of this method has been demonstrated by the formal total synthesis of the marine natural products lukianol A and lamellarin Q.[7]

β-Oxoketene-*N*,*S*-acetals are versatile building blocks widely used for heterocyclic synthesis.[8,9] In continuation of a research program directed towards the total synthesis of some pyrrole containing natural products like lamellarins[10] and the cholesterol lowering drug atorvastatin (Fig. 1),[11] we needed to develop an efficient method for the preparation of highly functionalized pyrroles.



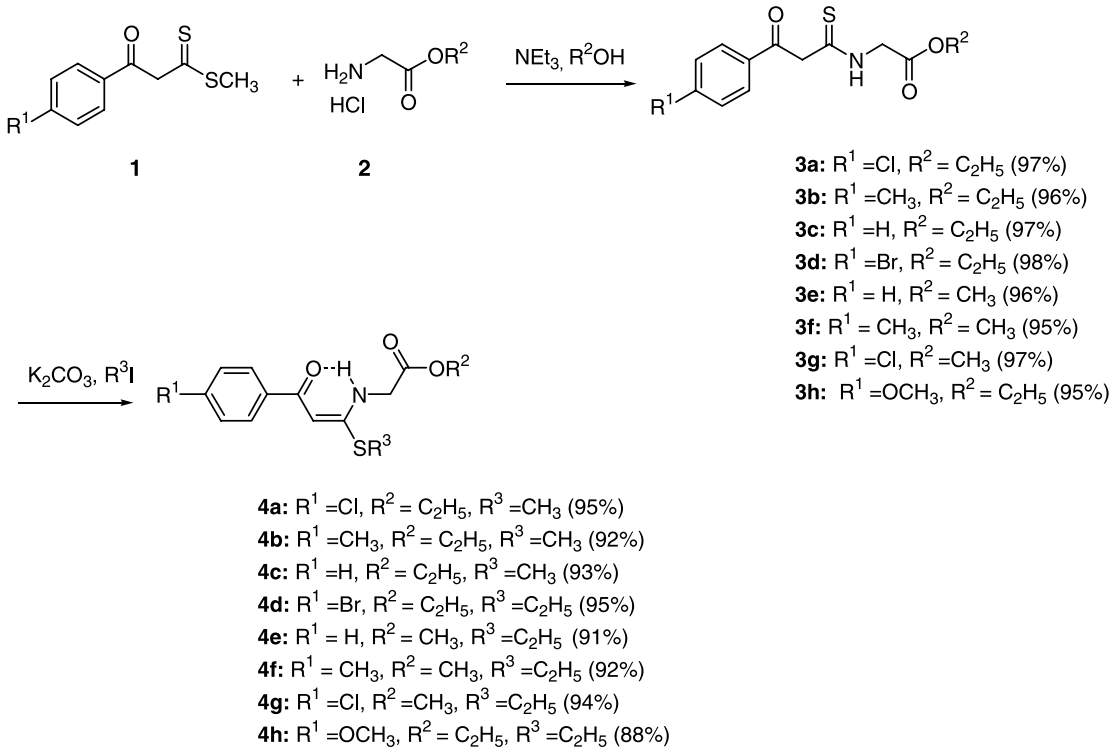
lamellarins atorvastatin (Lipitor®)

Figure 1.

We envisioned that appropriately substituted ketene-*N*,*S*-acetals, prepared by the reaction of dithiocarboxylates with alkyl glycinate followed by alkylation, could be transformed into the corresponding pyrrole derivatives. Herein we

Keywords: Pyrroles; Dithiocarboxylates; Ketene-*N*,*S*-acetals; Vilsmeier–Haack reagent.
* Corresponding author. Tel.: +91 481 2730751; fax: +91 481 2731009; e-mail: asokancv@yahoo.com
† Present address: Department of Chemistry, St. Thomas' College, Thrissur 680001, Kerala, India.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.076

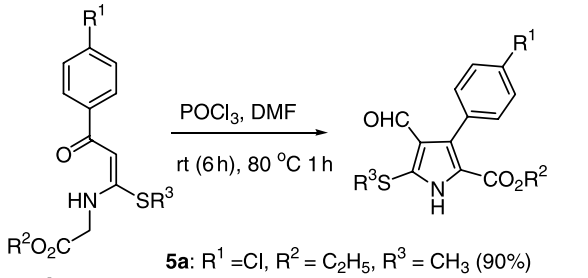


Scheme 1.

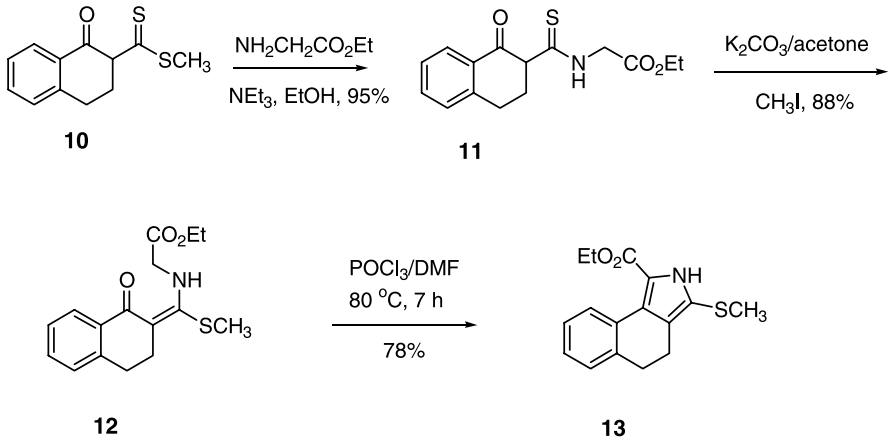
present a facile and high yielding regioselective method for synthesizing 2,3,4,5-tetra and 2,3,5-tri substituted pyrroles from readily available inexpensive starting materials by a simple sequence of reactions. The key step in this method is the iminium salt or base catalyzed cyclization of α-oxoketene-*N*,*S*-acetals **4**.

2. Results and discussion

Dithiocarboxylates **1**, prepared[12] by the condensation of enolates of active methylene ketones with dialkyl trithiocarbonates, are valuable multifunctional synthetic intermediates.[13,14] They are also used as precursors for α-oxoketene dithioacetals, α-oxoketene-*N*,*S*-acetals and α-oxoketene-*O*,*S*-acetals.[15] Reaction of enolizable carbonyl compounds with dialkyl trithiocarbonates in DMF using sodium hydride as base afforded β-oxodithiocarboxylates **1** in excellent yields within 1 h at room temperature. Treatment of the dithiocarboxylates **1** with ethyl glycinate in absolute alcohol in presence of triethyl amine at room temperature gave the thioamide **3** in nearly quatitative yields. The ^{1}H NMR spectrum of thioamide **3** in $CDCl_3$ shows two sets of peaks corresponding to the keto and enol forms. The thioamides **3** underwent facile alkylation in presence of potassium carbonate using alkyl iodide in acetone to give the *N*,*S*-acetal **4** in good yield. (Scheme 1). The ketene-*N*,*S*-acetals **4** thus generated were unstable in strongly basic medium and intractable mixture of products were formed during their attempted base catalyzed cyclization. However, in the presence of Vilsmeier–Haack reagent,[16] prepared from $POCl_3$ and DMF, they underwent iminoalkylation followed by intramolecular cyclization to afford substituted pyrroles **5** (Scheme 2). Interestingly the carbonyl group of the aroyl group rather than the iminium moiety was involved in the cyclization. Attempts to cyclize the *N*,*S*-acetal in presence of $POCl_3$ in THF or in the presence of other Lewis acid catalysts did not afford any cyclization product. When cyclization of the ketene *N*,*S*-acetals **4** was attempted by refluxing it in glacial acetic acid, partial

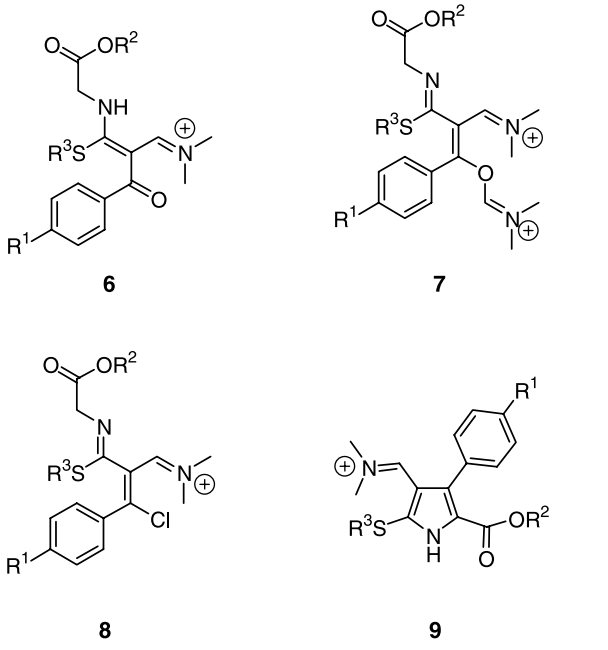


Scheme 2.



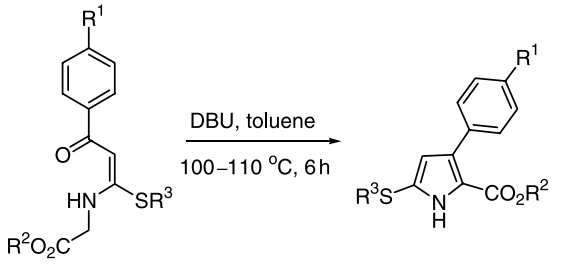
Scheme 3.

hydrolysis takes place leading to the formation of corresponding β-oxothiolesters.



The formation of pyrrole carbaldehydes **5** can be rationalized as follows. Sequential iminoalkylations of the ketene-*N*,*S*-acetal moiety and the enaminoketone functionality leads to the intermediate **6** and **7**, respectively. The chlorovinyl iminium salt **8** can be obtained by the displacement of *N*,*N*-dimethyl formamide by chloride ion from **7**. Cyclization of **8**, involving the imino acetate group and the chlorovinyl iminium moiety, leads to the formation of iminium salt **9**, which affords the pyrrole **5** on hydrolysis. The electron withdrawing nature of iminium salt moiety in **6** serve to increase the overall yields as it facilitates the cyclization. Vilsmeier–Haack reactions of β-oxodithiocarboxylates are known to afford β-chloro, β-methylthio α,β-unsaturated ketones.[17] Our efforts to synthesize pyrroles directly from thioamide **3** under Vilsmeier condition afforded complex product mixtures containing *N*,*N*-dimethylamino substituted pyrroles. Functionalized ketene-*N*,*S*-acetal **12** derived from cyclic carbonyl compounds like α-tetralone, which cannot iminoalkylate also underwent cyclization under Vilsmeier–Haack conditions to afford the annulated pyrrole **13** in 78% yield after heating at 80 °C for 7 h (Scheme 3).

Cyclization of the ketene *N*,*S*-acetals **4** was also examined under non nucleophilic bases. When **4** was heated in toluene in presence of DBU at 100–110 °C trisubstituted pyrroles **14** was formed in moderate yields (Scheme 4). The yield of **14** could be increased by adding DBU in three portions in equal intervals. The structure of **14** was confirmed on the basis of spectral and analytical data. In ^{1}H NMR, the single proton on the pyrrole ring appeared as a doublet at δ 6.39 (J= 3 Hz) ppm due to long range coupling with NH proton. Annulated pyrrole **13** was also formed in 56% yield when the *N*,*S*-acetal **12** derived from tetralone was heated in the presence of DBU for 8 h.



14a: R^1 = Cl, R^2 = CH_3, R^3 = C_2H_5 (34%)
14b: R^1 =H, R^2 = C_2H_5, R^3 = C_2H_5 (45%)
14c: R^1 = Cl, R^2 =C_2H_5, R^3 = CH_3 (32%)
14d: R^1 =Br, R^2 = C_2H_5, R^3 = C_2H_5 (28%)
14e: R^1 =CH_3, R^2 = CH_3, R^3 = CH_3 (24%)

Scheme 4.

In summary, we have developed straightforward and simple methods for the regiocontrolled formation of tetra and trisubstitued pyrroles starting from readily available and inexpensive dithioesters and glycine esters. The substitution pattern can be selectively tuned by the use of appropriately functionalized ketene-*N*,*S*-acetals. As an illustrative example, we have extended the scope of the cyclization procedure for the synthesis of a benzannulated isoindole ring system. The removable alkyl sulphanyl group present

on the pyrrole ring can extend the scope of this method for the synthesis of indoles, thienopyrroles, pyrridinopyrroles as well as isoquoline annulated pyrroles found in various natural products.

3. Experimental

3.1. General

Melting points are uncorrected and were obtained on a Buchi-530 melting point apparatus. Infrared spectra were recorded on Shimadzu JASCO FT/IR-5300 or ABB Bomem 104 spectrometer. Proton NMR spectra were recorded on a Bruker DRX-300 (300 MHz) spectrometer in $CDCl_3$. Chemical shifts are expressed in parts per million downfield from internal tetramethyl silane. Coupling constants J are given in Hertz. Mass spectra (EIMS) were obtained on a Finngen-Mat 312 instrument. Elemental analyses were recorded on an elementar vario EL III analyzer.

3.2. General procedure for the synthesis of dithio esters (1)

Sodium hydride (50% suspension in mineral oil, 0.96 g, 20 mmol) was washed with anhydrous petroleum ether and suspended in ice cooled anhydrous DMF (10 ml). To this was added the appropriate ketone (10 mmol) and stirred for 1 h, allowing the mixture to attain room temperature during this period. The reaction mixture was then poured over crushed ice (100 g) and extracted with diethyl ether (3× 50 mL). The organic layer was washed with water and dried using anhydrous Na_2SO_4. The solvent was removed in vacuum and the crude product was purified by passing through a short column of silica gel using hexane. The dithioesters prepared were characterized by comparing the spectral and physical data with reported values.[12]

3.3. General procedure for the synthesis of β-oxothio amides (3a–h)

Triethylamine (20 mmol) was added to a mixture of β-oxodithioester **1** (10 mmol) and glycine ester hydrochloride **2** (10 mmol) in appropriate dry alcohol (20 mL) at room temperature. After stirring for 4 h at room temperature the reaction mixture was poured into 100 mL of ice cold water. The reaction mixture was extracted with chloroform (3×50 mL), washed with water (2×25 mL), dried (Na_2SO_4) and evaporated to afford the crude product **3**, which were purified by recrystalizing from hexane–ethyl acetate (7/3).

3.3.1. Ethyl 2-{[3-(4-chlorophenyl)-3-oxopropanthioyl]-amino}acetate (3a). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.45 g, 10 mmol) with glycine ethylester hydrochloride (10 mmol) in ethanol. Yield 2.90 g (97%), mp 87–88 °C. IR (KBr) ν_{max}=3291, 1727, 1611, 1537, 1210, 1094, 818, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 1.32 ppm (t, 3H, J=7 Hz, OCH_2CH_3), 4.28 (m, 2H, OCH_2CH_3, keto and enol forms), δ 4.40 (d, 0.8H, J=4 Hz, NCH_2, enol form), δ 4.42 (d, 1.2H, J=4 Hz, NCH_2, keto form), δ 4.50 (s, 1.2H, methylene, keto form), 6.05 (s, 0.4H, vinylic, enol form), δ 7.39 (d, 0.4H, J=8 Hz, aromatic), δ 7.47 (d, 1H, J=8 Hz, aromatic+0.4H, N*H*, enol form), δ 7.72 (d, 0.4H, J=8 Hz, aromatic), 7.98 (d, 0.6H, J=8 Hz, aromatic), 9.50 (br s, 0.6H, NH, keto form) 14.36 (s, 0.4H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$)[18] δ=14.5, 48.1, 53.1, 62.5, 127.7, 129.6, 130.6, 141.2, 168.8, 192.1, 194.9. EIMS *m/z* (%) 301 (M^++2, 7), 299 (M^+, 18), 266 (12), 181 (17), 139 (100), 111 (54). Anal. Calcd for $C_{13}H_{14}ClNO_3S$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.15; H, 4.64; N, 4.71.

3.3.2. Ethyl 2-{[3-(4-methylphenyl)-3-oxopropanthioyl]-amino}acetate (3b). Obtained as pale yellow needles by the reaction of methyl 3-(4-methylphenyl)-3-oxopropanedithioate (2.24 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 2.60 g (96%), mp 120–121 °C. IR (KBr) ν_{max}=3316, 1751, 1668, 1535, 1218, 815 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 1.31 (t, 3H, J=7 Hz, CH_2CH_3), 2.42 (s, 3H, CH_3), 4.28 (q, 2H, J=7 Hz, CH_2CH_3), 4.41 (d, 0.6H, J=4 Hz, NCH_2, enol form), 4.44 (d, 1.4H, J=4 Hz, NCH_2, keto form), 4.51 (s, 1.4H, methylene, keto form), 6.08 (s, 0.3H, vinylic, enol form), 7.22 (d, 0.6H, J=8 Hz, aromatic) 7.28 (d, 1.4H, J=8 Hz, aromatic), 7.68 (d, 0.6H, J=8 Hz, aromatic) 7.93 (d, 1.4H, J=8 Hz, aromatic+0.3H, N*H*, enol form), 9.81 (br s, 0.7H, NH, keto form), 14.36 (s, 0.3H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 22.1, 48.1, 52.5, 62.5, 126.4, 129.2, 133.7, 145.8, 168.8, 192.3, 196.0. EIMS *m/z* (%) 279 (M^+, 22), 246 (15), 177 (12), 148 (13), 119 (100), 91 (54). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.07; H, 6.18; N, 5.12.

3.3.3. Ethyl 2-[(3-oxo-3-phenylpropanthioyl)amino]-acetate (3c). Obtained as pale yellow needles by the reaction of methyl 3-oxo-3-phenylpropanedithioate (2.1 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 2.5 g (97%), mp 82–83 °C. IR (KBr) ν_{max}=3292, 1724, 1609, 1538, 1208, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 1.33 (t, 3H, J=7 Hz, CH_2CH_3), 4.28 (q, 2H, J=7 Hz, CH_2CH_3), 4.41 (d, 0.6H, J=4 Hz, NCH_2, enol form), 4.45 (d, 1.4H, J=4 Hz, NCH_2, keto form), 4.54 (s, 1.4H, methylene, keto form), 6.10 (s, 0.3H, vinylic, enol form), 7.36–8.04 (m, 5.6H, aromatic+0.3 N*H* enol form), 9.66 (br s, 0.7H, N*H*, keto form), 14.35 (s, 0.3H, OH, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.0, 47.7, 52.4, 61.9, 126.4, 128.8, 134.2, 135.7, 168.4, 192.3, 195.8. EIMS *m/z* (%) 265 (M^+, 97), 232 (51), 163 (11), 121 (35), 105 (100). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.76; H, 5.61; N, 5.42.

3.3.4. Ethyl 2-{[3-(4-bromophenyl)-3-oxopropanthioyl]-amino}acetate (3d). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.80 g, 10 mmol) with glycine ethylester hydrochloride in ethanol. Yield 3.30 g (98%), mp 88–90 °C. IR (KBr) ν_{max}=3293, 1716, 1609, 1537, 1208, 766 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 1.32 ppm (t, 3H, J=7 Hz, OCH_2CH_3), 4.28 (m, 2H, OCH_2CH_3, keto and enol forms), δ 4.40 (d, 0.8H, J=4 Hz, NCH_2, enol form), δ 4.43 (d, 1.2H, J=4 Hz, NCH_2, keto form), δ 4.49 (s, 1.2H, methylene, keto form), 6.05 (s, 0.4H, vinylic, enol form), δ 7.37 (br s, 0.6H, N*H*, keto form), δ 7.54 (d, 0.6H, J=8 Hz, aromatic), δ 7.64 (d, 2.8H, J=8 Hz, aromatic), δ 7.91 (d, 0.6H, J=8 Hz, aromatic), 9.49 (br s, 0.4H, N*H*, enol form),

14.35 (s, 0.4H, O*H*, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 48.1, 52.9, 62.5, 127.9, 130.6, 132.6, 134.4, 168.6, 192.1, 195.2. EIMS *m/z* (%) 345 (M^++2, 22), 343 (M^+, 22), 312 (16), 243 (8), 183 (100), 155 (52) and 102 (12). Anal. Calcd for $C_{13}H_{14}BrNO_3S$: C, 45.36; H, 4.10; N, 4.07. Found: C, 45.44; H, 4.02; N, 4.21.

3.3.5. Methyl 2-[(3-oxo-3-phenylpropanthioyl)amino]-acetate (3e). Obtained as pale yellow needles by the reaction of ethyl 3-oxo-3-phenylpropanedithioate (2.10 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.40 g (96%), mp 90–92 °C. IR (KBr) ν_{max}=3301, 1726, 1609, 1537, 1211, 747 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=7:3; δ 3.82 (s, 2.1H, OCH_3 keto form), 3.84 (s, 0.9H, OCH_3, enol form), 4.44 (d, 0.6H, J=3 Hz, NCH_2 enol form), 4.48 (d, 1.4H, J=3 Hz, NCH_2 keto form), 4.55 (s, 1.4H, methylene, keto form), 6.09 (s, 0.3H, vinylic, enol form), 7.42–7.80 (m, 4.4H, aromatic+N*H* 0.3, keto form), 8.79 (d, 0.9H, J=8 Hz, aromatic), 9.72 (br s, 0.7H, N*H*, enol form), 14.35 (s, 0.3H, O*H*, enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=45.4, 47.9, 52.8, 126.4, 129.2, 131.4, 136.2, 169.3, 192.3, 196.4. EIMS *m/z* (%) 251 (M^+, 26), 236 (12), 187 (18), 149 (13), 105 (100) and 97 (44). Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57. Found: C, 57.46; H, 5.12; N, 5.68.

3.3.6. Methyl 2-{[3-(4-methylphenyl)-3-oxopropanthioyl]-amino}acetate (3f). Obtained as pale yellow needles by the reaction of methyl 3-(4-methylphenyl)3-oxopropanedithioate (2.24 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.5 g (95%), mp 110–111 °C. IR (KBr) ν_{max}=3314, 1726, 1611, 1211, 764 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=3:1; δ 2.39 (s, 0.75H, ArCH_3, enol form), 2.42 (s, 2.25H, ArCH_3, keto form), 3.82 (s, 3H, OCH_3), 4.43 (d, 0.5H, J=4 Hz, NCH_2, enol form), 4.45 (d, 1.5H, J=4 Hz, NCH_2, keto form), 4.52 (s, 1.5H, methylene, keto form), 6.10 (s, 0.25H, methyne, enol form), 7.22 (d, 0.5H, J=8 Hz, aromatic), 7.34 (d, 1.5H, J=8 Hz, aromatic), 7.68 (d, 0.5H, J=8 Hz, aromatic), 7.93 (1.5H, J=8 Hz, aromatic), 7.35 (br s, 0.75H, N*H*, keto form), 9.79 (br s, 0.25H, N*H*, enol form), 14.33 (s, 0.25H, O*H* enol form). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=21.1, 45.5, 47.9, 52.4, 129.2, 130.0, 133.7, 145.8, 169.2, 189.3, 196.0. EIMS *m/z* (%) 265 (M^+, 44), 232 (18), 204 (17), 177 (14), 144 (15), 119 (100) and (105). Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.94; H, 5.62; N, 5.19.

3.3.7. Methyl 2-{[3-(4-chlorophenyl)-3-oxopropanthioyl]-amino}acetate (3g). Obtained as pale yellow needles by the reaction of methyl 3-(4-chlorophenyl)-3-oxopropanedithioate (2.45 g, 10 mmol) with glycine methyl ester hydrochloride in methanol. Yield 2.7 g (97%), mp 80–81 °C. IR (KBr) ν_{max}=3340, 1736, 1611, 1513, 1204, 768 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=3:2; δ 3.80 (s, 1.8H, OCH_3, keto form), 3.81 (s, 1.2H, OCH_3, enol form), 4.42 (d, 0.8H, J=4.8 Hz, NCH_2, enol form), 4.45 (d, 1.2H, J=4 Hz, NCH_2, keto form), 4.50 (s, 1.2H, methylene, keto form), 6.09 (s, 0.4H, methyne, enol form), 7.36 (d, 0.8H, J=8 Hz, aromatic) 7.44 (d, 1.2H, J=8 Hz, aromatic), 7.68 (d, 0.8H, J=8.7 Hz, aromatic), 7.95 (d, 1.2H, J=8 Hz, aromatic), 9.51 (br s, 0.6H, N*H*, enol form), 14.31 (s, 0.4H, enol, O*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=45.7, 47.9, 53.1, 127.7, 129.6, 137.4, 141.3, 169.35, 192.2, 195.0. EIMS *m/z* (%) 287 (M^++2, 5), 285 (M^+, 16), 224 (18), 141 (24), 139 (100) and 111 (64). Anal. Calcd for $C_{12}H_{12}ClNO_3S$: C, 50.44; H, 4.23; N, 4.90. Found: C, 50.33; H, 4.34; N, 4.84.

3.3.8. Ethyl 2-{[3-(4-methoxyphenyl)-3-oxopropanthioyl]-amino}acetate (3h). Obtained as pale yellow needles by the reaction of ethyl 3-(4-methoxyphenyl)-3-oxopropane dithioate (2.4 g, 10 mmol) with glycine ethyl ester hydrochloride in ethanol. Yield 2.8 g (95%), mp 84–86 °C. IR (KBr) ν_{max}=3304, 1722, 1608, 1537, 1209, 771 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto form only δ 1.31 (t, 3H, J=6 Hz, OCH_2CH_3), 3.88 (s, 3H, ArOCH_3), 4.27 (q, 2H, J=6 Hz, CH_2CH_3), 4.44 (d, 2H, J=4 Hz, NCH_2), 4.48 (s, 2H, methylene), 6.94 (d, 2H, J=9 Hz, aromatic), 8.02 (d, 2H, J=9 Hz, aromatic), 9.81 (br s, 1H, N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 48.1, 52.4, 55.9, 62.2, 114.4, 129.1, 131.6, 164.8, 168.8, 194.7, 196.2. EIMS *m/z* (%) 295 (M^+, 34), 262 (15), 135 (100) and 121 (24). Anal. Calcd for $C_{14}H_{17}ClNO_4S$: C, 56.93; H, 5.80; N, 4.74. Found: C, 56.84; H, 5.89; N, 4.85.

3.3.9. Ethyl 2-{[(1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)carbothioyl]amino}acetate (11). Obtained as white needles by the reaction of methyl 1-oxo-1,2,3,4-tetrahydro-2-naphthalene-carbodithioate (2.3 g, 10 mmol) with glycine ethyl ester hydrochloride in ethanol. Yield 2.7 g (95%), mp 62–64 °C. IR (KBr) ν_{max}=3499, 3207, 1738, 1680, 1548, 1224, 785, 734 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), keto/enol=4:1; δ 1.29 (m, 3H, OCH_2CH_3, keto and enol forms), 2.68 (m, 2H, CH_2CH_2, keto and enol forms) 2.89 (m, 0.4H, CH_2CH_2, enol form), 3.05 (m, 0.8H, CH_2CH_2, keto form), 3.17 (m, 0.8H, CH_2CH_2, keto form), 3.76 (t, 0.8H, J=7 Hz, C*H*, keto form), 4.43 (m, 4H, OCH_2CH_3 and NCH_2, keto and enol forms), 6.16 (d, 0.2H, J=8 Hz, aromatic, enol form), 7.23–8.02 (m, 2.8H, aromatic, keto and enol forms), 7.90 (d, 0.2H, J=8 Hz, aromatic, enol form), 8.01 (d, 0.8H, J=8 Hz, aromatic, keto form), 9.27 (br s, 1H, N*H*), 14.76 (s, 0.2H, O*H*, enol). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 28.7, 30.1, 48.1, 59.6, 62.4, 127.2, 128.3, 129.1, 132.2, 134.6, 144.7, 169.1, 196.3, 200.6. EIMS *m/z* (%) 291 (M^+, 64), 273 (18), 240 (17), 187 (24), 145 (100), 128 (54), 115 (84) and 115 (34). Anal. Calcd for $C_{15}H_{17}NO_3S$: C, 61.83; H, 5.88; N, 4.81. Found: C, 61.95; H, 5.74; N, 4.89.

3.4. General procedure for the synthesis of alkyl 2-{[(*E*)-3-aryl-1-(alkylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4)

A suspension of the thioamide **3** (10 mmol) and anhydrous K_2CO_3 (3 g, 20 mmol) in dry acetone (30 ml) was refluxed with stirring for 30 min. The mixture was cooled and alkyl iodide (20 mmol) was added and again stirred at room temperature for 3 h. When the reaction was completed (TLC), the mixture was poured into ice-cold water (100 mL) and extracted using dichloromethane (2×50 mL). The organic layer was washed with water (2×100 mL) and dried using anhydrous Na_2SO_4. Evaporation of the solvent afforded a yellow glass, which solidifies on standing. Recrystallisation of the crude product from hexane–ethyl acetate (7/3) afforded title compound **4** in 88–95% yields.

3.4.1. Ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4a). Obtained

as yellow prisms by the methylation of ethyl 2-{[(3-4-chlorophenyl)-3-oxopropanthioyl]amino}acetate **3a** (2.60 g, 10 mmol) using methyl iodide. Yield 2.90 g (95%), mp 96–98 °C. IR (KBr) ν_{max}=3072, 1744, 1559, 1533, 1470, 1203, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, J=7 Hz, CH_2CH_3), 2.49 (s, 3H, SCH_3), 4.17 (d, 2H, J=5 Hz, NCH_2), 4.27 (q, 2H, J=7 Hz, CH_2CH_3), 5.68 (s, 1H, vinylic), 7.37 (d, 2H, J=8 Hz, aromatic), 7.80 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 14.9, 45.8, 62.2, 87.8, 128.2, 128.8, 137.1, 139.1, 168.8, 169.5, 184.9. EIMS *m/z* (%) 315 (M^++2), 313 (M^+, 23), 266 (36), 238 (25), 181 (24), 139 (100), 111 (43). Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.58; H, 5.14; N, 4.46. Found: C, 53.74; H, 5.03; N, 4.32.

3.4.2. Ethyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4b). Obtained as yellow prisms by the methylation of ethyl 2-{[(3-4-methylphenyl)-3-oxopropanthioyl]amino}acetate **3b** (2.70 g, 10 mmol) using methyl iodide. Yield 2.70 g (92%), mp 110–111 °C. IR (KBr) ν_{max}=2994, 1744, 1588, 1544, 1210, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, J=7 Hz, CH_2CH_3), 2.37 (s, 3H, $ArCH_3$), 2.42 (s, 3H, SCH_3), 4.15 (d, 2H, J=5 Hz, NCH_2), 4.25 (q, 2H, J=7 Hz, OCH_2CH_3), 5.72 (s, 1H, vinylic), 7.2 (d, 2H, J=8 Hz, aromatic), 7.78 (d, 2H, J=8 Hz, aromatic), 11.96 (br s, 1H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ=14.5, 14.9, 21.8, 45.8, 62.1, 88.0, 127.5, 129.3, 138.0, 141.4, 168.7, 168.9, 186.3. EIMS *m/z* (%) 293 (M^+, 27), 246 (37), 218 (15), 172 (19), 161 (14), 119 (100) and 91 (52). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.28; H, 6.65; N, 4.62.

3.4.3. Ethyl 2-{[(*E*)-1-(methylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate (4c). Obtained as yellow prisms by the methylation of ethyl 2-[(3-oxo-3-phenylpropanthioyl)-amino]acetate **3c** (2.7 g, 10 mmol) using methyl iodide. Yield 2.6 g (93%), mp 90–92 °C. IR (KBr) ν_{max}=3074, 1745, 15568, 1523, 1205, 727 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7 Hz, OCH_2CH_3), 2.48 (s, 3H, SCH_3), 4.17 (d, 2H, J=5 Hz, NCH_2), 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.73 (s, 1H, vinylic), 7.36–7.45 (m, 3H, aromatic), 7.85–7.89 (dd, 2H, aromatic), 11.98 (br s, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.5, 14.9, 45.8, 62.1, 88.2, 127.8, 128.6, 131.1, 140.7, 168.9, 169.1, 186.4. EIMS *m/z* (%) 279 (M^+, 17), 232 (35), 204 (15), 176 (8), 147 (24) and 105 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.07; H, 6.26; N, 4.87.

3.4.4. Ethyl 2-{[(*E*)-3-(4-bromophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4d). Obtained as yellow prisms by the ethylation of ethyl 2-{[(3-4-bromophenyl)-3-oxopropanthioyl]amino}acetate **3d** (3.40 g, 10 mmol) using ethyl iodide. Yield 3.50 g (95%), mp 97–98 °C. IR (KBr) ν_{max}=3093, 1750, 1587, 1526, 1210, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, J=7 Hz, SCH_2CH_3), 1.42 (t, 3H, J=7 Hz, OCH_2CH_3), 3.02 (q, 2H, J=7 Hz, SCH_2CH_3), 4.17 (d, 2H, J=3 Hz, NCH_2) 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.73 (s, 1H, vinylic), 7.53 (d, 2H, J=8 Hz, aromatic), 7.72 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, –NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.9, 14.5, 26.5, 45.8, 62.1, 88.5, 125.5, 129.0, 131.7, 139.6, 168.7, 168.8, 184.9. EIMS *m/z* (%) 373 (M^++2, 18), 371 (M^+, 17), 345 (15), 310 (19), 282 (14), 183 (100), 157 (42) and 102 (11). Anal. Calcd for $C_{15}H_{18}BrNO_3S$: C, 48.39; H, 4.87; N, 3.76. Found: C, 48.22; H, 5.97; N, 3.96.

3.4.5. Methyl 2-{[(*E*)-1-(ethylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate (4e). Obtained as yellow prisms by the ethylation of methyl 2-[(3-oxo-3-phenylpropanthioyl)-amino]acetate **3e** (2.50 g, 10 mmol) using ethyl iodide as a yellow glass. Yield 2.40 g (91%). ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, J=7 Hz, SCH_2CH_3), 3.80 (s, 3H, OCH_3), 3.01 (q, 2H, J=7 Hz, SCH_2CH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.37–7.44 (m, 3H, aromatic), 7.83–7.88 (m, 2H, aromatic), 12.09 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.8, 15.3, 46.0, 54.3, 88.6, 126.7, 129.2, 130.5, 136.3, 169.1, 171.4, 185.9. EIMS *m/z* (%) 279 (M^+, 22), 251 (17), 218 (23), 190 (28), 158 (14) and 105 (100). Anal. Calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.05; H, 6.23; N, 5.15.

3.4.6. Methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4f). Obtained as yellow prisms by the ethylation of methyl 2-{[(3-4-methylphenyl)-3-oxopropanthioyl]amino}acetate **3f** (2.60 g, 10 mmol) using ethyl iodide. Yield 2.70 g (92%), mp 90–91 °C. IR (KBr) ν_{max}=2932, 1742, 1589, 1555, 1243, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.41 (t, 3H, J=7 Hz, SCH_2CH_3), 2.38 (s, 3H, $ArCH_3$), 3.79 (s, 3H, OCH_3), 3.00 (q, 2H, J=7 Hz, SCH_2CH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.20 (d, 2H, J=8 Hz, aromatic), 7.76 (d, 2H, J=8 Hz, aromatic), 11.99 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.4, 21.3, 26.1, 45.2, 52.5, 88.5, 127.0, 128.8, 137.5, 140.9, 167.3, 169.0, 185.9. EIMS *m/z* (%) 293 (M^+, 27), 265 (15), 232 (39), 172 (8), 119 (100) and 105 (12). Anal. Calcd for $C_{15}H_{19}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.28; H, 6.45; N, 4.92.

3.4.7. Methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate (4g). Obtained yellow prisms by the ethylation of methyl 2-{[(3-4-chlorophenyl)-3-oxopropanthioyl]amino}acetate **3g** (2.80 g, 10 mmol) using ethyl iodide. Yield 3 g (94%), mp 94–95 °C. ν_{max}=3063, 2965, 1744, 1575, 1285, 755 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.42 (t, 3H, J=7 Hz, SCH_2CH_3), 3.02 (q, 2H, J=7 Hz, SCH_2CH_3), 3.80 (s, 3H, OCH_3), 4.20 (d, 2H, J=3 Hz, NCH_2), 5.79 (s, 3H, vinylic), 7.20 (d, 2H, J=8 Hz, aromatic), 7.76 (d, 2H, J=8 Hz, aromatic), 12.02 (br s, 1H, NH). ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=13.8, 26.5, 45.7, 52.0, 88.6, 128.3, 128.8, 137.1, 139.0, 168.6, 169.3, 184.9. EIMS *m/z* (%) 315 (M^++2, 9), 313 (M^+, 28) 285 (14), 252 (32), 224 (30), 192 (7), 139 (100) and 115 (42). Anal. Calcd for $C_{14}H_{16}ClNO_3S$: C, 53.58; H, 5.14; N, 4.46. Found: C, 53.45; H, 5.25; N, 4.34.

3.4.8. Ethyl 2-{[(*E*)-1-(ethylsulfanyl)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]amino}acetate (4h). Obtained as yellow prisms by the ethylation of ethyl 2-{[3-(4-methoxyphenyl)-3-oxopropanthioyl]amino}acetate **3h** (2.90 g, 10 mmol) using ethyl iodide. Yield 2.8 g (88%), mp 105–106 °C. IR (KBr) ν_{max}=3085, 1748, 1521, 1466, 1245, 770 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, J=7 Hz, SCH_2CH_3), 1.41 (t, 3H, J=7 Hz, OCH_2CH_3), 3.01 (q, 2H, J=7 Hz, SCH_2CH_3), 3.84 (s, 3H, $ArOCH_3$), 4.17 (d, 2H, J=3 Hz, NCH_2) 4.27 (q, 2H, J=7 Hz, OCH_2CH_3), 5.77 (s, 1H, vinylic), 6.90 (d, 2H, J=8 Hz, aromatic), 7.85

(d, 2H, $J=8$ Hz, aromatic), 11.92 (br s, 1H, –N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=13.9$, 14.5, 26.5, 45.8, 55.6, 62.0, 88.6, 113.7, 129.2, 133.3, 162.1, 167.3, 169.1, 185.6. EIMS *m/z* (%) 323 (M^+, 17), 262 (25), 234 (9), 188 (18), 135 (100) and 121 (22). Anal. Calcd for $C_{16}H_{21}NO_4S$: C, 59.42; H, 6.54; N, 4.33. Found: C, 59.57; H, 6.39; N, 4.43.

3.4.9. Ethyl 2-({methylsulfanyl)[1-oxo-3,4-dihydro-2(1*H*)-naphthalenyliden]amino}acetate (12). Obtained as white prisms by the methylation of ethyl 2-{[(1-oxo-1,2,3,4-tetrahydro-2-naphthalenyl)carbothioyl]amino}acetate **11** (2.90 g, 10 mmol) using methyl iodide. Yield 2.8 g (88%), mp 132–134 °C. IR (KBr) $\nu_{max}=2986$, 1736, 1315, 1022, 744 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.33 (s, 3H, SCH_3), 2.86 (m, 2H, CH_2), 2.97 (m, 2H, CH_2), 4.27 (q, 2H, $J=7$ Hz, OCH_2CH_3), 4.33 (s, 2H, NCH_2), 7.26–7.38 (m, 3H, aromatic), 8.08 (d, 1H, $J=8$ Hz, aromatic), 13.40 (br s, N*H*). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 18.0, 27.7, 29.9, 47.3, 61.8, 108.0, 126.9, 127.3, 127.7, 131.7, 135.9, 142.1, 162.4, 170.4, 186.1. EIMS *m/z* (%) 305 (M^+, 24), 258 (78), 228 (23), 184 (72), 173 (100), 128 (58), 115 (92) and 105 (34). Anal. Calcd for $C_{16}H_{19}NO_3S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.78; H, 6.37; N, 4.42.

3.5. General procedure for the synthesis of alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates (5)

Vilsmeier reagent was prepared by mixing ice cold, dry DMF (25 mL) and $POCl_3$ (2 mL, 20 mmol). The mixture was then stirred for 30 min at room temperature. The *N*,*S*-acetal **4** (3.25 g, 10 mmol) was dissolved in dry DMF (10 mL) and added to the Vilsmeier reagent keeping the temperature at 0–5 °C. The reaction mixture was stirred for 6 h at room temperature, heated to 80 °C for 1 h with stirring and was cooled and poured into cold, aqueous saturated K_2CO_3 (200 mL). It was then extracted with diethyl ether (3×50 mL). The organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to afford the crude product, which was chromatographed over silica gel using hexane–ethylacetate (4/1) as eluent to give alkyl 3-aryl-4-formyl-5-(alkylsulfanyl)-1*H*-pyrrole-2-carboxylates **5**.

3.5.1. Ethyl 3-(4-chlorophenyl)-4-formyl-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (5a). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4a** (3.13 g, 10 mmol) as colorless plates. Yield 2.91 g (90%), mp 118–119 °C. IR (KBr) $\nu_{max}=3234$, 1660, 1539, 1249, 1170, 1018, 835, 794, 725 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.62 (s, 3H, SCH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.33 (d, 2H, $J=8$ Hz, aromatic), 7.38 (d, 2H, $J=8$ Hz, aromatic) 9.43 (br s, 1H, N*H*), 9.62 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.3$, 15.5, 61.3, 120.7, 123.0, 128.2, 130.4, 132.2, 133.7, 134.4, 138.9, 160.8, 186.3; EI-MS *m/z* (%)= 325 ($M^+ +2$, 39) 323 (M^+, 100), 276 (38), 244 (20), 216 (42), 179 (20), 161 (5), 113 (3). Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33. Found: C, 55.50; H, 4.48; N, 4.42.

3.5.2. Ethyl 4-formyl-3-(4-methylphenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (5b). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4b** (2.93 g, 10 mmol) as colorless plates. Yield 2.60 g (87%), mp 108–109 °C. IR (KBr) $\nu_{max}=3378$, 1670, 1640, 1233, 1162, 1020, 799, 776 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 2.61 (s, 3H, SCH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.20 (d, 2H, $J=8$ Hz, aromatic), 7.29 (d, 2H, $J=8$ Hz, aromatic) 9.43 (br s, 1H, N*H*), 9.63 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.4$, 15.3, 21.1, 61.1, 120.3, 123.1, 128.6, 128.7, 130.8, 135.5, 138.2, 138.3, 160.9, 186.8; EI-MS *m/z* (%)=303 (M^+, 100), 257, 256 (33), 224 (27), 196 (31), 159 (15), 115 (9). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.18; H, 5.52; N, 4.73.

3.5.3. Ethyl 4-formyl-5-(methylsulfanyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (5c). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-1-(methylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate **4c** (2.80 g, 10 mmol) as colorless plates. Yield 2.54 g (88%), mp 119–120 °C. IR (KBr) $\nu_{max}=3247$, 1692, 1655, 1549, 1247, 1173, 1021, 795 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.04 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.55 (s, 3H, SCH_3), 4.11 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.32 (m, 5H, aromatic) 9.34 (br s, 1H, N*H*), 9.55 (s, 1H, C*H*O). ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=13.9$, 15.1, 60.8, 120.2, 123.0, 127.6, 128.0, 130.6, 131.5, 134.9, 137.7, 160.6, 186.2; EI-MS *m/z* (%)=289 (M^+, 90), 288 (84), 242 (76), 214 (33), 181 (100), 171 (23), 144 (71). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.12; H, 4.70; N, 4.95.

3.5.4. Ethyl 3-(4-bromophenyl)-5-(ethylsulfanyl)-4-formyl-1*H*-pyrrole-2-carboxylate (5d). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-3-(4-bromophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4d** (3.70 g, 10 mmol) as colorless plates. Yield 3.4 g (89%), mp 148–149 °C. IR (KBr) $\nu_{max}=3254$, 1673, 1538, 1418, 1234, 1013, 777 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, $J=7$ Hz, OCH_2CH_3), 1.37 (t, 3H, $J=7$ Hz, SCH_2CH_3), 3.06 (q, 2H, $J=7$ Hz, SCH_2CH_3), 4.19 (q, 2H, $J=7$ Hz, OCH_2CH_3), 7.26 (d, 2H, $J=8$ Hz, aromatic), 7.53 (d, 2H, $J=8$ Hz, aromatic) 9.74 (br s, 1H, N*H*), 9.85 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.2$, 27.3, 51.7, 119.9, 123.8, 127.7, 128.0, 130.4, 131.3, 134.8, 135.9, 160.8, 186.3, 186.4; EI-MS *m/z* (%)=383 ($M^+ +2$, 100) 381 (M^+, 96), 350 (84), 348 (84), 302 (72), 304 (70), 276 (24), 274 (23), 225 (29), 223 (38), 199 (17), 144 (16). Anal. Calcd for $C_{16}H_{16}BrNO_3S$: C, 50.27; H, 4.22; N, 3.66. Found: C, 50.45; H, 4.11; N, 3.52.

3.5.5. Methyl 5-(ethylsulfanyl)-4-formyl-3-phenyl-1*H*-pyrrole-2-carboxylate (5e). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-1-(ethylsulfanyl)-3-oxo-3-phenyl-1-propenyl]amino}acetate **4e** (2.65 g, 10 mmol) as colorless plates. Yield 2.36 g (82%), mp 86–87 °C. IR (KBr) $\nu_{max}=3358$, 1682, 1651, 1539, 1386, 1233, 1154, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, $J=7$ Hz, SCH_2CH_3), 3.08 (q, 2H, $J=7$ Hz, SCH_2CH_3), 3.69 (s, 3H, OCH_3), 7.39 (m, 5H, aromatic), 9.69 (s, 1H, C*H*O), 9.72 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=$

14.8, 28.4, 61.4, 120.6, 122.6, 124.4, 130.9, 131.0, 132.5, 133.0, 136.3, 160.7, 186.4; EI-MS *m/z* (%)=289 (M^+, 78), 256 (76), 224 (100), 196 (39), 172 (16), 145 (60), 102 (11). Anal. Calcd for $C_{15}H_{15}NO_3S$: C, 62.26; H, 5.23; N, 4.84. Found: C, 62.08; H, 5.38; N, 4.71.

3.5.6. Methyl 4-formyl-3-(4-methylphenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (5f). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4f** (2.93 g, 10 mmol) as colorless plates. Yield 2.45 g (85%), mp 108–109 °C. IR (KBr) ν_{max}=3155, 1717, 1642, 1563, 1510, 1260, 1151, 1098, 778 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, 3H, *J*=7 Hz, SCH_2CH_3), 2.40 (s, 3H, $ArCH_3$), 3.09 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.72 (s, 3H, OCH_3), 7.21 (d, 2H, *J*=8 Hz, aromatic), 7.29 (d, 2H, *J*=8 Hz, aromatic) 9.71 (s, 1H, C*H*O), 9.79 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.6, 21.7, 27.7, 52.1, 120.2, 124.2, 128.6, 128.8, 130.7, 135.4, 136.3, 138.2, 161.2, 187.0; EI-MS *m/z* (%)=303 (M^+, 88), 270 (55), 238 (100), 210 (35), 186 (10), 159 (36), 128 (6), 115 (16). Anal. Calcd for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62. Found: C, 63.48; H, 5.54; N, 4.47.

3.5.7. Methyl 3-(4-chlorophenyl)-5-(ethylsulfanyl)-4-formyl-1*H*-pyrrole-2-carboxylate (5g). Obtained by the Vilsmeier reaction of methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4g** (3.1 g, 10 mmol) as colorless plates. Yield 2.8 g (88%), mp 128–129 °C. IR (KBr) ν_{max}=3124, 1696, 1649, 1439, 1242, 1084, 878, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (t, 3H, *J*=7 Hz, SCH_2CH_3), 3.07 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.71 (s 3H, OCH_3), 7.32 (d, 2H, *J*=8 Hz, aromatic), 7.36 (d, 2H, *J*=8 Hz, aromatic), 9.74 (s, 1H, C*H*O), 10.13 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.7, 28.2, 52.2, 120.7, 124.3, 128.4, 130.3, 132.1, 133.8, 134.5, 136.7, 161.0, 186.5; EI-MS *m/z* (%)=325 (M^++2, 37) 323 (M^+, 93), 290 (94), 258 (100), 230 (31), 207 (12), 179 (52), 144 (9), 113 (5). Anal. Calcd for $C_{15}H_{14}ClNO_3S$: C, 55.64; H, 4.36; N, 4.33. Found: C, 55.48; H, 5.50; N, 4.12.

3.5.8. Ethyl (5-ethylsulfanyl)-4-formyl-3-(4-methoxyphenyl)-1*H*-pyrrole-2-carboxylate (5h). Obtained by the Vilsmeier reaction of ethyl 2-{[(*E*)-1-(ethylsulfanyl)-3-(4-methoxyphenyl)-3-oxo-1-propenyl]amino}acetate **4h** (3.2 g, 10 mmol) as colorless plates. Yield 2.9 g (88%), mp 92–93 °C. IR (KBr) ν_{max}=3247, 1661, 1509, 1247, 1176, 1034, 816, 781 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (t, 3H, *J*=7 Hz, SCH_2CH_3), 1.42 (t, 3H, *J*=7 Hz, OCH_2CH_3), 3.12 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.90 (s, 3H, $ArOCH_3$), 4.26 (q, 2H, *J*=7 Hz, OCH_2CH_3), 6.98 (d, 2H, *J*=8 Hz, aromatic), 7.38 (d, 2H, *J*=8 Hz, aromatic), 9.61 (br s, 1H, N*H*), 9.77 (s, 1H, C*H*O) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.0, 14.3, 27.7, 55.2, 60.8, 113.1, 120.3, 123.7, 124.2, 131.8, 134.4, 135.4, 159.5, 160.5, 186.5; EI-MS *m/z* (%)=333 (M^+, 63), 300 (23), 254 (100), 226 (41), 174 (55), 158 (16), 132 (24). Anal. Calcd for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.39; H, 5.92; N, 4.07.

3.5.9. Ethyl 3-(methylsufanyl)-4,5-dihydro-2*H*-benzo(*e*)-isoindole-1-carboxylate (13). Obtained by the Vilsmeier reaction of ethyl 2-({methylsulfanyl)[1-oxo-3,4-dihydro-2(1*H*)naphthalenyliden]amino}acetate **12** (3 g, 10 mmol) as colorless plates. Yield 2 g (78%), mp 131–133 °C. IR (KBr) ν_{max}=3271, 3057, 2986, 1660, 1412, 1209, 1020, 761 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.40 (t, 3H, *J*=7 Hz, OCH_2CH_3), 2.33 (s, 3H, SCH_3), 2.68 (t, 2H, *J*=6 Hz, CH_2CH_2), 2.85 (t, 2H, *J*=6 Hz, CH_2CH_2), 4.38 (q, 2H, *J*=7 Hz, OCH_2CH_3), 7.21 (m, 3H, aromatic), 8.40 (d, 1H, *J*=7 Hz, aromatic), 9.15 (br s, 1H, N*H*) ppm. ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.8, 20.1, 20.8, 31.1, 61.0, 118.7, 122.5, 126.8, 127.4, 127.6, 127.8, 128.4, 128.8, 130.9, 137.8, 160.8 ppm. EI-MS *m/z* (%)=287 (M^+, 94), 241 (56), 213 (43), 198 (72), 179 (100), 167 (32), 127 (35), 109 (18). Anal. Calcd for $C_{16}H_{17}NO_2S$: C, 66.87; H, 5.96; N, 4.87. Found: C, 66.72; H, 6.08; N, 4.72.

3.6. General procedure for the base catalyzed cyclization of β-oxoketene-*N*,*S*-acetals (14)

A solution of ketene-*N*,*S*-acetal **4** (10 mmol) in dry toluene (15 mL) was heated at 100–110 °C for 3 h. During this period DBU (20 mmol) was added in three equal portions to the reaction mixture. After the completion of the reaction (TLC), toluene was evaporated under reduced pressure and the residue was dissolved in dichloromethane, washed with 5% HCl (2×20 mL), then with saturated bicarbonate (2×20 mL) and finally with water (2×50 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a dark brown oil, which on column chromatography using hexane–ethyl acetate (9/1) as eluent afforded moderated yields of the 3-aryl pyrrole-2-carboxylates **14**.

3.6.1. Methyl 3-(4-chlorophenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (14a). Obtained by the cyclization of methyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4a** (3.10 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1 g (34%), mp 138–139 °C. IR (KBr) ν_{max}=3297, 1673, 1447, 1262, 1002, 816, 732 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (t, 3H, *J*=7 Hz, SCH_2CH_3), 2.81 (q, 2H, *J*=7 Hz, SCH_2CH_3), 3.78 (s, 3H, OCH_3), 6.39 (d, 1H, *J*=3 Hz, pyrrole C*H*), 7.33 (d, 2H, *J*=8 Hz, aromatic), 7.46 (d, 2H, *J*=8 Hz, aromatic), 9.26 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=15.6, 31.2, 51.8, 118.3, 119.7, 126.6, 128.3, 131.0, 133.4, 133.5, 161.0; EI-MS *m/z* (%)=297 (M^++2, 35) 295 (M^+, 91), 235 (92), 206 (56), 167 (78), 149 (67), 129 (100), 111 (42). Anal. Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.74. Found: C, 56.68; H, 4.88; N, 4.82.

3.6.2. Ethyl 5-(ethylsulfanyl)-3-phenyl-1*H*-pyrrole-2-carboxylate (14b). Obtained by the cyclization of ethyl 2-{[(*E*)-3-phenyl-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4b** (2.90 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1.2 g (45%), mp 63–64 °C. IR (KBr) ν_{max}=3292, 1678, 1426, 1265, 1016, 822, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.28 (m, 6H, *J*=7 Hz, SCH_2CH_3+OCH_2CH_3), 2.80 (q, 2H, *J*=7 Hz, SCH_2CH_3), 4.26 (q, 2H, *J*=7 Hz, OCH_2CH_3), 6.42 (d, 1H, *J*=3 Hz, pyrrole C*H*), 7.31 (m, 3H, *J*=7.8 Hz, aromatic), 7.53 (d, 2H, *J*=7 Hz, aromatic), 9.38 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) δ=14.1, 15.1, 30.8, 60.4, 118.2, 119.6, 125.6, 127.0, 127.6, 129.4, 132.9, 134.5, 160.5; EI-MS *m/z* (%)=275 (M^+, 92), 232 (84), 168 (52), 147 (54), 115 (19) and 105 (100). Anal. Calcd for $C_{15}H_{17}NO_2S$: C, 65.43; H, 6.22; N, 5.09. Found: C, 65.62; H, 6.08; N, 5.22.

3.6.3. Ethyl 3-(4-chlorophenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (14c). Obtained by the cyclization of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4c** (3.10 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 0.94 g (32%), mp 129–130 °C. IR (KBr) $\nu_{max}=3275$, 1672, 1493, 1259, 1087, 815, 733 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (t, 3H, $J=7$ Hz, OCH_2CH_3), 2.47 (s, 3H, SCH_3), 4.23 (q, 2H, $J=7$ Hz, OCH_2CH_3), 6.33 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.31 (d, 2H, $J=7$ Hz, aromatic), 7.46 (d, 2H, $J=7$ Hz, aromatic), 9.22 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 19.8, 60.91, 116.0, 119.6, 128.2, 128.6, 131.1, 132.2, 133.4, 160.6; EI-MS *m/z* (%)=297 ($M^+ +2$, 35) 295 (M^+, 91), 249 (72), 221 (100), 206 (33), 187 (26), 149 (48), 136 (38). Anal. Calcd for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.74. Found: C, 56.68; H, 4.88; N, 4.87.

3.6.4. Ethyl 3-(4-bromophenyl)-5-(ethylsulfanyl)-1*H*-pyrrole-2-carboxylate (14d). Obtained by the cyclization of ethyl 2-{[(*E*)-3-(4-chlorophenyl)-1-(ethylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4d** (3.70 g, 10 mmol) in presence of DBU (20 mmol) as colorless plates. Yield 1 g (28%), mp 110–111 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 1.27 (m, 6H, $J=7$ Hz, $SCH_2CH_3+OCH_2CH_3$), 2.81 (q, 2H, $J=7$ Hz, SCH_2CH_3), 4.26 (q, 2H, $J=7$ Hz, OCH_2CH_3), 6.44 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.13 (d, 2H, $J=7$ Hz, aromatic), 7.20 (d, 2H, $J=7$ Hz, aromatic), 9.38 (br s, 1H, N*H*) ppm. ^{13}C NMR (75.47 MHz, $CDCl_3$) $\delta=14.6$, 15.6, 31.3, 61.0, 118.3, 120.0, 121.6, 126.4, 131.1, 131.5, 132.1, 133.9 and 160.7; EI-MS *m/z* (%)=355 ($M^+ +2$, 31) 353 (M^+, 94), 294 (75), 249 (100), 230 (25), 181 (36), 157 (78). Anal. Calcd for $C_{15}H_{16}BrNO_2S$: C, 50.86; H, 4.55; N, 3.95. Found: C, 50.98; H, 4.68; N, 3.80.

3.6.5. Methyl 3-(4-methylphenyl)-5-(methylsulfanyl)-1*H*-pyrrole-2-carboxylate (14e). Obtained by the cyclization of methyl 2-{[(*E*)-3-(4-methylphenyl)-1-(methylsulfanyl)-3-oxo-1-propenyl]amino}acetate **4e** (2.80 g, 10 mmol) as colorless plates. Yield 0.62 g (24%), mp 120–121 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 2.17 (s, 3H, $ArCH_3$), 2.46, (s 3H, SCH_3), 3.77 (s, 3H, OCH_3), 6.34 (d, 1H, $J=3$ Hz, pyrrole C*H*), 7.17 (d, 2H, $J=8$ Hz, aromatic), 7.42 (d, 2H, $J=8$ Hz, aromatic), 9.09 (br s, 1H, N*H*) ppm. EI-MS *m/z* (%)=261 (M^+, 100), 229 (48), 201 (83), 186 (58), 168 (34), 115 (38) and 100 (16). Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.79; N, 5.36. Found: C, 64.18; H, 5.88; N, 5.52.

Acknowledgements

This work was supported by Kerala State CSTE and CSIR New Delhi (Project No. 01(1954)/04/EMR-II). We thank MK University, Madurai for providing spectral and analytical data. P.M. thanks the UGC for assistance under the Faculty Improvement Program.

References and notes

1. Sundberg, R. J. In Katritzky, A., Rees, C. W., Scriven, E. F. V., Eds.; Comprehensive Heterocyclic Chemistry; Pergamon: Oxford, 1996; Vol. 2, pp 119–206.
2. (a) Tao, H.; Hwang, I.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5979–5981. (b) Boger, D. L.; Boyce, C. W.; Labroli, M. A.; Sehon, C. A.; Jin, Q. *J. Am. Chem. Soc.* **1999**, *121*, 54–62.
3. (a) Baumgarten, M.; Tyutyulkov, N. *Chem. Eur. J.* **1998**, *4*, 987–989. (b) Deronzier, A.; Moutet, J.-C. *Curr. Top. Electrochem.* **1994**, *3*, 159–200. (c) Pagani, G. A. *Heterocycles* **1994**, *37*, 2069–2086.
4. (a) Paal, C. *Ber.* **1885**, *18*, 367–371. (b) Knorr, L. *Ber.* **1885**, *18*, 299–311.
5. Hantzsch, A. *Ber.* **1890**, *23*, 1474–1483.
6. (a) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238–6241. (b) Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* **2003**, *68*, 7853–7861. (c) Ooi, T.; Ohmatsu, K.; Ishii, H.; Saito, A.; Maruoka, K. *Tetrahedron Lett.* **2004**, *45*, 9315–9317. (d) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (e) Quiclet-Sire, B.; Quintero, L.; Sanchez-Jimenez, G.; Zard, S. Z. *Synlett* **2003**, 75–78. (f) Ranu, B. C.; Dey, S. S. *Tetrahedron Lett.* **2003**, *44*, 2865–2868.
7. Mathew, P.; Asokan, C. V. *Tetrahedron Lett.* **2005**, *46*, 475–478.
8. (a) Chakrabarti, S.; Panda, K.; Misra, N. C.; Ila, H.; Junjappa, H. *Synlett* **2005**, 1437–1441. (b) Venkatesh, C.; Singh, B.; Mahata, P. K.; Ila, H.; Junjappa, H. *Org. Lett.* **2005**, *7*, 2169–2172.
9. Suma, S.; Ushakumari, N. K.; Asokan, C. V. *Phosphorus, Sulfur Silicon Relat. Elem.* **1997**, *131*, 161–171.
10. Bailly, C. *Curr. Med. Chem. Anti-Canc. Agents* **2004**, *4*, 363–378.
11. Roth, B. D. *Prog. Med. Chem.* **2002**, *40*, 1–22.
12. Singh, G.; Bhattacharjee, S. S.; Ila, H.; Junjappa, H. *Synthesis* **1982**, 693–694.
13. (a) Junjappa, H.; Ila, H.; Asokan, C. V. *Tetrahedron* **1990**, *46*, 5423–5506. (b) Roy, A.; Nandi, S.; Ila, H.; Junjappa, H. *Org. Lett.* **2001**, *3*, 229–232.
14. (a) Tominaga, Y.; Okuda, H.; Kohra, S.; Mazume, H. *J. Heterocycl. Chem.* **1991**, *5*, 245. (b) Bouillon, J. P.; Shermolovich, Y. G.; Portella, C. *Tetrahedron Lett.* **2001**, *42*, 2133–2135.
15. Ila, H.; Junjappa, H.; Mohanta, P. K. In Gribble, G. W., Gilchrist, T. L., Eds.; Progress in Heterocyclic Chemistry; Pergamon: New York, 2001; Vol. 13, Chapter 1, p 1.
16. (a) Cheng, Y.; Liu, Q.-X.; Meth-Cohn, O. *Tetrahedron Lett.* **2000**, *41*, 3475–3478. (b) Thomas, A. D.; Josemin; Asokan, C. V. *Tetrahedron* **2004**, *60*, 5069–5076.
17. Suma, S.; Asokan, C. V. *Synth. Commun.* **1996**, *26*, 847–853.
18. ^{13}C NMR spectra of compound **3** showed signals of keto and enol tautomers. The values given are of the major tautomer.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1717–1725

Domino Mukaiyama–Michael reactions in the synthesis of polycyclic systems

Florence C. E. Sarabèr,[a] Svetlana Dratch,[b] Geke Bosselaar,[a] Ben J. M. Jansen[a] and Aede de Groot[a,*]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220141, Minsk, Belarus*

Received 20 May 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—Good results were obtained in the Mukaiyama–Michael reaction of the silyl enol ether of cyclohexanone with 2-methyl-2-cyclopentenone and carvone, with transfer of the silyl group to the receiving enone and with $TrSbCl_6$ as catalyst. A second Mukaiyama–Michael reaction of this new silyl enol ether with methyl vinyl ketone and cyclization of the resulting adduct leads to tricyclic compounds in one-pot domino sequences. The scope and limitations of this domino reaction have been investigated.

1. Introduction

The usefulness of sequential Michael additions in domino reactions has been demonstrated several times[1–16] and also the Lewis acid-promoted Michael addition of silyl enol ethers to enones, originally devised by Mukaiyama et al. is a valuable tool in this field.[17,18] Recently it has been shown that an enantiomerically pure trans-hydrindane derivative can be synthesised using a double Mukaiyama–Michael reaction,[4,6] and also a highly substituted cyclohexene has been obtained in a domino reaction using a double Mukaiyama–Michael addition, followed by an intramolecular 1,6-aldol condensation.[1] It is evident that the intermediate enolate has to be preserved for such a sequence, so that the second Mukaiyama–Michael addition can take place. Transfer of the silyl group from the starting silyl enol ether to the receiving enone is in this respect a very convenient side reaction, which has been noticed early on to occur in some Mukaiyama–Michael additions.[10] This newly formed silyl enol ether can be isolated but can also be reacted further in one-pot in a second Mukaiyama–Michael addition, potentially with a different enone, or with other reagents.[1–11]

Based on these premises, the enantioselective construction of highly substituted polycyclic compounds should be possible starting with cyclic silyl enol ethers and cyclic enones using two consecutive Mukaiyama–Michael reactions followed by a ring-closing 1,6-aldol cyclization. To probe the feasibility of such an approach, first two reaction sequences starting with a cyclohexanone-derived silyl enol ether **1** in additions with carvone **2**, as a chiral receiving enone, and with 2-methyl-2-cyclopentenone **3** have been investigated. In both cases the intermediate adducts **4** have been reacted further with methyl vinyl ketone (MVK) **5** as the second enone (see Scheme 1). This should lead to adducts **6**, which can undergo an intramolecular 1,6-aldol condensation with the carbonyl group of the cyclohexanone moiety, which originates from the first silyl enol ether, to give the tricyclic endproducts **7**.

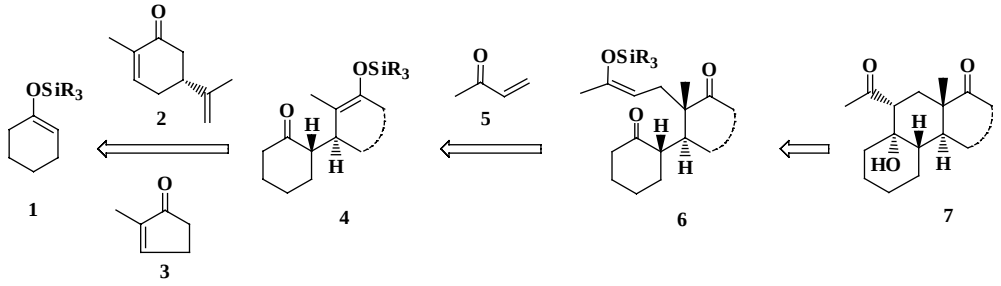
Variations in the starting silyl enol ether would open possibilities for further transformations of the tricyclic systems, which have potential as intermediates in the synthesis of polycyclic natural products. With carvone as the first receiving enone, stereochemical guiding of the configuration around the rings will be possible. The use of 2-methyl-2-cyclopentenone as the first receiving enone should give a tricyclic compound with possible use for the synthesis of steroid skeletons.

2. Results and discussion

To investigate the feasibility of the approach and to find the optimal conditions and stoichiometry for the reaction sequence mentioned in Scheme 1, several catalysts,

Keywords: Mukaiyama–Michael addition; Domino reactions; Tricyclic systems; Carvone.
* Corresponding author. Tel.: +31 317482370; fax: +31 317484914; e-mail: aede.degroot@wur.nl

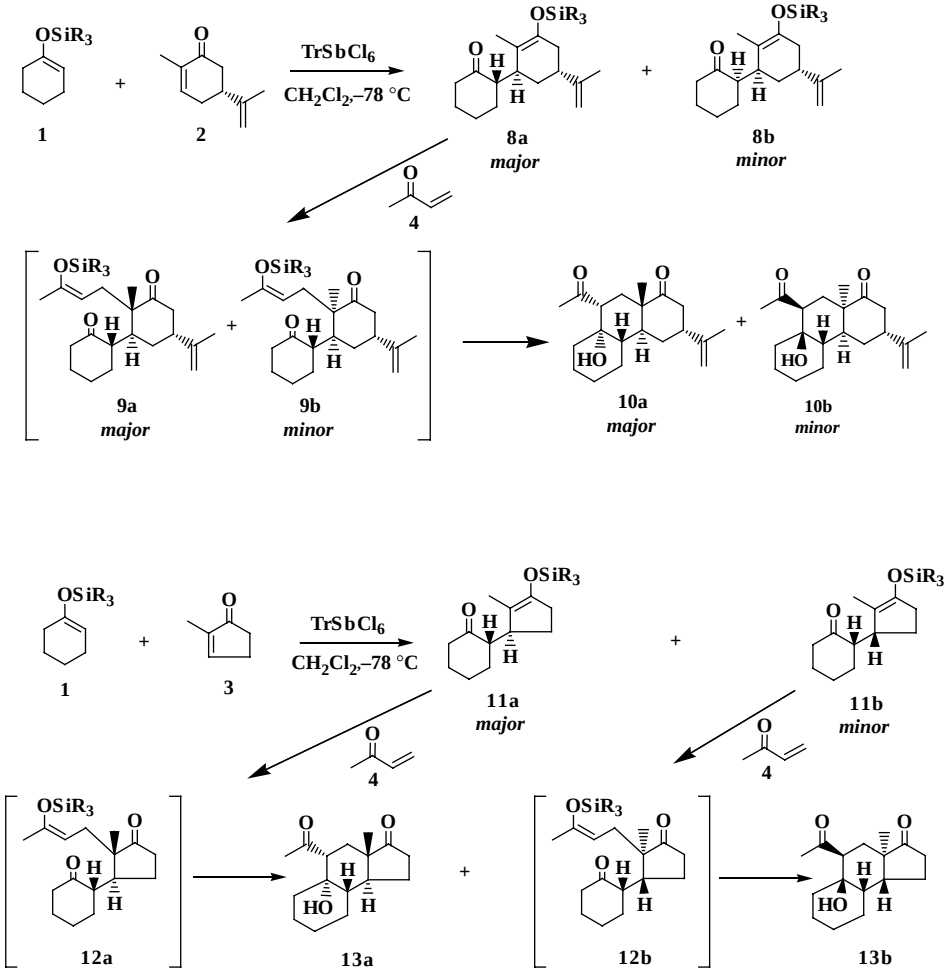
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.059



Scheme 1.

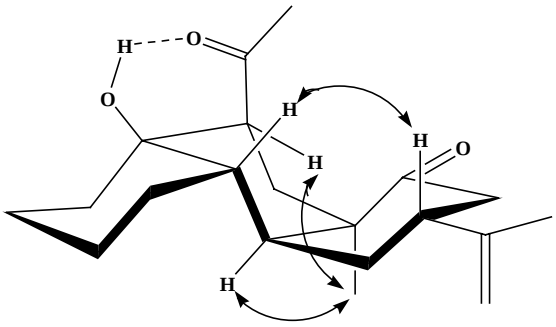
different addition orders, reaction temperatures and reagent ratios were researched. Many Lewis acids have been used as catalysts in Mukaiyama reactions but relatively few have been reported to give also transfer of the silyl group.[19–27] In our reaction, SmI_2, $TMSNTf_2$, $BuSn(OTf)_2$, $TrClO_4$ and $TrSbCl_6$ were investigated and the trityl salts were found to give the best results, as was expected from literature. Since $TrSbCl_6$ is commercially available and can be stored at $+4\,^{\circ}C$ without decomposition or loss of activity, this catalyst was chosen for all the following reactions. While the addition order of reagents and catalyst did not influence in any way the reaction yield or product ratios, the reaction temperature had to be kept low ($-78\,^{\circ}C$) to avoid hydrolysis of the starting silyl enol ether. At temperatures above $-60\,^{\circ}C$ an increase in desilylated starting material could clearly be detected on TLC. In the reaction of silyl enol ether **1** with carvone it was found that the use of 1, 1.25 or 1.5 equiv of **1** led to yields of 72, 82 and 89%, respectively, and therefore an excess of 1.5 equiv of silyl enol ether was applied in all reactions performed thereafter.

From both reaction sequences only two isomers of the final tricyclic products were isolated, and no other isomers were detected (see Scheme 2). The intermediate second adducts **9a**, **9b**, **12a** and **12b** have never been isolated because they reacted further to the tricyclic products under the applied conditions. The relative stereochemistry of compounds **10a**, **13a** and **13b** was determined by X-ray crystallography[28] and



Scheme 2.

for compound **10b** this was done using COSY and NOESY experiments (for the most important NOE interactions see Fig. 1), as this compound could not be obtained in a crystalline form. The position of the hydroxyl group was determined using IR-concentration experiments, showing an intramolecular H-bridge, between the hydroxy and the acetyl group.



10b

Figure 1.

The formation of the obtained products in the reaction with carvone can be explained by addition of the cyclohexanone silyl enol ether **1** from the less hindered side of the enone, opposite to the isopropenyl group. Epimeric mixtures of adducts are formed that differ in configuration only at C2 of the cyclohexanone moiety. The second addition of MVK **4** to the newly formed silyl enol ether takes place only with the major epimer. Steric factors probably are the reason for this difference but these factors are difficult to specify further. During this research it became clear that even small differences in steric hindrance can have significant influence on the yields and products of these Mukaiyama additions (see below). The second addition with MVK is not completely stereoselective, and occurs predominantly trans with respect to the cyclohexanone moiety. With 2-methyl-2-cyclopentenone as the receiving enone, diastereomeric racemates are obtained with trans-positioned substituents in the cyclopentanone part of the molecules. In this case, both products from the first addition (**11**) react further with MVK to afford tricyclic products.

Three silyl enol ethers with different steric effects (TMS, TBDMS and TES) were tested under the conditions mentioned above (1.5 equiv of silyl enol ether, 0.05 equiv of $TrSbCl_6$ as catalyst, at −78 °C). The reactions were quenched after the first Mukaiyama–Michael addition and then reacted further in a separate reaction with MVK, in order to get an impression of the stereoselectivity of the separate steps of the domino reaction. The TBDMS enol ether gave the best result in the reaction with carvone as the receiving enone (see Table 1), but the consecutive reaction with MVK gave a slightly better yield with the TMS enol ether. The reaction sequence with the TES enol ether gave only a moderate yield for the first addition step with carvone, and the domino reaction sequence gave a very low yield. This lower yield in the addition of the TES ether may be caused by a small increase in steric hindrance. The TES ether has less possibilities to minimize steric effects by rotation around the Si–O bond in comparison with the TBDMS ether. With 2-methyl-2-cyclopentenone as the receiving enone, no differences in yields between the TMS and TBDMS groups were found in the first step, but for the second Mukaiyama–Michael addition the best results were again obtained with the TMS enol ether. Apparently steric hindrance from the bulky TBDMS group has a greater influence in the second addition step, substantially lowering the yield in the five-membered ring compounds.

With respect to the stereoselectivity in the first step, the three silyl enol ethers all gave an addition to the enone of carvone opposite to the isopropenyl group, with comparable ratios of isomers in the cyclohexanone part of the molecules. In the consecutive MVK addition step, the reaction with the TBDMS enol ether led to the formation of only one isomer, thus giving a much higher stereoselectivity than the reaction with the TMS enol ether. The absence of steric hindrance in the starting enol ether gives the bulky TBDMS group the possibility to steer out of range, in this way not interfering with the approach to the enone for addition. When substituents are present in the neighbourhood of the enol ether moiety, the TBDMS group can not freely rotate and consequently its bulkiness interferes with the approach to the second enone (MVK) and influences the stereoselectivity of the reaction to a greater extent, which confirms the findings of Heathcock et al.[29,30]

In the TMS and in the TBDMS enol ether of the intermediate, the 2*S* isomer **8a** reacts much easier than the 2*R* isomer **8b**, as no final or intermediate product derived from the latter has been isolated.

In the Mukaiyama–Michael additions with 2-methyl-2-cyclopentenone, the bulkiness of the TBDMS enol ether already influences the stereoselectivity of the first Mukaiyama reaction, improving the isomer ratio to 4:1 in comparison with the almost 1:1 ratio for the TMS enol ether. However, in the second Mukaiyama–Michael addition with MVK, the higher stereoselectivity of the TBDMS enol ether shown in the first addition has disappeared and a much better selectivity was obtained with the TMS enol ether. A conceivable explanation could be that the TBDMS isomer **11a** reacts slower with MVK than isomer **11b**, possibly due

Table 1

Enone	Silyl group	Yield first addition (%)	Isomeric ratio (*a*:*b*)	Yield second addition (%)	Isomeric ratio (*a*:*b*)	Yield domino reaction (%)
2	TMS	89	2:1	49	5:1	45
2	TBDMS	94	2:1	45	1 (**10a**)	38
2	TES	46	3:2	—	—	5
3	TMS	85	6:5		4:1	61
3	TBDMS	83	4:1	—	2:1	32

All reactions have been carried out in duplicate.

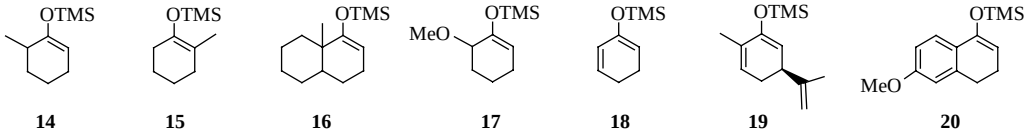


Figure 2.

to the higher steric strain in the latter, in combination with an easy desilylating side reaction in isomer **11a**. These factors could also explain the much lower yield for the domino reaction with the TBDMS enol ether (see below), pointing to a low-yielding second addition step. Interestingly, the MVK addition in the TMS enol ether resembles the one in the carvone route, having a strong preference for isomer **11a** of the intermediate, although in this case less pronounced.

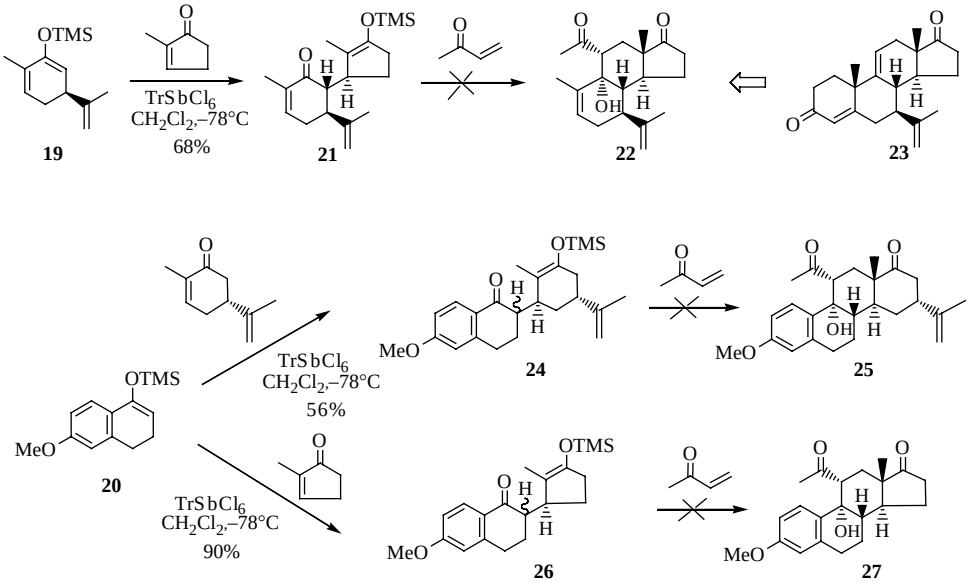
The reaction sequences were also performed as one-pot procedures, in which the second enone (MVK) was added at low temperature to the reaction mixture after completion of the first Mukaiyama–Michael addition. Although this domino reaction procedure[31] did not usually increase the overall yield dramatically, giving typically 40–50% of the tricyclic products, it did simplify the total reaction process considerably by taking out one complete purification step.

Variation in the starting silyl enol ether would give an impression about the scope and limitations of the domino sequence and maybe open up possibilities for enantioselective and short syntheses of steroids and D-homosteroids. For this reason, silyl enol ethers derived from cyclic ketones with more steric hindrance in the molecule (compounds **14–17**) or with a double bond or benzene ring conjugated with the carbonyl group (compounds **18** and **20**) were investigated (see Fig. 2) in their reactions with *R*-carvone as the first receiving enone and with MVK as the second enone. Compounds **19** and **20** were also reacted with 2-methyl-2-cyclopentenone as the first receiving enone, followed by addition of MVK (see Scheme 3).

An additional reason to select compounds **17–19** was to introduce functionality in the left ring, enabling further conversion of the tricyclic skeleton. The use of silyl enol ether **19** derived from (*S*)-(+)-carvone in an addition with 2-methyl-2-cyclopentenone as the receiving enone could possibly lead to an enantioselective synthesis of a tricyclic intermediate **22** that would enable completion of a steroid skeleton **23** (see Scheme 3). (D-homo) steroids could rapidly become accessible using silyl enol ether **20** derived from 6-methoxy-1-tetralone, a compound that has already been used extensively in steroid total synthesis.[32–38]

Although in the previous results with the cyclohexanone-derived silyl enol ethers, the TBDMS enol ether gave the best and most selective domino Mukaiyama–Michael addition, this silyl group proved not always to be the best choice. Sometimes the TBDMS enol ethers appeared troublesome to obtain or the first addition reaction gave no products. Therefore, the TMS enol ethers were used in all reaction sequences, which were carried out under the standart reaction conditions (1.5 equiv of silyl enol ether, 0.05 equiv of $TrSbCl_6$ as catalyst, at −78 °C). However, the overall results were disappointing.

The Mukaiyama–Michael addition of silyl enol ethers **14–16** to carvone proceeded in modest yields varying from 30 to 53%, but in all cases unseparable mixtures of stereoisomers were obtained. The reaction with the methoxy compound **17** did not proceed at all and the product from dienolsilyl enol ether **18**, proved to be unstable. The reaction of the carvone derived silyl enol ether **19** with 2-methyl-2-cyclopentenone led to product **21** in a reasonable 68% yield. It was published before that addition of the TMS enol ether



Scheme 3.

of 6-methoxytetralone **20** to carvone gave a 3:2 mixture of stereoisomers **24** in 56% yield, and that the stereoselectivity and the yield are dependent on the type of starting silyl enol ether. It was found also that the addition of **20** to 2-methyl-2-cyclopetenone gives a 2:1 mixtures of stereoisomers of **26** in 90% yield.[39]

In the consecutive addition reactions with MVK small amounts (24 and 14%) of tricyclic products were obtained from the product mixtures of silyl enol ethers resulting from **14** and **15**, respectively, but the stereochemistry of these products could not be established unambiguously. No reaction to tricyclic products was observed in all other cases and mostly only the desilylated intermediate adducts could be isolated. These results show again that the reaction sequence is sensitive for steric effects and especially the yields of the second addition reaction with MVK drop dramatically when extra substituents are present in the molecule.

The failure of the second addition with MVK in the silyl enol ethers **21**, **24** and **26** either could be caused by steric hindrance and/or by electronic effects in the 1,6-aldol cyclization due to electron delocalisation in the receiving enones. It seems that the electronic effects are the most important, as it appeared to be possible to react the intermediates **24** and **26** with carbocation precursors in irreversible reactions.[40] When the first carbonyl group is conjugated with a double bond or an aromatic system, the positive polarisation of the C-atom of the carbonyl group is less pronounced and hence this group is less reactive in aldol cyclizations. However, also uncyclised products similar to compound **6** never have been isolated. This can be explained by the equilibrium of the MVK addition lying on the side of the intermediates like **4**. Only if ring closure takes place, the equilibrium is shifted, finally to the tricyclic product. When ring closure does not take place, MVK will leave the molecule again and therefore almost no uncyclised products like **6**, or their desilylated equivalents, were found.

3. Experimental

3.1. General procedure

All reagents used were purchased from Aldrich or Acros, except for carvone, which was donated by Quest, and used without further purification unless otherwise stated. The used solvents were freshly distilled, except for benzene, which was stored over mol sieves (4 Å); dichloromethane was distilled over calcium hydride and tetrahydrofuran (THF) over sodium benzophenone ketyl. The glass equipment used was dried overnight in an oven of 150 °C and cooled down to room temperature under nitrogen. Reactions under dry conditions were performed under a steady flow of dry nitrogen or argon.

Reactions were monitored by thin-layer chromatography (TLC) on Merck silica gel $60F_{254}$ plastic sheet plates and compounds were visualized by potassium permanganate or by acidic molybdate solution and subsequent heating. Product solutions were dried over Na_2SO_4 or $MgSO_4$ before evaporation under reduced pressure using a rotary evaporator. Column chromatography was performed with Fluka silica gel mean pore size 60 (SiO_2, 230–400 mesh) with mixtures of distilled petroleum ether, boiling range 40–60 °C (PE) and distilled ethyl acetate (EA) as eluents, unless reported otherwise. ^1H and ^{13}C NMR experiments were, unless otherwise stated, conducted on a Bruker AC-E 200, at 200 and 50 MHz, respectively, using $CDCl_3$ or C_6D_6 as solvents. Chemical shifts are reported in ppm (parts per million) (δ), referenced to residual $CHCl_3$ or C_6H_6 as internal standard, and coupling constants are expressed in Hz. ^1H NMR multiplicities are mentioned as singlet (s), doublet (d), triplet (t), quadruplet (q), broad singlet (br s), multiplet (m), double doublet (dd), etc. Multiplicities of the ^{13}C NMR signals were determined using the DEPT technique and are mentioned as q (CH_3), t (CH_2), d (CH) or s (C). When two isomers were detected and specific peaks could be assigned in the spectra, the data referred to the major isomer are marked as (*M*) and those of the minor isomer as (*m*). When the isomers are equally present, the data is presented as 14.35 and 17.87 (q). Melting points were determined on a C. Reichert, Vienna, hot stage apparatus, and are uncorrected. Infrared spectra were recorded on a FT-IR Biorad FTS-7 spectrometer using carbon tetrachloride (CCl_4) or chloroform ($CHCl_3$) as solvents when a solution was used. Only the characteristic absorptions were reported. The isomeric ratio of all the crude products was determined using GC–MS detection at 70 eV on a Hewlett Packard 5890B series Mass Selective Detector, coupled with a Hewlett Packard 5973 GC provided with a DB-17 fused silica capillary column, 30 m×0.25 mm i.d., film thickness 0.25 μm with helium as the carrier gas, programmed from 100–250 °C at a rate of 10 °C/min, followed by an isothermic period at 250 °C. MS and HRMS data were obtained with a Finnigan MAT 95 spectrometer. The ratios *m/e* and relative intensities (%) are indicated for significant peaks. Elemental analyses were performed on a Carlo Erba 1106 elemental analyser. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter at 20 °C in chloroform solutions and concentrations are specified in units of g/100 ml.

3.2. General method for thermodynamic silylation

3.2.1. (1-Cyclohexen-1-yloxy)(trimethyl)silane (1[TMS]).[41] To a stirred solution of cyclohexanone (2.45 g, 25 mmol) in CH_3CN (100 ml) under nitrogen were added Et_3N (5.56 ml, 40 mmol), TMSCl (4.32 g, 40 mmol) and NaI (6.00 g, 40 mmol), in this order. After overnight stirring at room temperature, the reaction mixture was diluted with PE (100 ml) and the acetonitrile layer was extracted with PE (2×100 ml). The combined organic layers were washed with a saturated $NaHCO_3$ solution (100 ml) and brine (100 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by bulb-to-bulb distillation (br pt 44 °C at 4 Torr) to give **1**[TMS] as a colourless liquid (3.32 g, 78%). IR (CCl_4 sol) cm^{-1} 2933, 1668, 1549, 1252; ^1H NMR ($CDCl_3$): −0.12 (s, 9H), 1.30–1.38 (m, 2H), 1.38–1.53 (m, 2H), 1.77–1.92 (m, 4H), 4.66–7.71 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.3 (3q), 22.3 (t), 23.2 (t), 23.8 (t), 29.9 (t), 104.3 (d), 150.3 (s). HRMS: M^+, found 170.1123. $C_9H_{18}OSi$ requires 170.1127. MS *m/e* (%): 170 (M^+, 100), 169 (41), 155 (64), 142 (23), 127 (49), 75 (86), 73 (55). These data are in accordance with literature values.

3.2.2. *tert*-Butyl(1-cyclohexen-1-yloxy)dimethylsilane (1[TBDMS]).[42] See method description of compound **1**[TMS] for procedure and reaction scale. Yield: 83%, as a clear oil (br pt 55 °C at 0.3 Torr). IR (CCl_4 sol) cm^{-1}: 2931, 2859, 1668, 1549, 1254; ^1H NMR ($CDCl_3$): 0.01 (s, 9H), 0.12 (s, 6H), 1.45–1.59 (m, 2H), 1.59–1.72 (m, 2H), 1.94–2.08 (m, 4H), 4.85–4.90 (m, 1H); ^{13}C NMR ($CDCl_3$): −4.4 (q), −2.9 (q), 18.0 (s), 22.4 (t), 23.2 (t), 23.8 (t), 25.7 (q), 29.9 (t), 104.3 (d), 150.5 (s). HRMS: M^+, found 212.1598. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%): 212 (M^+, 22), 75 (80), 73 (19). These data are in accordance with literature values.

3.2.3. (1-Cyclohexen-1-yloxy)(triethyl)silane (1[TES]).[43] See method description of compound **1**[TMS] for procedure and reaction scale. Yield: quantitative, as a colourless oil (br pt 54 °C at 0.5 Torr). IR (CCl_4 sol) cm^{-1}: 2956, 2877, 1667, 1550; ^1H NMR ($CDCl_3$): 0.60 (s, 9H), 0.60–0.88 (m, 6H), 1.50–1.58 (m, 2H), 1.58–1.71 (m, 2H), 1.96–2.00 (m, 4H), 4.84–4.87 (m, 1H); ^{13}C NMR ($CDCl_3$): 5.0 (q), 5.8 (t), 6.4 (t), 6.5 (q), 6.8 (q), 23.8 (t), 29.8 (t), 41.5 (t), 41.9 (t), 103.9 (d), 150.4 (s). HRMS: M^+, found 212.1598. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%): 212 (M^+, 23), 169 (18), 156 (12), 155 (17), 103 (47), 75 (43). These data are in accordance with literature values.

3.2.4. 2-{(5*R*)-5-Isopropenyl-2-methyl-3[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}cyclohexanone (8[TMS]). (*R*)-(−)-Carvone (150 mg, 1 mmol) and **1**[TMS] (255 mg, 1.50 mmol) were dissolved in dichloromethane (6 ml) and stirred under nitrogen. The reaction mixture was cooled to −78 °C. Trityl antimony hexachloride ($TrSbCl_6$) (29 mg, 0.05 mmol) was added and the reaction was followed by TLC. When all the carvone had reacted (1 h), the catalyst was quenched by adding a few drops of pyridine, until the yellow colour disappeared. The reaction mixture was allowed to warm to room temperature and diluted with dichloromethane (14 ml). The mixture was washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a short SiO_2 column (PE/EtOAc/pyridine 98:1:1) to give **8**[TMS] (286 mg, 89%) as a colourless oil composed of two isomers, which could not be separated, in a ratio of 2:1 (GC). IR (film) cm^{-1}: 2936, 1709, 1644, 1251; ^1H NMR ($CDCl_3$): 0.15 (s, 9H), 1.53 (s, 3H), 1.52–1.69 (m, 5H), 1.69 (s, 3H), 1.91–2.07 (m, 4H), 2.20–2.40 (m, 4H), 2.90–2.92 (m, 1H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$): 0.8 (3q), 17.5 (q), 20.5 (q), 25.4 (*M*) and 27.1 (*m*) (t), 27.9 (*M*) and 28.6 (*m*) (t), 29.2 (*m*) and 32.6 (*M*) (t), 33.7 (t), 35.1 (t), 35.7 (d), 37.8 (*M*) and 39.2 (*m*) (d), 42.4 (t), 52.9 (*m*) and 56.3 (*M*) (d), 109.0 (t), 112.9 (s), 144.9 (s), 148.7 (*m*) and 148.9 (*M*) (s), 212.4 (s). HRMS: M^+, found 320.2173. $C_{19}H_{32}O_2Si$ requires 320.2172. MS *m/e* (%): 320 (M^+, 100), 181 (12), 75 (5), 73 (33).

3.2.5. 2-{(5*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-5-isopropenyl-2-methyl-2-cyclohexen-1-yl}cyclohexanone (8[TBDMS]). See method description of compound **8**[TMS] for procedure and reaction scale. Yield: 94%, as a colourless oil (mixture of 2 isomers, 2:1). IR (film) cm^{-1}: 2932, 1710, 1678, 1449, 1254; ^1H NMR ($CDCl_3$): 0.11 (s, 6H), 0.88 (*m*) and 0.94 (*M*) (s, 9H), 1.52–1.72 (m, 5H), 1.51 (*m*) and 1.54 (*M*) (s, 3H), 1.69 (*M*) and 1.70 (*m*) (s, 3H), 1.85–2.11 (m, 5H), 2.12–2.50 (m, 4H), 2.86 (s, 1H), 4.69 (s, 2H); ^{13}C NMR ($CDCl_3$): −3.7 (2q), 14.4 (*m*) and 17.9 (*M*) (q), 18.2 (s), 20.5 (*M*) and 20.7 (*m*) (q), 25.4 (t), 25.9 (3q), 27.2 (*m*) and 28.0 (*M*) (t), 28.7 (*M*) and 29.3 (*m*) (t), 32.7 (*m*) and 33.6 (*M*) (t), 35.1 (*m*) and 35.3 (*M*) (t), 35.8 (*m*) and 36.1 (*M*) (d), 37.8 (*M*) and 39.3 (*m*) (d), 42.2 (*m*) and 42.4 (*M*) (t), 52.9 (*m*) and 56.4 (*M*) (d), 109.0 (t), 111.4 (*m*) and 112.6 (*M*) (s), 145.0 (s), 148.7 (*m*) and 148.9 (*M*) (s), 212.6 (*M*) and 212.8 (*m*) (s). HRMS: M^+, found 362.2652. $C_{22}H_{38}O_2Si$ requires 362.2641. MS *m/e* (%): 362 (M^+, 9), 305 (2), 155 (10), 75 (12), 73 (31).

3.2.6. 2-{(5*R*)-5-Isopropenyl-2-methyl-3-[(triethylsilyl)oxy]-2-cyclohexen-1-yl}cyclohexanone (8[TES]). See method description of compound **8**[TMS] for procedure and reaction scale. Yield: 46%, as a colourless oil (2 isomers, 3:2). IR (film) cm^{-1}: 2936, 1710, 1449, 1238; ^1H NMR (C_6D_6): 0.64 (q, $J=7.9$ Hz, 6H), 0.97 (t, $J=7.9$ Hz, 9H), 1.53 (*m*) and 1.56 (*M*) (s, 3H), 1.70 (s, 3H), 1.45–1.71 (m, 5H), 1.88–2.12 (m, 4H), 2.26–2.45 (m, 4H), 2.89 (m, 1H), 4.70 (s, 2H); ^{13}C NMR (C_6D_6): 5.9 (3t), 6.9 (3q), 14.9 (*m*) and 17.6 (*M*) (q), 20.4 (*M*) and 20.7 (*m*) (q), 25.2 (t), 26.9 (*m*) and 27.6 (*M*) (t), 28.6 (*m*) and 32.4 (*M*) (t), 29.2 (*m*) and 33.7 (*M*) (t), 35.2 (*m*) and 35.5 (*M*) (t), 35.6 (*m*) and 36.1 (*M*) (d), 38.1 (*M*) and 39.5 (*m*) (d), 41.9 (t), 53.5 (*m*) and 56.1 (*M*) (d), 109.2 (t), 113.1 (s), 145.9 (s), 149.2 (*m*) and 149.6 (*M*) (s), 210.6 (*M*), 210.7 (*m*) (s). HRMS: M^+, found 362.2648. $C_{22}H_{38}O_2Si$ requires 362.2641. MS *m/e* (%): 362 (M^+, 26), 333 (9), 239 (12), 115 (13), 87 (24), 59 (11).

3.2.7. (3*R*)-9-Acetyl-8a-hydroxy-3-isopropenyl-10a-methyldodecahydro-1(2*H*)-phenanthrenone (10). *Mukaiyama–Michael addition of intermediate* **8**[TMS] *with MVK*. A stirred solution of $TrSbCl_6$ (29 mg, 0,05 mmol) in dichloromethane (10 ml) under nitrogen was cooled to −78 °C. A solution of **8**[TMS] (320 mg, 1 mmol) and methyl vinyl ketone (MVK, 0.17 ml, 2 mmol) in dichloromethane (5 ml) was added dropwise over a period of 2.5 h. The reaction mixture was stirred at −78 °C for another 2 h and was then allowed to warm to room temperature. Water (10 ml) was added and, after stirring for a further 1 h, the reaction mixture was diluted with dichloromethane (20 ml) and washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml). The organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc 9:1) to give two isomers **10a** (122 mg, crystals) and **10b** (25 mg, colourless oil) in a total 49% yield in a 5:1 ratio. Compound **10a** was recrystallised from pentane to give white needles.

Mukaiyama–Michael addition of intermediate **8**[TBDMS] *with MVK*. The reaction of **8**[TBDMS] (362 mg, 1 mmol) with MVK was carried out as described for **8**[TMS]. Compound **10a** (143 mg) was obtained as a single isomer in 45% yield as white crystals (needles) after recrystallisation from pentane.

Domino Mukaiyama reaction of **1**[TMS]. At room temperature, (*R*)-(−)-carvone (450 mg, 3 mmol) was added to a stirred solution of **1**[TMS] (765 mg, 4.5 mmol) in dichloromethane (20 ml) under nitrogen. The solution was cooled to −78 °C and $TrSbCl_6$ was added (87 mg, 0.15 mmol). After

2.5 h of stirring at −78 °C MVK (0.5 ml, 6 mmol) was added dropwise over a period of 3.5 h. The reaction mixture was stirred for another 2 h at −78 °C, before slow warming to room temperature overnight. No TLC control was done during the reaction due to the sensitivity of the compounds towards desilylation. Water (10 ml) was added and after further stirring for 1 h the reaction mixture was diluted with dichloromethane (20 ml). The organic layer was washed with a saturated $NaHCO_3$ solution (20 ml) and brine (20 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE/EA 20:1, with 1% pyridine) to give a total 45% yield of **10a** (119 mg) and **10b** (24 mg) in a 5:1 ratio.

Domino Mukaiyama reaction of **1**[TBDMS]. The reaction of **1**[TBDMS] (954 mg, 4.5 mmol) was carried out as described for **1**[TMS]. Compound **10a** (120 mg) was obtained as a single isomer in 38% yield as white crystals (needles) after recrystallisation from pentane.

Compound **10a**. Mp 68–72 °C (from pentane); IR (CCl_4 sol) cm^{-1}: 3488, 2937, 1707, 1252; ^1H NMR ($CDCl_3$): 1.01–1.22 (2H, m), 1.18 (3H, s), 1.22–1.48 (4H, m), 1.55–1.84 (9H, m), 1.88–2.13 (2H, m), 2.19 (3H, s), 2.35–2.55 (2H, m), 2.64 (d, $J=6.7$ Hz, 1H), 3.02 (dd, $J_1=3.3$ Hz, $J_2=9.9$ Hz, 1H), 3.99 (OH), 4.65 (1H, s), 4.81 (1H, s); ^{13}C NMR ($CDCl_3$): 19.9 (q), 22.3 (q), 23.8 (t), 25.7 (t), 26.4 (t), 26.9 (t), 31.6 (q), 31.9 (t), 33.6 (d), 38.8 (t), 40.5 (d), 41.1 (t), 45.6 (d), 47.4 (s), 48.2 (d), 72.1 (s), 112.5 (t), 146.6 (t), 214.6 (s), 215.4 (s). HRMS: M^+, found 318.2203. $C_{20}H_{30}O_3$ requires 318.2195. MS *m/e* (%): 318 (M^+, 42), 248 (86), 221 (63), 204 (96), 179 (77), 161 (84), 151 (98), 98 (67).

Compound **10b**. IR (CCl_4 sol) cm^{-1}: 3488, 2937, 1707, 1252; ^1H NMR ($CDCl_3$): 1.14 (3H, s), 1.04–1.28 (2H, m), 1.32–1.85 (13H, m), 1.93–2.12 (2H, m), 2.17 (3H, s), 2.50–2.62 (2H, m), 2.62–2.74 (2H, m), 3.67 (OH), 4.69 (1H, s), 4.80 (1H, s); ^{13}C NMR ($CDCl_3$): 16.9 (q), 20.7 (t), 21.5 (q), 23.7 (t), 25.3 (t), 26.1 (t), 31.4 (q), 32.1 (t), 36.3 (d), 37.5 (t), 39.4 (d), 40.7 (t), 42.8 (d), 47.2 (s), 53.3 (d), 70.8 (s), 112.0 (t), 146.8 (s), 215.7 (s), 215.9 (s). HRMS: M^+, found 318.2203. $C_{20}H_{30}O_3$ requires 318.2195. MS *m/e* (%): 318 (M^+, 42), 248 (86), 221 (63), 204 (96), 179 (77), 161 (84), 151 (98), 98 (67).

3.2.8. 2-{2-Methyl-3-[(trimethylsilyl)oxy]-2-cyclopenten-1-yl}cyclohexanone (11[TMS]). 2-Methyl-2-cyclopentenone (384 mg, 4 mmol) and **1**[TMS] (1.36 g, 8 mmol) were dissolved in dichloromethane (25 ml) and stirred under nitrogen. The reaction mixture was cooled to −78 °C. Trityl antimony hexachloride ($TrSbCl_6$) (58 mg, 0.05 mmol) was added and the reaction was followed by TLC. When all the carvone had reacted (1 h), the catalyst was quenched by adding a few drops of pyridine, until the yellow colour disappeared. The reaction mixture was allowed to warm to room temperature and diluted with dichloromethane (15 ml). The mixture was washed with saturated $NaHCO_3$ solution (25 ml) and brine (25 ml), dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified on a short column (PE/EtOAc/pyridine 98:1:1) to give **11**[TMS] (906 mg, 85%) as a colourless oil composed of two isomers, which could not be separated, in a ratio of 6:5. IR (film) cm^{-1}: 2937, 2860, 1709, 1691, 1330, 1252, 1211; ^1H NMR ($CDCl_3$): 0.01 (s, 9H), 1.24 (s, 3H), 1.11–2.38 (m, 13H), 2.86–3.09 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.6 (3q), 10.1 (*M*) and 12.1 (*m*) (q), 22.9 (t), 24.9 (*M*) and 25.4 (*m*) (t), 26.5 (*M*) and 27.0 (*m*) (t), 27.2 (*M*) and 28.5 (*m*) (t), 32.6 (*m*) and 33.2 (*M*) (t), 42.0 (*m*) and 42.2 (*M*) (t), 42.7 (*m*) and 43.2 (*M*) (d), 52.3 (*M*) and 54.8 (*m*) (d), 113.1 (*M*) and 114.4 (*m*) (s), 147.7 (*M*) and 148.3 (*m*) (s), 211.9 (*m*) and 212.8 (*M*) (s). MS *m/e* (%): 266 (M^+, 2), 169 (100), 155 (3), 75 (11), 73 (66).

3.2.9. 2-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methyl-2-cyclopenten-1-yl)cyclohexanone (11[TBDMS]). See method description of compound **11**[TMS] for procedure and reaction scale. Yield: 83%, as a colourless oil (2 isomers, 4:1). IR (CCl_4 sol) cm^{-1}: 2923, 2858, 1711, 1549, 1253; ^1H NMR ($CDCl_3$): 0.10 (s, 6H), 0.93 (s, 9H), 1.31–1.52 (m, 5H), 1.54–1.70 (m, 2H), 1.79–2.53 (m, 9H), 3.09 (s, 1H); ^{13}H NMR ($CDCl_3$) −4.0 (2q), 10.1 (q), 18.1 (s), 22.9 (t), 25.1 (t), 25.7 (3q), 26.5 (t), 27.2 (t), 33.2 (t), 42.4 (t), 43.1 (d), 52.4 (d), 112.7 (s), 147.9 (s), 213.1 (s). HRMS: M^+, found 308.2178. $C_{18}H_{32}O_2Si$ requires 308.2172. MS *m/e* (%): 308 (M^+, 14), 75 (25), 73 (33).

3.2.10. 5-Acetyl-5a-hydroxy-3a-methyldodecahydro-3*H*-cyclopenta[*a*]naphthalen-3-one (13). For general procedures and scale see the syntheses of **10**. From **11**[TMS] a total yield of 161 mg (61%), of **13a** and **13b** was obtained as white crystals in a 4:1 ratio, respectively. From **11**[TBDMS] a total yield of 84 mg (32%) of **13a** and **13b** was obtained in a 2:1 ratio, respectively.

Compound **13a**. Mp 86–90 °C (from pentane); IR (CCl_4 sol) cm^{-1}: 3469, 2933, 2860, 1739, 1692, 1398, 1359, 1190; ^1H NMR ($CDCl_3$): 0.92 (s, 3H), 1.08–2.18 (m, 15H), 2.18 (s, 3H), 2.41 (dd, $J_1=8.0$ Hz, $J_2=16.4$ Hz, 1H), 2.61 (dd, $J_1=5.1$ Hz, $J_2=11.5$ Hz, 1H), 3.81 (s, 1H); ^{13}C NMR ($CDCl_3$): 13.4 (q), 21.1 (2t), 23.4 (t), 25.7 (t), 31.3 (q), 31.8 (t), 35.7 (t), 37.0 (t), 42.8 (d), 42.9 (d), 47.2 (s), 53.7 (d), 72.0 (s), 215.9 (s), 219.5 (s). HRMS: M^+, found 264.1724. $C_{16}H_{24}O_3$ requires 264.1725. MS *m/e* (%): 264 (M^+, 2), 246 (9), 249 (8), 246 (10), 203 (18), 194 (54), 98 (100), 97 (92), 55 (18), 43 (15).

Compound **13b**. Mp 79–82 °C (from pentane); ^1H NMR ($CDCl_3$): 1.05 (s, 3H), 1.05–1.55 (m, 5H), 1.64–1.93 (m, 9H), 2.12 (dd, $J_1=8.5$ Hz, $J_2=19.1$ Hz, 1H), 2.24 (s, 3H), 2.32–2.57 (m, 1H), 3.10 (dd, $J_1=5.1$ Hz, $J_2=11.1$ Hz, 1H), 4.19 (s, 1H); ^{13}C NMR ($CDCl_3$): 16.9 (q), 20.8 (t), 24.0 (t), 25.7 (t), 26.1 (t), 31.5 (q), 31.7 (t), 35.7 (t), 38.8 (t), 41.6 (d), 46.3 (2d), 46.6 (s), 73.1 (s), 215.4 (s), 219.0 (s). HRMS: M^+, found 264.1726. $C_{16}H_{24}O_3$ requires 264.1725. MS *m/e* (%): 264 (M^+, 20), 249 (15), 246 (22), 221 (7), 203 (33), 194 (99), 98 (93). 97 (100), 43 (29).

3.2.11. {[(3*S*)-3-Isopropenyl-6-methyl-cyclohexa-1,5-dienyl]oxy}(trimethyl)silane (19[TMS]).[44] A solution of diisopropylamine (2.25 ml, 16 mmol) in THF (20 ml) was cooled to −10 °C, and butyllithium (1.45 M in THF, 10 ml) was added in one portion. The solution was allowed to warm to 0 °C and stirred for 30 min, after which the solution was cooled to −78 °C and a solution of (*S*)-(+)-carvone (2.0 g, 13.2 mmol) in THF (20 ml) was added dropwise over a period of 30 min. The solution was kept at −78 °C and

stirred for 20 min, followed by dropwise addition of TMSCl (2.0 ml, 16 mmol) over a period of 10 min. The solution was allowed to warm to room temperature over a period of 1 h and poured in a cold solution of brine and $NaHCO_3$ (10%). The water-layer was extracted with petrol-ether, and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude product was purified by bulb-to-bulb distillation yielding 2.76 g of **19**[TMS] (94%) s a colourless oil. IR (CCl_4 sol) cm^{-1} 2963, 1660, 1605, 1550, 1451, 1375, 1253, 1214; ^1H NMR ($CDCl_3$): 0.18 (s, 9H), 1.67 (s, 3H), 1.71 (s, 3H), 2.11 (m, 2H), 2.99 (m, 1H), 4.69 (m, 1H), 4.76 (m, 2H), 5.54 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.1 (3q), 17.3 (q), 20.5 (q), 28.6 (t), 41.8 (d), 105.7 (d), 109.9 (t), 123.0 (d), 131.8 (s), 148.4 (s), 149.8 (s). HRMS: M^+, found 222.1439. $C_{13}H_{22}OSi$ requires 222.1440. MS *m/e* (%): 222 (100, M^+), 207 (83), 181 (65), 165(62), 91 (24), 82 (17), 75 (21), 73 (79), 45 (16). Data are in accordance with literature values.

3.2.12. [(6-Methoxy-3,4-dihydro-1-naphthalenyl)oxy]-(trimethyl)silane (20[TMS]).[45] See method description of compound **1** for procedure and reaction scale. Yield: 92%, as a colourless oil. IR (CCl_4 sol) cm^{-1}: 2958, 2835, 1683, 1639, 1607, 1252; ^1H NMR δ: 0.31 (s, 9H), 2.24–2.35 (m, 2H), 2.79 (t, $J=7.8$ Hz, 2H), 3.83 (s, 3H), 5.12 (t, $J=4.6$ Hz, 1H), 6.74 (s, 1H), 6.76 (d, $J=8.6$ Hz, 1H), 7.41 (d, $J=8.2$ Hz, 1H); ^{13}C NMR δ: 0.2 (3q), 22.2 (t), 28.7 (t), 55.1 (q), 102.9 (d), 110.7 (d), 113.2 (d), 123.1 (d), 126.6 (s), 138.9 (s), 147.9 (s), 158.9 (s). HRMS: M^+, found 248.1229. $C_{14}H_{20}O_2Si$ requires 248.1233. MS *m/e* (%): 248 (M^+, 100), 247 (64), 233 (30), 217 (13), 73 (21). Data are in accordance with literature values.

3.2.13. 2-{(1*S*,5*R*)-5-Isopropenyl-2-methyl-3-[(trimethylsilyl)oxy]-2-cyclohexen-1-yl}-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (24). See method description of compound **8** for procedure and reaction scale. Yield: 56%, as a mixture of 2 isomers (3:2), white crystals (mp 55–56 °C from pentane). IR (CCl_4) cm^{-1}: 2939, 1680, 1602, 1252; ^1H NMR δ: 0.15 and 0.19 (s, 9H), 1.39 and 1.58 (s, 3H), 1.68 and 1.73 (s, 3H), 1.45–2.65 (m, 7H), 2.75 (dt, $J_1=13.0$ Hz, $J_2=3.7$ Hz, 1H), 2.91–2.93 (m, 2H), 3.23 and 3.35 (br s, 1H), 3.83 (s, 3H), 4.72–4.74 (m, 2H), 6.67 (br s, 1H), 6.80 (dd, $J_1=8.7$ Hz, $J_2=2.5$ Hz, 1H), 8.02 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (isomer 1) δ: 1.3 (3q), 11.9 (q), 21.4 (q), 25.5 (t), 27.2 (t), 28.1 (t), 34.4 (d), 40.6 (d), 42.2 (t), 46.6 (d), 55.4 (q), 77.0 (s), 111.7 (t), 112.3 (d), 113.4 (d), 125.9 (s), 129.9 (d), 145.6 (s), 146.7 (s), 163.5 (s), 198.9 (s), 213.8 (s); (isomer 2) 1.9 (3q), 12.2 (q), 21.1 (q), 26.8 (t), 29.1 (t), 29.5 (t), 36.5 (d), 42.4 (d), 44.1 (t), 47.9 (d), 55.4 (q), 77.7 (s), 111.0 (t), 112.3 (d), 113.2 (d), 125.2 (s), 130.0 (d), 145.8 (s), 147.0 (s), 163.5 (s), 198.8 (s), 213.8 (s). HRMS: M^+, found 398.2275. $C_{24}H_{34}O_3Si$ requires 398.2277. MS *m/e* (%): 398 (M^+, 12), 329 (3), 248 (31), 223 (100), 222 (49), 176 (21), 73 (33).

3.2.14. (5*S*,6*R*)-5-Isopropenyl-2-methyl-6-(2-methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-cyclohex-2-enone (24). The reaction was carried out as described for compound **11**. The reaction was carried out several times on a scale that varied from 100 mg to 1 g. The product was obtained in an average of 68% yield as a colourless oil. IR (CCl_4) cm^{-1}: 2960, 2957, 2945, 1741, 1671; ^1H NMR ($CDCl_3$): −0.01 (s, 9H), 1.28 (s, 3H), 1.51 (s, 3H), 1.54 (s, 3H), 1.15–2.68 (m, 9H), 4.59 (s, 2H), 6.38–6.44 (m, 1H); ^{13}C NMR ($CDCl_3$): 0.6 (3q), 10.7 (q), 15.6 (q), 18.8 (q), 22.9 (t), 30.3 (t), 32.6 (t), 45.1 (d), 46.2 (d), 50.0 (d), 113.0 (t), 114.8 (s), 136.1 (s), 142.0 (d), 146.1 (s), 146.5 (s), 200.3 (s). HRMS: M^+, found 318.2017. $C_{19}H_{30}O_2Si$ requires 318.2015. MS *m/e* (%): 318 (M^+, 9), 222 (15), 182 (6), 169 (100), 150 (5), 73 (34).

3.2.15. 6-Methoxy-2-(2-methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-3,4-dihydro-2*H*-naphthalen-1-one (26). See method description of compound **11** for procedure and reaction scale. Yield: 90%, as a colourless oil (2 isomers, 2:1). IR (CCl_4 sol) cm^{-1}: 2941, 2851, 1673, 1600, 1333, 1252; ^1H NMR ($CDCl_3$) δ: 0.14 (*M*) and 0.18 (*m*) (s, 9H), 1.27 (*M*) and 1.50 (*m*) (s, 3H), 1.41–2.73 (m, 7H), 2.86–3.00 (dd, $J_1=3.7$ Hz, $J_2=8.3$ Hz, 2H), 3.40–3.55 (*m*) and 3.55–3.65 (*M*) (m, 1H), 3.83 (s, 3H), 6.66 (d, $J=2.5$ Hz, 1H), 6.81 (dd, $J_1=2.5$ Hz, $J_2=8.7$ Hz, 1H), 8.00 (*m*) and 8.01 (*M*) (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$): δ: 0.6 (3q), 10.3 (*m*) and 11.9 (*M*) (q), 22.4 (*m*) and 23.6 (*M*) (t), 22.9 (*m*) and 25.0 (*M*) (t), 29.8 (*M*) and 29.9 (*m*) (t), 32.9 (*M*) and 33.1 (*m*) (t), 43.3 (*M*) and 43.9 (*m*) (d), 49.7 (*m*) and 52.2 (*M*) (d), 55.4 (q), 112.4 (d), 113.0 (d), 114.4 (s), 126.5(*M*) and 127.1 (*m*) (s), 129.7 (*m*) and 123.0 (*M*) (d), 146.5 (*M*) and 146.8 (*m*) (s), 147.9 (*m*) and 148.1 (*M*) (s), 163.3 (s), 197.8 (*M*) and 199.0 (*m*) (s). HRMS: M^+, found 344.1807. $C_{20}H_{28}O_3Si$ requires 344.1808. MS *m/e* (%): 344 (M^+, 9), 249 (8), 248 (34), 138 (8), 176 (36), 170 (15), 169 (100).

Acknowledgements

The authors gratefully acknowledge financial support from the Dutch Technology Foundation (Grant CW/STW-project 790.35.215) and from Organon International. The authors thank B. van Lagen for NMR and IR spectroscopic data, and M.A. Posthumus for mass spectroscopic measurements.

References and notes

1. Paulsen, H.; Antons, S.; Brandes, A.; Lögers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3373.
2. Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999.
3. Prowotorow, I.; Stepanenko, W.; Wicha, J. *Eur. J. Org. Chem.* **2002**, 2727.
4. Gorobets, E.; Urbanczyk-Lipkowska, Z.; Stepanenko, V.; Wicha, J. *Tetrahedron Lett.* **2001**, *42*, 1135.
5. Gorobets, E.; Miftakhov, M. S.; Valeev, F. A. *Russ. Chem. Rev.* **2000**, *69*, 1001.
6. Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1998**, *39*, 885.
7. Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218.
8. Marczak, S.; Wicha, J. *Tetrahedron Lett.* **1993**, *34*, 6627.
9. Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293.
10. Kobayashi, S.; Mukaiyama, T. *Chem. Lett.* **1986**, 221.

11. Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1047.
12. Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.
13. Posner, G. H.; Asirvatham, E. *Tetrahedron Lett.* **1986**, *27*, 663.
14. Posner, G. H.; Lu, S. B.; Asirvatham, E. *Tetrahedron Lett.* **1986**, *27*, 659.
15. Posner, G. H.; Lu, S. B.; Asirvatham, E.; Silversmith, E. F.; Shulman, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 511.
16. Wakselman, C.; Mondon, M. *Tetrahedron Lett.* **1973**, *14*, 4285.
17. Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503.
18. Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.
19. Kobayashi, S.; Murakami, M.; Mukaiyama, T. *Chem. Lett.* **1985**, 953.
20. Kobayashi, S. *Eur. J. Org. Chem.* **1999**, 15.
21. Cossy, J.; Lutz, F.; Alauze, V.; Meyer, C. *Synlett* **2002**, 45.
22. Chen, J.; Otera, J. *Tetrahedron* **1997**, *53*, 14275.
23. Sato, T.; Wakahara, Y.; Otera, J.; Nozaki, H. *Tetrahedron* **1991**, *47*, 9773.
24. Bernardi, A.; Colombo, G.; Scolastico, C. *Tetrahedron Lett.* **1996**, *37*, 8921.
25. Grieco, P. A.; Cooke, R. J.; Henry, K. J.; VanderRoest, J. M. *Tetrahedron Lett.* **1991**, *32*, 4665.
26. Harada, T.; Iwai, H.; Takatsuki, H.; Fujita, K. *Org. Lett.* **2001**, *3*, 2101.
27. Van de Weghe, P.; Collin, J. *Tetrahedron Lett.* **1993**, *34*, 3881.
28. Kooijman, H.; Saraber, F. C. E.; de Groot, A.; Spek, A. L. *Acta Crystallogr., Sect. E* **2005**, *61*, 3921 for compound **10a**. Spek, A. L.; Menzer, S.; Meulemans, T.; de Groot, A. CCDC 227434 for compound **13b** and CCDC227438 for compound **13a**.
29. Heathcock, C. H.; Norman, M. H.; Ühling, D. E. *J. Am. Chem. Soc.* **1985**, *107*, 2797.
30. Heathcock, C. H.; Ühling, D. E. *J. Org. Chem.* **1986**, *51*, 279.
31. This one-pot procedure is termed a domino reaction although not all reagents are present in the reaction mixture from the start. On the other hand, the reaction conditions remain the same during the whole reaction time and for this reason, we estimate this term appropriate for the situation.
32. Quinkert, G.; Grosso, M. d.; Bucher, A.; Bats, J. W.; Dürner, G. *Tetrahedron Lett.* **1991**, *32*, 3357.
33. Posner, G. H.; Mallamo, J. P.; Black, A. Y. *Tetrahedron* **1981**, *37*, 3921.
34. Nazarov, I. N.; Torgov, I. V.; Verkholetova, G. P. *Dokl. Akad. Nauk SSSR* **1957**, *112*, 1067.
35. Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.
36. Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1984**, *25*, 2121.
37. Gauthier, V.; Cazes, B.; Goré, J. *Tetrahedron Lett.* **1991**, *32*, 915.
38. Das, J.; Kubela, R.; MacAlpine, G. A.; Stojanac, Z.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3308.
39. Dratch, S.; Charnikhova, T.; Sarabèr, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287.
40. Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047.
41. Hydrio, J.; van de Weghe, P.; Collin, J. *Synthesis* **1997**, 68.
42. Kopka, I.; Rathke, M. W. *J. Org. Chem.* **1981**, *46*, 3771.
43. Kruglaya, O. A.; Belousova, L. I.; Gendin, D. V.; Kalikhman, I. D.; Vyazankin, N. S. *J. Organomet. Chem.* **1980**, *201*, 69.
44. Hong, S. P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042.
45. Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1726–1742
Tetrahedron

New approaches toward the synthesis of (D-homo) steroid skeletons using Mukaiyama reactions

Florence C. E. Sarabèr,[a] Alexander Baranovsky,[a,b] Ben J. M. Jansen,[a] Maarten A. Posthumus[a] and Aede de Groot[a,*]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220141 Minsk, Belarus*

Received 20 May 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—New, short, and flexible procedures have been developed for syntheses of steroid and D-homo steroid skeletons. A Mukaiyama reaction between the silyl enol ether of 6-methoxytetralone and 2-methyl-2-cyclopentenone or carvone, with transfer of the silyl group to the receiving enone, gave a second silyl enol ether. Addition of a carbocation, generated under Lewis acid conditions from 3-methoxy-2-butenol, 3-ethoxy-3-phenyl-2-propenol or 3-methoxy-2-propenol to this second silyl enol ether gave adducts, which could not be cyclized by aldol condensation to (D-homo) steroid skeletons. The Mukaiyama–Michael reaction of the silyl enol ether of 6-methoxy tetralone with 2-methyl-2-cylopentenone gave a second silyl enol ether, which reacted in high yield with a carbocation generated from 3-hydroxy-3-(4-methoxyphenyl)propene. Ozonolysis of the double bond in this adduct gave a tricarbonyl compound (Zieglers triketone), which has been used before in the synthesis of 9,11-dehydroestrone methyl ether. A second synthesis of C17 substituted CD-trans coupled (D-homo) steroid skeletons has been developed via addition of a carbocation, generated with $ZnBr_2$ from a Torgov reagent, to a silyl enol ether containing ring D precursor. The obtained seco steroids have been cyclized under formation of the 8–14 bond by treatment with acid. The double bonds in one of the cyclized products have been reduced to a C17-substituted all trans steroid skeleton.

1. Introduction

The application of sequential Michael additions or Mukaiyama reactions in domino reactions is well known.[1–14] In some Mukaiyama–Michael additions transfer of the silyl group from the starting silyl enol ether to the receiving enone is a convenient variant, because this newly formed silyl enol ether can undergo a second Mukaiyama–Michael addition, potentially with a different enone.[1–10] With methyl vinyl ketone (MVK) as the second enone an intermediate is obtained, which can undergo a ring closing 1,6-aldol cyclisation and in this way polycyclic compounds can be obtained in short one pot domino sequences.[1,15]

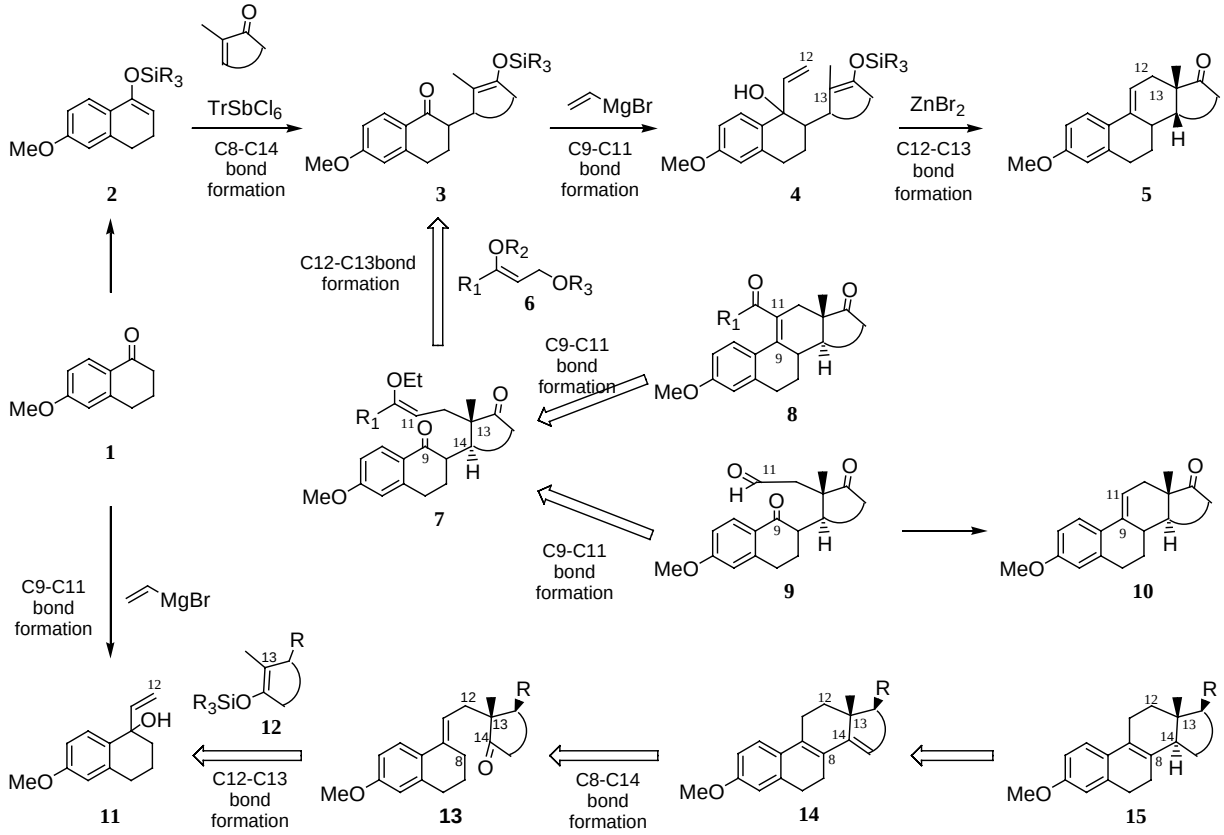
With a silyl enol ether derived from 6-methoxytetralone as the starting compound, high yielding additions to carvone and 2-methyl cyclopetenone have been achieved with transfer of the silyl group to new silyl enol ethers.[16] However, it appeared not to be possible to add methyl vinyl ketone via a Mukaiyama–Michael addition to these second silyl enol ethers.[15]

On the other hand alkylations of silyl enol ethers derived from 2-methyl-2-cyclopentanones with carbocation precursors are known in literature[17,18] and offer good prospect for steroid synthesis. Recently, we have published a short synthesis of (D-homo) steroid skeletons with cis fused CD ring systems using such an approach.[16] The key step in this synthesis is an intramolecular reaction of a carbocation precursor derived from a Torgov type reagent with a silyl enol ether in ring D, thus closing ring C by formation of the C12–C13 bond as the last step (see Scheme 1, **1**→**2**→**3**→**4**→**5**).

Short syntheses for trans CD fused (D-homo) steroids, also relying on the addition of easily generated carbocations to silyl enol ethers as key transformation, seemed feasible as well. Two such approaches, in which the sequence of bond formation in the nascent ring C has been varied, have been investigated. The first route should start again from adduct **3**, but now first the trans-fusion of the CD ring system should be secured via the introduction of an appropriately

Keywords: Mukaiyama–Michael addition; Silyl enol ethers; Torgov reagent; (D-homo) steroid synthesis; Carvone.
* Corresponding author. Tel.: +31 317482370; fax: +31 317484914; e-mail: aede.degroot@wur.nl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.056



Scheme 1.

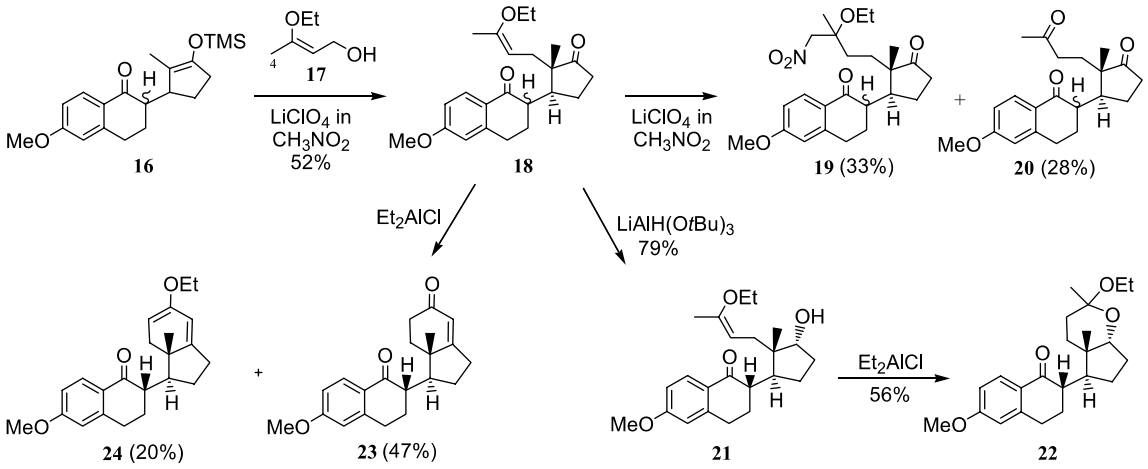
functionalised substituent at C13. For this purpose a congener of 3-methoxy-2-butenol[19–21] seemed most appropriate, as from this reagent a carbocation can be generated under mild Lewis acid conditions, compatible with the presence of a silyl enol ether in ring D. The enol ether in the introduced moiety in adduct **7** is located in the correct position for the closure of ring C by an aldol type cyclisation to steroid skeleton **8**, which should have a functional group at C11 as an additional advantage. Ozonolysis of the double bond in adduct **8** can be carried out as an alternative leading to Ziegler's triketone **9**, an intermediate, which has been cyclized before to steroid **10** using a McMurry reaction.[22–25] In these approaches the construction of the C9–C11 bond should be the last step in the closure of ring C (see Scheme 1, **1**→**2**→**3**→**7**→**8** or **1**→**2**→**3**→**7**→**9**→**10**).

A second approach to CD-trans-fused (D-homo) steroid skeletons might be possible in which the C12–C13 bond should be formed in the second step. An intermolecular Lewis acid catalysed reaction of the Torgov reagent **11** with a silyl enol ether containing ring D precursor **12** should lead to secosteroid **13** and an acid catalyzed cyclisation then should close ring C, now with formation of the C8–C14 bond as the last step. This method should give a quick access to a wide variety of C17-substituted steroid skeletons with a similar set of double bonds in the C and D rings as in the products from the normal Torgov reaction. Selective catalytic reduction then should yield the CD-trans-fused (D-homo) steroid skeletons (Scheme 1, **1**→**11**→**13**→**14**→**15**).[26]

2. Results and discussion

When silyl enol ether **16**, obtained from the reaction of the TMS ether of 6-methoxytetralone with 2-methyl -2-cyclopentenone as a 2:1 mixture of stereoisomers in 90% yield,[16] was brought in reaction with MVK, only desilylation of the starting material took place. However, it was found that the more reactive allylic alcohol **17**[27] did react with silyl enol ether **16** in a reasonable 52% yield, using 0.05–0.7 M concentrations of $LiClO_4$ in nitromethane[28–30,31] (Scheme 2). This result indicates that steric hindrance in the MVK addition with **16** is probably not the reason for the failure of this reaction, but that the lower reactivity of the carbonyl group in the tetralone part of the molecule for the aldol reaction fails to shift the equilibria toward cyclisation.[15] This was confirmed by the failure of other attempts to construct the C9–C11 bond via aldol type reactions (see Schemes 2 and 3).

Prolonged reaction times in a more concentrated $LiClO_4$ solution (4 M) did consume the addition product **18** but no cyclisation was observed and the isolated product was compound **19** in 28% yield, next to compound **20** in 33% yield; in the latter hydrolysis of the enol ether function has taken place. A selective reduction of the ring D carbonyl group of the main isomer of **18** led to one isomer of compound **21**, which was assumed to have the indicated structure. Application of mild Lewis acid cyclisation conditions rapidly led to acetal formation with the hydroxyl group of ring D, giving acetal **22** in 56% yield. Cyclisation of the main isomer of **18** under Lewis acid conditions did



Scheme 2.

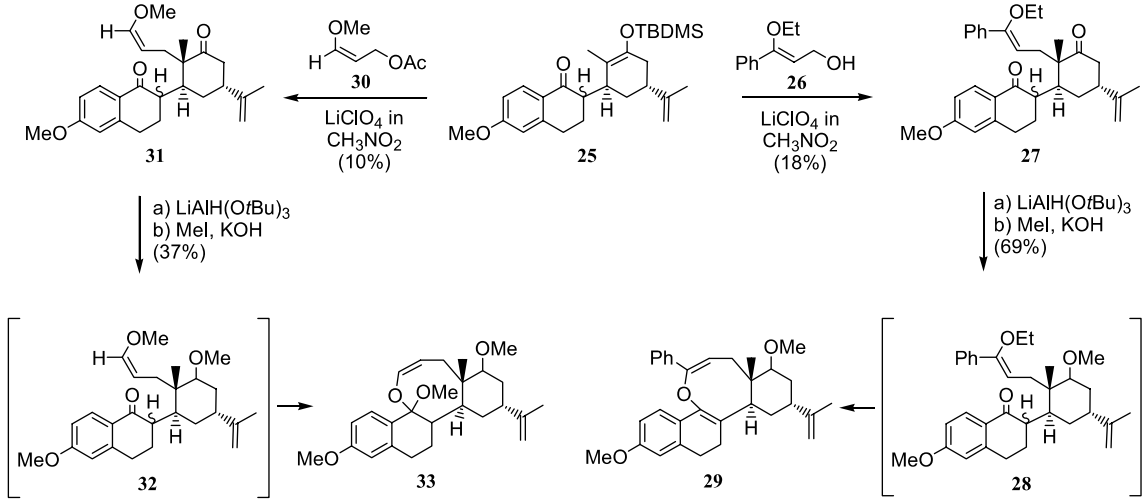
lead to an aldol type reaction but with the carbonyl group of ring D, giving compound **23** in 47% yield, together with its partially enolised compound **24** in 20% yield.

Also, with *R*-carvone as potential ring D precursor we have not been successful in the construction of the C9–C11 carbon bond. To exclude aldol condensation with the carbonyl group in ring D, position 4 in compound **17** (Scheme 2) was blocked by replacing the methyl group by a phenyl as in compound **26**, or by a hydrogen as in compound **30**,[32] the latter also minimizes steric hindrance. To prevent acetal formation, the carbonyl group in ring D was selectively reduced and the hydroxyl groups were protected as their methyl ethers **28** and **32** (Scheme 3). Moreover the more stable *tert*-butyldimethylsilyl (TBDMS) enol ether **25**[16] was used, instead of the trimethylsilyl (TMS) enol ether, to enhance the yield in the addition of the carbocation in favour of desilylation.

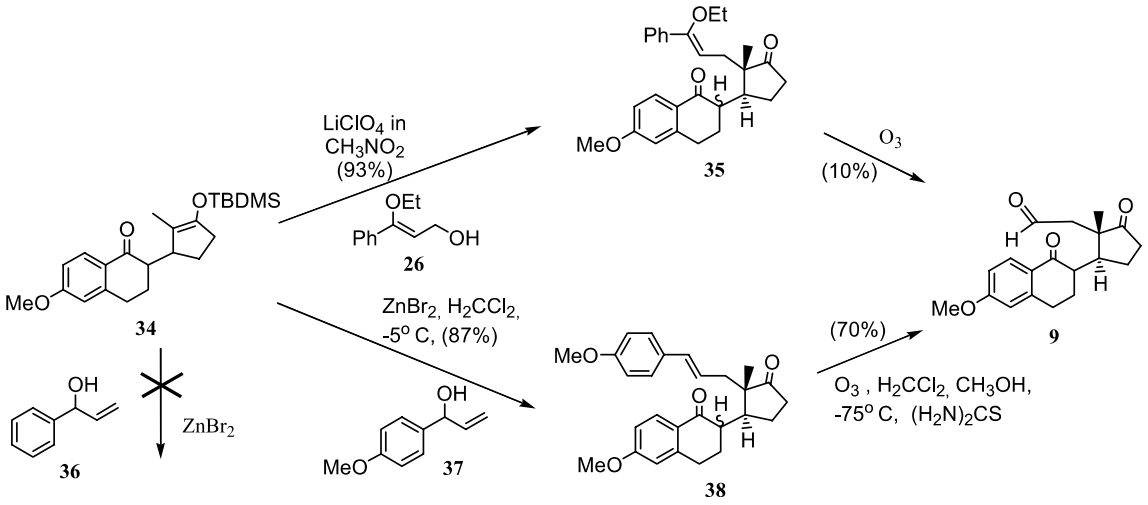
Desilylation of **25** in the addition with compound **26** could indeed be avoided using the TBDMS enol ether, but improvement of the yield of 20% in the addition reaction could not be achieved, the remaining being unreacted **25** in the best cases. Also in the reaction of **25** with the more reactive compound **30**, only 10% of the desired addition product **31** could be isolated next to desilylated products. However, when the same addition reactions were performed with a five-membered ring D silyl enol ether, good yields of the desired products were obtained (see below).

Although the yields of the addition reactions of carbocation precursors **26** and **30** with silyl enol ether **25** were low, enough of both products **27** and **31** had been isolated to proceed with the reaction sequence. In both compounds, the carbonyl group in ring D was reduced and the hydroxyl groups were immediately protected as their methyl ethers, as acetal formation similar to compound **24** quickly took place. Also, the methyl ethers **28** and **32** appeared to be very reactive and rapidly cyclized to ethers **29** and **33** during isolation. Apparently enolisation of the carbonyl group in the tetralone moiety is easily leading to alternative reactions preventing the desired aldol type cyclisation.

Although the experiments mentioned above did not lead to steroid skeletons, they did show that substituents can be introduced at C13 via reaction of carbocation precurors with the silyl enol ether in ring D. Especially in five-membered ring D silyl enol ethers this reaction proved to work very well and in this way compounds can be obtained with a double bond in the introduced side chain, which can be



Scheme 3.



Scheme 4.

ozonolysed to a carbonyl group, thus enabling a short synthesis of steroid precursor **9**, first synthesized by Ziegler.[22]

To enhance the yield of the carbocation addition reaction leading to compound **35**, several other Lewis acid catalysts ($BF_3 \cdot Et_2O$, $TrSbCl_6$, Tf_2O, MgI_2, TMSOTf, $ZnBr_2$) were compared with the results of the $LiClO_4$ reaction, but only $ZnBr_2$ proved to be equally effective. Finally, the use of $LiClO_4$ as catalyst in a reaction of carbocation precursor **26** with the TBDMS enol ether **34** gave an excellent 93% yield of **35** (Scheme 4). However, the ozonolysis of this adduct did not go well and only 10% of the desired triketone **9** could be isolated.[33–35]

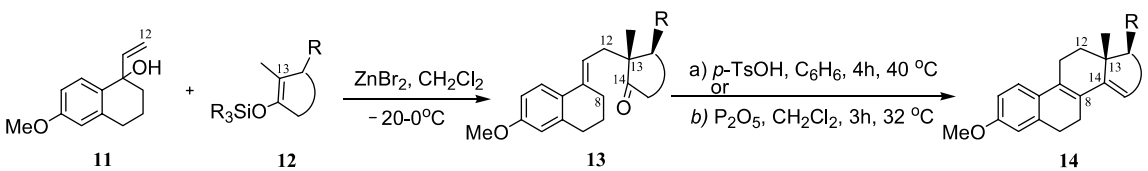
A solution for this problem was investigated by using a carbocation derived from alcohol **36**, which can be synthesised easily by the Grignard addition of vinyl magnesium bromide to benzaldehyde.[36] Addition of such a carbocation to silyl enol ether **34**, followed by ozonolysis of the now less substituted double bond in the adduct should lead to **9** in a very short and direct way. Surprisingly when the reaction of **34** with **36** was tried, no addition could be observed and only hydrolysis of silyl enol ether **34** took place. The main difference between compounds **36** and **26** is the presence of an extra ethoxy group in the latter. In the literature a successful addition of reagent **37**, with an extra methoxy group in the phenyl ring, has been reported.[18] The presence of this extra alkoxy group indeed proved to be important for the stabilisation of the carbocationic intermediate, because compound **37**, obtained from *para*-anisaldehyde and vinyl magnesium bromide,[37] afforded an excellent 87% yield of the addition product **38** when reacted with silyl enol ether **34**. Ozonolysis of **38** now proceeded in a good 70% yield to give steroid precursor **9**. In this way, a short and efficient synthesis of Zieglers triketone **9** could be achieved in 61% overall yield from 6-methoxytetralone in only four easy steps.

The second approach to CD-trans-fused steroid skeletons is based on a Lewis acid catalysed intermolecular addition of the Torgov reagent **11** to a silyl enol ether-containing ring D precursor **12**. (Scheme 5, Table 1).[26] The silyl enol ethers **12** were obtained by conjugate addition followed by capture of the enolate with a silylating agent (compounds **40**, **41**, **43** and **45**–**48**), via Mukaiyama–Michael reactions on enones with transfer of the silyl group from the starting enol ether to the enol of the adduct (compounds **42** and **50**), or by direct silylation of ketones (compounds **39**, **44** and **51**). In the case of silyl enol ether **49** Kharash conditions[38] were used to form the dienol ether from *R*-(−)-carvone.

In our experience, the TBDMS enol ethers are often the best compromise between stability and reactivity in Lewis acid catalysed reactions (see also above), but sometimes the more reactive trimethylsilyl (TMS) enol ethers were used. $ZnBr_2$ was chosen as Lewis acid catalyst, and all reactions were performed between −20 and 0 °C, in CH_2Cl_2 as solvent.

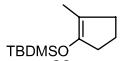
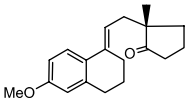
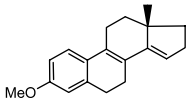
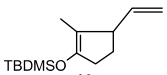
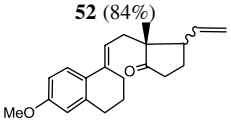
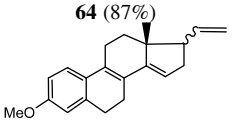
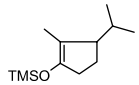
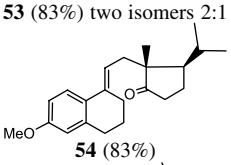
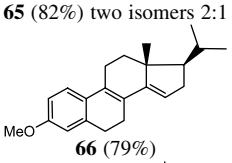
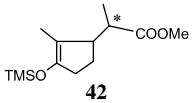
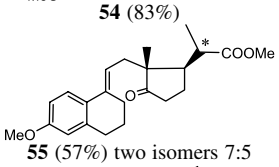
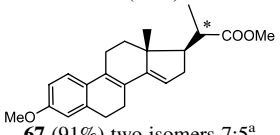
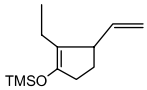
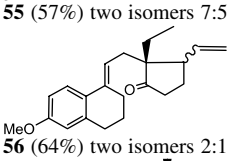
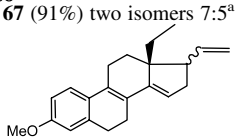
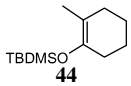
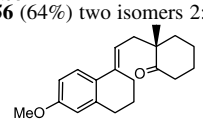
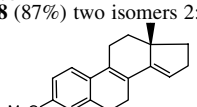
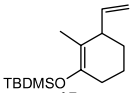
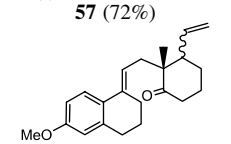
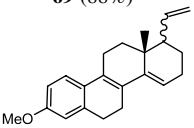
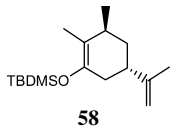
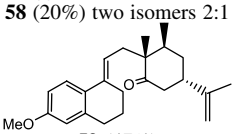
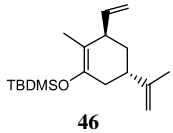
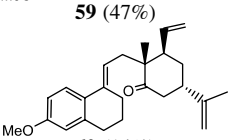
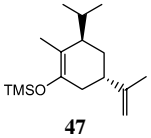
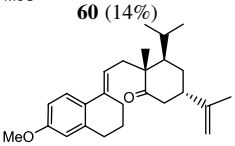
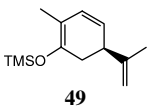
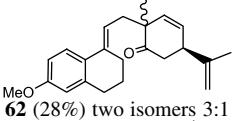
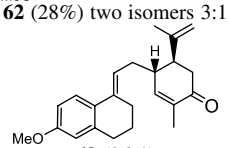
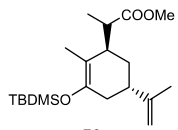
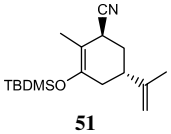
Under these conditions the reactions of the Torgov reagent **11** with silyl enol ethers of the cyclopentanones **39**–**43** to seco steroids **52**–**56** proceeded in excellent yields, as can be seen in Table 1.

Steric hindrance did not hamper the yields and improved the stereoselectivity from good to complete as shown by the results with compounds **53** and **54**. Even when the silyl enol ether had an ethyl group at C2, as in **43**, a good yield in the coupling with the Torgov reagent could be achieved,

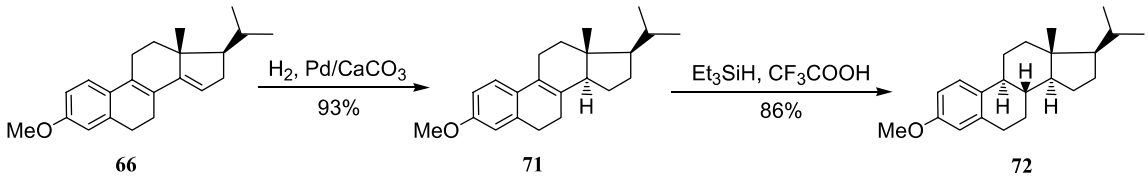


Scheme 5.

Table 1

Silyl enol ethers	Coupling product (% yield)	Cyclisation product (% yield)
 **39**	 **52** (84%)	 **64** (87%)
 **40**	 **53** (83%) two isomers 2:1	 **65** (82%) two isomers 2:1
 **41**	 **54** (83%)	 **66** (79%)
 **42**	 **55** (57%) two isomers 7:5	 **67** (91%) two isomers 7:5[a]
 **43**	 **56** (64%) two isomers 2:1	 **68** (87%) two isomers 2:1
 **44**	 **57** (72%)	 **69** (88%)[b]
 **45**	 **58** (20%) two isomers 2:1	 **70** (75%) two isomers 2:1
 **58**	 **59** (47%)	
 **46**	 **60** (14%)	Complex mixtures
 **47**	 **61** (18%)	
 **49**	 **62** (28%) two isomers 3:1	
	 **63** (26%)	
 **50**	 **51**	No product formation

[a] For both isomers of **67** the depicted stereochemistry was confirmed using NOE experiments.
[b] For all cyclisations *p*-TsOH in C^6H_6 was used except for compound **69**, where P_2O_5 was applied.



Scheme 6.

leading to seco steroid **56** with an angular ethyl group. The 2-ethyl substituted cyclopentanone derivatives often show a lower reactivity than their 2-methyl congeners.[39]

Similar reactions with silyl enol ethers derived from cyclohexanones, leading to D-homo steroid skeletons, gave more diverse results. The reaction of the 2-methyl cyclohexanone derivative **44** with the Torgov reagent proceeded in good yield, but higher substitution (compounds **45**–**48** and **50**) quickly lowered the yield, although the increase in stereoselectivity noticed in the reactions with the five-membered rings was maintained. Apparently in six-membered rings, steric hindrance influences the yield to a larger extend than in the corresponding five-membered rings. The silyl dienol ether derivative of carvone (**49**) reacted both on the α and on the γ position next to the ether function in a 1:1 ratio, yielding compounds **62** and **63**. The absence of reactivity of **51** probably has to be attributed to the lower nucleophilicity of the silyl enol ether due to the negative inductive effect of the cyano group.[40]

The ring closure of the seco steroids **52**–**56** to the unsaturated steroid skeletons **64**–**68** all gave very good results under mildly acidic conditions (catalytic *p*-TsOH in benzene at 40 °C). The cyclisation of D-homo seco steroid **57** was performed using P_2O_5 as catalyst (in CH_2Cl_2). When *p*-TsOH was used the reaction yielded next to 19% of the desired cyclized product **69** also 27% of the $\Delta_{9,11}-14$-hydroxycompound in which the dehydration after the cyclisation step had not taken place. Similar problems with the cyclisation step have been reported previously in literature for compounds with a carbonyl on C17a,[41] although good cyclisation results of these compounds using *p*-TsOH also have been reported.[42] Compound **57** could be cyclized in reasonable yield using *p*-TsOH but the higher substituted D-homo seco steroids all gave complex mixtures upon cyclisation, both with *p*-TsOH and P_2O_5. Probably the double bond of the isopropenyl group migrates before or after cyclisation, leading to aromatisation and to inseparable mixtures of several similar but not identical compounds.

The double bonds in the C and D rings in the steroid and D-homo steroid skeletons can be reduced catalytically to CD-trans fused steroid skeletons according to well known literature procedure.[43–47] As a trial this reduction was tested on compound **66** using $Pd/CaCO_3$ as catalyst, which gave the 13,14-trans reduced compound **71** in 93% yield (Scheme 6). Further reduction to an all-trans ring system has also been extensively reported in literature, and usually a reduction in liquid ammonia is used for the trans reduction of the $\Delta^{8,9}$ double bond, but a strong variation in yields is reported for these conditions.[43–52] Birch reduction conditions can be used when reduction of ring A to enones is also desired. Ionic reduction using triethylsilane and trifluoroacetic acid[46] also appeared effective and gave a 86% yield of **72** in our hands.[53,54]

In conclusion two short routes to CD-trans-fused steroid and D-homo steroid skeletons have been developed. The key feature in both approaches is the reaction of silyl enol ethers with functionalized carbocations, which can be generated under mild conditions. These reactions lead to seco steroid skeletons, which can be cyclized using known methods.

3. Experimental

3.1. General procedure. See[15]

3.1.1. [2-(6-Methoxy-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-1-methyl-5-oxo-cyclopentyl]-acetaldehyde (9). A solution of **38** (210 mg, 0.502 mmol) in 6.5 ml of CH_2Cl_2 and 26 ml of MeOH was cooled to −78 °C, and ozone was bubbled through the reaction mixture until the solution turned blue (15 min). The mixture was then purged with nitrogen for 15 min at −78 °C and treated with 0.6 equiv of thiourea (23 mg). The cold bath was removed and the reaction mixture was allowed to stir at room temperature for 1 h. The solvents were evaporated and the crude mixture was purified by column chromatography, yielding 110 mg of **9** (70%) as white crystals, which were recrystallised from *t*BuOMe (mp 110–112 °C; lit.[23] 108–110 °C from Et_2O). ^1H NMR (C_6D_6) δ: 1.07 (s, 3H), 1.50–1.75 (m, 2H), 1.95–3.15 (m, 10H), 3.82 (s, 3H), 6.64 (d, $J=2.5$ Hz, 1H), 6.79 (dd, $J=2.5$, 8.7 Hz, 1H), 7.89 (d, $J=8.7$ Hz, 1H), 9.33 (s, 1H); data are in accordance with literature values.[23]

3.1.2. (1*RS*)-6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (11). To an ice-cooled solution of vinyl magnesium bromide (65 ml, 1 M in THF) a solution of 6-methoxy-1-tetralone (3.0 g, 17 mmol) in THF (30 ml) was added dropwise over a period of 30 min. After complete addition the ice-bath was removed and the reaction mixture was stirred at 40 °C for 1 h. The reaction mixture was then cooled on ice again and a saturated water solution of NH_4Cl (25 ml) was carefully added, followed by EtOAc (25 ml). The layers were separated and the water layer was extracted with EtOAc (2×25 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc 9:1) yielding 3.2 g (92%) of pure **11** as a slightly yellow oil. IR (CCl_4 sol.) cm^{-1}: 3617, 3021, 2940, 2869, 2837, 1608, 1575, 1499, 1277, 1243; ^1H NMR ($CDCl_3$) δ: 1.72–2.07 (m, 5H), 2.62–2.91 (m, 2H), 3.78 (s, 3H), 5.18 (dd, $J_1=10.5$ Hz, $J_2=1.5$ Hz, 1H), 5.29 (dd, $J_1=17.1$ Hz, $J_2=1.5$ Hz, 1H), 6.02 (dd, $J_1=10.5$ Hz,

J_2=17.1 Hz, 1H), 6.62 (d, J=2.7 Hz, 1H), 6.74 (dd, J_1=8.6 Hz, J_2=2.7 Hz, 1H), 7.30 (d, J=8.6 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 19.32 (t), 30.12 (t), 37.91 (t), 55.215 (q), 73.03 (s), 112.58 (d), 112.88 (t), 113.18 (d), 129.43 (d), 132.19 (s), 138.62 (s), 145.08 (d), 158.73 (s). HRMS: M^+, found 204.1150. $C_{13}H_{16}O_2$ requires 204.1150. MS *m/e* (%) 204 (M^+, 46), 187 (13), 177 (100), 175 (32), 161 (17), 121 (12), 91 (6).

3.1.3. 6-Methoxy-2-(2-methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-3,4-dihydro-2*H*-naphthalen-1-one (16). To a solution of trimethylsilylenol ether **2**[TMS] (1.73 g, 7 mmol) and 2-methyl-2-cyclopentenone (0.5 g, 5.25 mmol) in CH_2C1_2 (30 ml), at −78 °C, was added $TrSbC1_6$ (0.03 g, 0.07 mmol). After 1 h some drops of pyridine were added to destroy the catalyst, and the yellow colour of the reaction mixture immediately disappeared. The reaction mixture was allowed to warm to room temperature, washed with brine, dried (Na_2SO_4), and the solvent was evaporated. Compound **16** was obtained as a mixture of two diastereomers in a 2:1 ratio in 90% yield (1.63 g, colourless oil). IR (CCl_4 sol.) cm^{-1}: 2941, 2851, 1673, 1600, 1333, 1252; ^{1}H NMR ($CDCl_3$) δ: 0.14 (*M*) and 0.18 (m) (s, 9H), 1.27 (*M*) and 1.50 (m) (s, 3H), 1.41–2.73 (m, 7H), 2.86–3.00 (dd, J_1=3.7 Hz, J_2=8.3 Hz, 2H), 3.40–3.55 (m) and 3.55–3.65 (*M*) (m, 1H), 3.83 (s, 3H), 6.66 (d, J=2.5 Hz, 1H), 6.81 (dd, J_1=2.5 Hz, J_2=8.7 Hz, 1H), 8.00 (m) and 8.01 (*M*) (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 0.6 (3q), 10.3 (m) and 11.9 (*M*) (q), 22.4 (m) and 23.6 (*M*) (t), 22.9 (m) and 25.0 (*M*) (t), 29.8 (*M*) and 29.9 (m) (t), 32.9 (*M*) and 33.1 (m) (t), 43.3 (*M*) and 43.9 (m) (d), 49.7 (m) and 52.2 (*M*) (d), 55.4 (q), 112.4 (d), 113.0 (d), 114.4 (s), 126.5 (*M*) and 127.1 (m) (s), 129.7 (m) and 123.0 (*M*) (d), 146.5 (*M*) and 146.8 (m) (s), 147.9 (m) and 148.1 (*M*) (s), 163.3 (s), 197.8 (*M*) and 199.0 (m) (s). HRMS: M^+, found 344.1807. $C_{20}H_{28}O_3Si$ requires 344.1808. MS *m/e* (%) 344 (M^+, 9), 249 (8), 248 (34), 138 (8), 176 (36), 170 (15), 169 (100).

3.1.4. 2-[2-(3-Ethoxy-but-2-enyl)-2-methyl-3-oxo-cyclopentyl]-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (18). A solution of silyl enol ether **16** (415 mg, 1.2 mmol) and $LiClO_4$ (370 mg, 3.5 mmol, which was previously dried at 90 °C/20 mm for 1 h), in nitromethane (5 ml) was cooled to 5 °C and allyl alcohol **17**[27] (183 mg, 1.54 mmol) was added dropwise over a period of 2 h. The resulting solution was stirred for 3 h at room temperature, then water was added and organic phase was extracted with EtOAc, washed with brine, dried and evaporated. Separation by column chromatography on silica gel (PE/EtOAc 4:1, with 2% of pyridine) gave **18** (234 mg, 52%) as a colourless oil (mixture of two isomers 2:1). IR (film): 2975, 1738, 1668, 1601, 1252, 734; ^{1}H NMR ($CDCl_3$): 0.93 (*M*) and 0.97 (m) (s, 3H), 1.08 (m) and 1.18 (*M*) (t, J=7.0 Hz, 3H), 1.54 (m) and 1.71 (*M*) (s, 3H), 1.50–2.40 (m, 9H), 2.45–3.05 (m, 3H), 3.30 (m) and 3.55 (*M*) (q, J=7.0 Hz, 2H), 3.77 (s, 3H), 3.87 (m) and 4.13 (*M*) (t, J=7.4 Hz, 1H), 6.61 (d, J=2.4 Hz, 1H), 6.73 (dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H), 7.88 (*M*) and 7.91 (m) (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): 14.6 (q), 16.4 (m) and 16.6 (*M*) (q), 18.0 (q), 22.6 (m) and 23.1 (*M*) (t), 26.2 (m) and 27.9 (*M*) (t), 28.1 (t), 34.2 (m) and 36.3 (*M*) (t), 36.8 (*M*) and 37.1 (m) (t), 39.6 (m) and 42.6 (*M*) (d), 47.7 (m) and 48.9 (*M*) (d), 52.4 (m) and 53.0 (*M*) (s), 55.4 (q), 61.7 (m) and 62.0 (*M*) (t), 91.9 (m) and 92.2 (*M*) (d), 112.4 (d), 113.2 (d), 126.2 (m) and 126.4 (*M*) (s), 129.8 (*M*) and 130.2 (m) (d), 145.6 (m) and 145.9 (*M*) (s), 154.5 (s), 163.5 (s), 198.5 (s), 222.0 (*M*) and 222.9 (m) (s). HRMS: M^+, found 370.2141. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 3), 342 (8), 285 (5), 272 (25), 271 (9), 176 (97), 117 (16), 99 (100), 71 (34), 73 (13).

3.1.5. 2-(2′-(3″-Ethoxy-3″-methyl-4″-nitrobutyl)-2′-methyl-3′-oxocyclopentyl)-6-methoxy-3,4-dihydro-2*H*naphalene-1-one (19). To a solution of ethyl enol ether **18** (140 mg, 0.38 mmol) in nitromethane (5 ml) at −5 °C was added $LiClO_4$ (2.13 g, 20 mmol, previously dried for 1 h at 90 °C/20 mm). The reaction mixture was stirred for 48 h at room temperature, then water (5 ml) and EtOAc (20 ml) were added and the layers separated. The water phase was extracted once with EtOAc (10 ml) and the combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 6:4) yielding **19** as a colourless oil in 33% yield (54 mg), next to compound **20** (28%, 36 mg).

Compound **19**. IR (film): 2977, 1731 (CO), 1672 (CO), 1650, 1600, 1551, 1252, 732; ^{1}H NMR: 0.99 (s, 3H), 1.00–1.12 (m, 4H), 1.27 (s, 3H), 1.30–2.50 (m, 10H), 2.55–2.73 (m, 1H), 2.85–3.05 (m, 2H), 3.37 (q, J=7.0 Hz, 2H), 3.82 (s, 3H), 4.42 (m, 2H), 6.66 (d, J=2.6 Hz, 1H), 6.78 (dd, J_1=2.6 Hz, J_2=8.6 Hz, 1H), 7.91 (d, J=8.6 Hz, 1H); ^{13}C NMR: 15.5 (q), 17.8 and 18.0 (q), 21.4 and 21.6 (q), 23.0 (t), 27.7 (t), 27.9 (t), 28.1 and 28.3 (t), 31.4 and 31.6 (t), 36.6 (t), 42.7 and 43.1 (d), 48.7 (d), 51.5 (s), 55.4 (q), 57.3 (t), 75.4 and 75.6 (s), 80.3 and 80.7 (d), 112.3 (d), 113.4 (d), 126.2 (s), 129.8 (d), 145.9 (s), 163.6 (s), 198.3 and 198.4 (s), 221.7 and 221.8 (s).

3.1.6. 2-(2′-Methyl-3′-oxo-2′-(3″-oxobutyl)-cyclopentyl)-6-methoxy-3,4-dihydro-2*H*naphalene-1-one (20). IR (film): 2941, 1732 (CO), 1714 (CO), 1667 (CO), 1600, 1252; ^{1}H NMR: 0.92 (s, 3H), 2.06 (s, 3H), 2.92 (t, J=6 Hz, 2H), 3.77 (s, 3H), 6.61 (d, J=2.4 Hz, 1H), 6.73 (dd, J=2.4, 8.3 Hz, 1H), 7.88 (d, J=8.3 Hz, 1H); ^{13}C NMR: 17.2 (q), 22.6 (t), 28.0 (t), 28.4 (t), 30.1 (q), 32.0 (t), 36.3 (t), 38.5 (t), 44.7 (d), 49.0 (d), 50.9 (s), 55.4 (q), 112.4 (d), 113.3 (d), 126.3 (s), 129.8 (d), 145.9 (s), 163.6 (s), 198.3 (s), 208.2 (s), 221.4 (s).

3.1.7. *E*-2-(3′-Hydroxy-2′-(3″-ethoxybut-2″-enyl)-2′-methylcyclopentyl)-6-methoxy-3,4-dihydro-2*H*naphalene-1-one (21). The main isomer of ethyl enol ether **18** (117 mg, 0.31 mmol) was dissolved in THF (7 ml) and the solution was refluxed for 36 h. During this period (tBuO)$_3$-LiAlH (190 mg, 0.75 mmol) was added in two portions. Then the solution was cooled on ice, treated with EtOAc (2 ml), a saturated solution of K_2CO_3 (0.5 ml) and filtered over a short plug of Na_2SO_4. After removal of the solvent, column chromatography (PE/EtOAc 4:1, with 5% of Et_3N) afforded one isomer of alcohol **21** (92 mg, 79%). IR (film): 3400 (OH), 2940, 1650, 1585, 1264, 740; ^{1}H NMR: 0.92 (s, 3H), 1.18 (t, J=7.0 Hz, 3H), 1.73 (s, 3H), 2.56 (m, 1H), 2.92 (m, 2H), 3.55 (q, J=7.0 Hz, 2H), 3.77 (m, 1H), 3.77 (obsc. s, 3H), 4.38 (t, J=7.8 Hz, 1H), 6.60 (d, J=2.4 Hz, 1H), 6.73 (dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H), 7.89

(d, J=8.8 Hz, 1H); ^{13}C NMR: 14.6 (q), 15.2 (q), 16.5 (q), 25.0 (t), 28.5 (t), 29.8 (t), 31.0 (t), 39.7 (t), 46.0 (d), 48.3 (d), 48.6 (s), 55.3 (q), 61.8 (t), 79.5 (d), 93.0 (d), 112.2 (d), 113.0 (d), 126.6 (s), 129.9 (d), 146.0 (s), 154.0 (s), 163.4 (s), 200.0 (s). HRMS: M^+, found 372.2296. $C_{23}H_{32}O_4$ requires 372.2301. MS *m/e* (%) 372 (M^+, 5), 326 (14), 178 (28), 176 (100), 99 (46), 71 (20), 43 (13).

3.1.8. 2-(2-Ethoxy-2,4a-dimethyl-octahydro-cyclopenta-[*b*]pyran-5-yl)-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (22). Compound **21** (82 mg, 0.22 mmol) was dissolved in CH_2Cl_2 (20 ml) and 1 M solution of Et_2AlCl in hexane (0.24 ml) was added at −70 °C. The reaction mixture was stirred for 1 h at this temperature and then 1 M HCl solution was added and the reaction mixture was diluted with Et_2O, washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (PE/EtOAc 4:1) afforded **22** (46 mg, 56%) as a thick oil. IR (film) cm^{-1}: 2948, 1673, 1600, 1271; ^{1}H NMR ($CDCl_3$) δ: 0.87 (s, 3H), 1.12 (t, J=7.2 Hz, 3H), 1.10–3.23 (m, 14H), 3.40 (q, J=7.2 Hz, 2H), 3.55 (d, J=5.5 Hz, 1H), 3.83 (s, 3H), 6.64 (d, J=2.5 Hz, 1H), 6.79 (dd, J_1=2.5 Hz, J_2=8.7 Hz, 1H), 7.87 (d, J=8.7 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 11.4 (q), 15.9 (q), 21.3 (t), 21.8 (q), 24.1 (t), 24.8 (t), 29.3 (t), 29.4 (t), 36.1 (t), 39.6 (s), 42.6 (d), 44.8 (d), 55.2 (q), 56.1 (t), 80.6 (d), 101.2 (s), 112.4 (d), 113.1 (d), 131.2 (s), 131.2 (d), 142.5 (s), 163.6 (s), 205.9 (s). HRMS: M^+, found 372.2310. $C_{23}H_{32}O_4$ requires 372.2301. MS *m/e* (%) 372 (M^+, 0.5), 344 (1), 326 (42), 189 (8), 176 (100), 175 (16), 148 (9), 137 (8), 109 (7).

3.1.9. 2-(7′a-Methyl-5′-oxo-1′,2′,3′,6′,7′,7′a-hexahydroindenyl)-6-methoxy-3,4-dihydro-2*H*-naphalene-1-one (23). The main isomer of ethyl enol ether **18** (229 mg, 0.62 mmol) was dissolved in dichloromethane (6 ml) and a 1 M solution of Et_2AlCl in hexane (0.7 ml) was added at −70 °C. The solution was stirred for 30 min at indicated temperature and then for another 30 min at room temperature. HCl solution (1 M) was added and the reaction mixture was diluted with Et_2O, washed with water and brine, dried ($MgSO_4$) and the solvent was evaporated. Column chromatography (PE/EtOAc 4:1, with 2% of pyridine) afforded 95 mg **23** (47%) and 43 mg of **24** (20%), both as colourless oils.

Compound **23**. IR (KBr) cm^{-1}: 2960, 2940, 2879, 2863, 1669, 1598, 1348, 1256; ^{1}H NMR ($CDCl_3$): 1.18 (s, 3H), 2.85 (dt, J_1=4.5 Hz, J_2=17.5 Hz, 2H), 3.12 (m, 2H), 3.82 (s, 3H), 5.72 (s, 1H), 6.66 (d, J=2.4 Hz, 1H), 6.80 (dd, J_1=2.4 Hz, J_2=8.8 Hz, 1H), 7.91 (d, J=8.8 Hz, 1H); ^{13}C NMR ($CDCl_3$): 16.4 (q), 26.1 (t), 26.6 (t), 26.9 (t), 29.0 (t), 33.5 (t), 36.6 (t), 45.3 (s), 47.0 (d), 47.9 (d), 55.5 (q), 112.4 (d), 113.4 (d), 121.8 (d), 125.9 (s), 130.0 (d), 145.4 (s), 157.3 (s), 163.5 (s), 178.8 (s), 198.7 (s), 198.8 (s). HRMS: M^+, found 324.1723. $C_{21}H_{24}O_3$ requires 324.1725. MS *m/e* (%) 324 (M^+, 10), 202 (5), 176 (100), 175 (13), 161 (7), 148 (15), 121 (8), 91 (7).

3.1.10. 2-(5-Ethoxy-7a-methyl-2,3,7,7a-tetrahydro-1*H*-inden-1-yl)-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (24). IR (film): 2964, 2939, 1668, 1600, 1259, 732; ^{1}H NMR ($CDCl_3$): 0.98 (s, 3H), 1.30 (t, J=7 Hz, 3H), 1.66 (dt, J_1=5.8 Hz, J_2=12.2 Hz, 2H), 2.40 (m, 2H), 2.78 (m, 2H), 3.15 (m, 1H), 3.76 (m, 2H), 3.82 (s, 3H), 5.11 (br s, 1H), 5.26 (d, J=1.4 Hz, 1H), 6.66 (d, J=2.4 Hz, 1H), 6.78 (dd, J_1=2.4 Hz, J_2=8.6 Hz, 1H), 7.91 (d, J=8.6 Hz, 1H); ^{13}C NMR ($CDCl_3$): 14.6 (q), 15.5 (q), 25.7 (t), 26.2 (t), 26.4 (t), 35.6 (t), 35.9 (t), 45.9 (s), 46.7 (d), 47.8 (d), 55.4 (q), 62.4 (t), 93.7 (d), 112.4 (d), 113.2 (d), 116.5 (d), 126.1 (s), 129.9 (d), 145.7 (s), 147.5 (s), 157.3 (s), 163.3 (s), 199.9 (s).

3.1.11. 3-Ethoxy-3-phenyl-prop-2-en-1-ol (26). Ethylbenzoylacetate (19.2 g, 100 mmol) and triethylorthoformate (14.8 g, 100 mmol) were stirred at room temperature and five drops of concentrated H_2SO_4 were added. The reaction mixture was left to stir overnight after which ethanol and ethylformate were removed under reduced pressure. The residue was purified by distillation (135 °C, 2 Torr), yielding 17.9 g of a colourless oil. This product was dissolved in Et_2O (50 ml) and added dropwise, at 0 °C, to a suspension of lithium aluminum hydride ($LiAlH_4$, 2.94 g, 77.5 mmol) in Et_2O (300 ml). The reaction mixture was stirred for 5 h at room temperature, until TLC showed no remaining starting material. The excess of $LiAlH_4$ was destroyed by addition of water (3.9 ml), 4 M NaOH solution (3.9 ml) and again water (11.7 ml). The white precipitate was filtered off and washed carefully with Et_2O (100 ml). The filtrate was dried over Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (PE/Et_2O 2:1) yielded **26** as a colourless oil in 37% overall yield (6.66 g, mixture of two isomers *E*/*Z*[55] 3:2). IR (CCl_4 sol.) cm^{-1}: 3621, 3479 (br), 3062, 3028, 2981, 2932, 2881, 1645, 1231, 1134, 989; ^{1}H NMR ($CDCl_3$) δ: 1.26 (m, t, J=7.0 Hz) and 1.36 (*M*, t, J=6.9 Hz) (3H), 1.88 (*M*) and 2.30 (m) (br s, 1H), 3.73 (m, q, J=7.0 Hz) and 3.87 (*M*, q, J=6.9 Hz) (2H), 4.13 (*M*, d, J=7.7 Hz) and 4.38 (m, d, J=6.7 Hz) (2H), 4.98 (*M*, t, J=7.7 Hz) and 5.49 (m, t, J=6.7 Hz) (1H), 7.10–7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 14.6 (*M*) and 15.2 (m) (q), 57.6 (m) and 59.6 (*M*) (t), 63.2 (*M*) and 66.3 (m) (t), 99.1 (*M*) and 113.1 (m) (d), 126.3 (d), 127.1 (d), 128.0 (d), 128.4 (d), 128.6 (d), 135.5 (s), 155.7 (m) and 158.7 (*M*) (s). HRMS: M^+, found 178.0987. $C_{11}H_{14}O_2$ requires 178.0994. MS *m/e* (%) 178 (M^+, 19), 177 (6), 149 (13), 135 (28), 105 (100), 103 (14), 91 (12), 77 (29).

3.1.12. 2-[2-(3-Ethoxy-3-phenyl-allyl)-5-isopropenyl-2-methyl-3-oxo-cyclohexyl]-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (27). Silyl enol ether **25** was prepared as described in the literature[16] and reacted further as described for compound **18**. Yield: 18% (78% relative to reacted **25**), as two separate main isomers **27a** and **27b** and a small amount of an inseparable mixture of two minor isomers **27c** and **27d** (isomeric ratio a/b/c/d=26.5:22:4:1). Next to the desired product were isolated: 77% of compound **25**[16] and about 25% of unreacted **26**, together with approximately 2% of desilylated **25** and small amounts of unidentified products.

Isomer **27a**. IR (CCl_4 sol.) cm^{-1}: 2962, 2931, 2871, 1711, 1675, 1601, 1250; ^{1}H NMR ($CDCl_3$) δ: 0.76–3.15 (m, 13H), 1.01 (s, 3H), 1.30 (t, J=7.0 Hz, 3H), 1.59 (s, 3H), 3.81 (dq obsc., J_1=2.3 Hz, J_2=7.0 Hz, 2H), 3.84 (s obsc., 3H), 4.62 (s, 1H), 4.71 (dd, J_1=5.7 Hz, J_2=8.3 Hz, 1H), 4.77 (s, 1H), 6.60 (d, J=2.5 Hz, 1H), 6.82 (dd, J_1=2.5 Hz, J_2=8.8 Hz, 1H), 7.10–7.43 (m, 5H), 8.01 (d, J=8.8 Hz, 1H); ^{13}C NMR

($CDCl_3$) δ: 14.7 (q), 17.2 (q), 21.6 (q), 25.3 (t), 26.7 (t), 28.8 (t), 31.0 (t), 40.5 (d), 41.3 (d), 43.4 (t), 47.5 (d), 51.0 (s), 55.5 (q), 63.0 (d), 94.4 (d), 110.9 (t), 112.2 (d), 113.5 (d), 125.4 (s), 128.0 (2d), 128.1 (d), 128.7 (2d), 130.8 (d), 136.1 (s), 144.4 (s), 147.3 (s), 155.6 (s), 163.4 (s), 198.5 (s), 214.8 (s). HRMS: M^+, found 486.2771. $C_{32}H_{38}O_4$ requires 486.2770. MS *m/e* (%) 486 (M^+, 8), 457 (10), 440 (2), 336 (40), 335 (39), 308 (23), 179 (34), 161 (100), 133 (30), 105 (33), 55 (20).

Isomer **27b**. White crystals (mp 119–123 °C, from hexane/ethyl acetate). IR (CCl_4 sol.) cm^{-1}: 2976, 2938, 2875, 1704, 1679, 1602, 1249; ^1H NMR ($CDCl_3$) δ: 1.06 (s, 3H), 1.26 (d, $J=7.2$ Hz, 1H), 1.32 (t, $J=6.9$ Hz, 3H), 1.62 (s, 3H), 1.60–3.25 (m, 12H), 3.80 (q obsc., $J=6.9$ Hz, 2H), 3.84 (s obsc., 3H), 4.51 (dd, $J_1=5.9$ Hz, $J_2=9.3$ Hz, 1H), 4.62 (s, 1H), 4.77 (s, 1H), 6.60 (d, $J=2.5$ Hz, 1H), 6.82 (dd, $J=2.5$, 8.7 Hz, 1H), 7.05–7.55 (m, 5H), 7.99 (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.8 (q), 20.7 (q), 20.8 (q), 26.4 (t), 27.0 (t), 30.5 (t), 35.6 (t), 37.1 (d), 42.3 (d), 42.5 (t), 49.1 (d), 52.1 (s), 55.5 (q), 63.1 (d), 95.2 (d), 111.0 (t), 112.3 (d), 113.0 (d), 126.6 (s), 127.8 (2d), 127.9 (d), 129.0 (2d), 129.9 (d), 136.1 (s), 145.8 (s), 147.5 (s), 156.4 (s), 163.2 (s), 197.3 (s), 216.0 (s). HRMS: M^+, found 486.2773. $C_{32}H_{38}O_4$ requires 486.2770. MS *m/e* (%) 486 (M^+, 2), 457 (1), 440 (1), 326 (4), 176 (100), 161 (26), 150 (10), 105 (8).

Mixture of isomers **27c** *and* **27d**. ^1H NMR ($CDCl_3$) δ: 0.77–3.30 (m), 1.05 (*M*) and 1.32 (m) (t, $J=7.1$ Hz, 3H), 1.17 (m) and 1.21 (*M*) (s, 3H), 1.61 (m) and 1.76 (*M*) (s, 3H), 3.56 (*M*, dq, $J_1=5.3$ Hz, $J_2=7.1$ Hz) and (3.79 (m, q, $J=7.1$ Hz) (2H), 3.83 (s, 3H), 4.50 (m, dd, $J_1=5.7$ Hz, $J_2=9.3$ Hz) and 5.00 (*M*, t, $J=8.7$ Hz) (1H), 4.61 (m) and 4.72 (*M*) (s, 1H), 4.80 (br s, 1H), 6.60 (m) and 6.66 (*M*) (d, $J=2.6$ Hz, 1H), 6.80 (dd, $J=2.6$, 8.7 Hz, 1H), 7.03–7.65 (m, 5H), 7.97 (*M*) and 7.99 (m) (d, $J=8.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.8 (m) and 15.4 (*M*) (q), 20.4 (*M*) and 20.7 (m) (q), 20.8 (q), 27.1 (t), 27.4 (t), 30.7 (t), 34.4 (*M*) and 35.4 (m) (t), 37.2 (m) and 38.8 (*M*) (d), 42.2 (m) and 42.5 (*M*) (d), 42.6 (t), 49.1 (m) and 49.7 (*M*) (d), 51.4 (*M*) and 52.0 (m) (s), 55.5 (q), 63.1 (m) and 65.6 (*M*) (t), 108.8 (d), 110.8 (t), 112.3 (d), 113.1 (d), 126.5 (s), 126.6 (d), 127.9 (d), 128.2 (2d), 128.9 (d), 130.0 (d), 136.2 (s), 145.9 (s), 147.5 (s), 155.7 (s), 163.3 (s), 197.5 (s), 216.3 (s).

3.1.13. 3-Isopropenyl-1,8, 10b-trimethoxy-14a-methyl-1,2,3,4,4a,4b,5,6,10b,14,14a-undecahydro-11-oxa-benzo-[3,4]cycloocta[1,2-*a*]naphthalene (29). Compound **27b** (100 mg, 0.21 mmol) was dissolved in THF (7 ml) and $Li(tBuO)_3AlH$ (104 mg, 0.42 mmol) was added in two portions (second portion after 1 h reaction time). The reaction mixture was refluxed during 3 h and then the solution was cooled on ice, treated with EtOAc (2 ml), 1 M $NaHSO_4$ solution (0.5 ml) and filtered over a short plug of Na_2SO_4. The solvent was evaporated and the residue was dissolved in DMSO (2 ml) and cooled on ice before pulverised KOH (47 mg, 0.84 mmol) was added. After stirring for 5 min, MeI (26 µl, 0.42 mmol) was added and stirring was continued for 2 h at room temperature. The reaction mixture was diluted with CH_2Cl_2 (10 ml) and washed with water (10 ml) and brine (10 ml), dried ($MgSO_4$) and solvent removed under reduced pressure. Column chromatography (PE/EtOAc 3:1) afforded compound **29** as a slightly yellow oil (22 mg, 23%) and compound **28** (48 mg, 46%), which rapidly cyclized to **29** upon evaporation of the solvent, next to some remaining starting material **27b**. ^1H NMR (C_6D_6) δ: 1.01 (s, 3H), 1.50–2.70 (m, 10H), 1.65 (s, 3H), 3.15–3.30 (m, 1H), 3.43 (s, 6H), 4.18 (dd, $J_1=4.2$ Hz, $J_2=11.9$ Hz, 1H), 5.02 (s, 1H), 5.07 (s, 1H), 5.35 (dd, $J_1=2.4$ Hz, $J_2=5.7$ Hz, 1H), 6.77 (dd, $J_1=2.6$ Hz, $J_2=8.4$ Hz, 1H), 6.85 (d, $J=2.6$ Hz, 1H), 7.05–7.35 (m, 3H), 7.43 (d, $J_1=8.4$ Hz, 1H), 7.79 (d, $J_1=9.7$ Hz, 2H); ^{13}C NMR (C_6D_6) δ: 12.9 (q), 22.6 (q), 26.9 (t), 28.5 (t), 29.3 (2t), 36.5 (t), 37.0 (s), 38.9 (d), 39.0 (d), 54.6 (q), 58.8 (q), 77.4 (d), 97.0 (d), 111.1 (d), 111.3 (t), 113.8 (d), 122.4 (s), 123.8 (d), 124.5 (2d), 127.5 (2d), 128.4 (d), 136.3 (s), 139.4 (s), 146.1 (2s), 149.9 (s), 150.6 (s), 159.1 (s). HRMS: M^+, found 456.2658. $C_{31}H_{36}O_3$ requires 456.2664. MS *m/e* (%) 456 (M^+, 100), 441 (26), 308 (23), 269 (17), 216 (28), 105 (35).

3.1.14. 2-[5-Isopropenyl-2-(3-methoxy-allyl)-2-methyl-3-oxo-cyclohexyl]-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (31). The reaction was carried out as described for compound **18**. A complex mixture was obtained from which a 10.5% yield of **31** could be isolated as a slightly yellow oil and as a mixture of two isomers (2:3), next to minor amounts of other compounds. IR (CCl_4 sol.) cm^{-1}: 2956, 2938, 2869, 2839, 1707, 1678, 1601, 1250; ^1H NMR (C_6D_6) δ: 0.85–3.02 (m, 10H), 0.94 (s, 3H), 1.13 (d, $J=6.7$ Hz, 2H), 1.45 (m) and 1.63 (*M*) (s, 3H), 3.23 (s, 3H), 3.26 (s, 3H), 3.38–3.54 (m, 1H), 4.75 (dt, $J_1=7.8$ Hz, $J_2=12.6$ Hz, 1H), 4.86 (s, 1H), 4.89 (*M*) and 4.94 (m) (s, 1H), 6.35 (d, $J=12.6$ Hz, 1H), 6.40–6.69 (m, 3H), 8.25 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 13.0 (*M*) and 21.8 (m) (q), 20.8 (*M*) and 20.9 (m) (q), 26.5 (*M*) and 26.7 (m) (t), 27.0 (*M*) and 29.4 (m) (t), 29.4 (m) and 30.1 (*M*) (t), 35.1 (*M*) and 40.5 (m) (d), 35.6 (t), 41.6 (*M*) and 47.8 (m) (d), 42.5 (*M*) and 44.0 (m) (t), 48.4 (m) and 48.7 (*M*) (d), 51.8 (s), 54.6 (q), 55.1 (q), 97.1 (d), 111.4 (*M*) and 112.6 (m) (t), 112.7 (2d), 129.8 (m) and 130.1 (*M*) (d), 130.1 (s), 145.7 (s), 146.5 (s), 147.1 (s), 149.7 (d), 163.3 (s), 196.0 (*M*) and 196.8 (m) (s), 210.4 (m) and 213.1 (*M*) (s). HRMS: M^+, found 396.2307. $C_{25}H_{32}O_4$ requires 396.2301. MS *m/e* (%) 396 (M^+, 2), 364 (2), 326 (6), 325 (5), 176 (100), 161 (6), 150 (15), 71 (13).

3.1.15. 3-Isopropenyl-1,8-dimethoxy-14a-methyl-12-phenyl-1,2,3,4,4a,4b,5,6,10b,14,14a-undecahydro-11-oxa-benzo[3,4]cycloocta[1,2-*a*]naphthalene (33). The reaction was carried out as described for compound **29**. The acetal **33** was obtained as a slightly yellow oil in 37% yield. IR (CCl_4 sol.) cm^{-1}: 2937, 2833, 1649, 1607, 1496, 1449, 1252, 1039; ^1H NMR (C_6D_6) δ: 0.93 (s, 3H), 1.70 (s, 3H), 1.34–2.62 (m, 12H), 3.10–3.35 (m, 1H), 3.24 (s, 3H), 3.40 (s, 3H), 3.46 (s, 3H), 3.92 (dd, $J_1=3.9$ Hz, $J_2=11.7$ Hz, 1H), 5.03 (s, 1H), 5.08 (s, 1H), 5.24 (dt, $J_1=7.8$ Hz, $J_2=12.7$ Hz, 1H), 6.31 (d, $J=12.6$ Hz, 1H), 6.69 (dd, $J_1=2.5$ Hz, $J_2=8.4$ Hz, 1H), 6.77 (d, $J=2.5$ Hz, 1H), 7.33 (d, $J=8.4$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 13.8 (q), 22.7 (q), 25.1 (t), 29.2 (t), 29.4 (t), 32.5 (t), 36.5 (d), 37.8 (t), 39.0 (d), 43.5 (s), 54.6 (q), 55.2 (q), 58.7 (q), 70.8 (d), 100.1 (d), 110.7 (t), 111.1 (d), 113.6 (d), 123.7 (d), 124.3 (s), 124.6 (s), 139.3 (s), 147.1 (s), 148.4 (d), 149.6 (s), 159.0 (s). HRMS: M^+, found 412.2612. $C_{26}H_{36}O_4$ requires 412.2614. MS *m/e* (%) 412 (M^+, 100), 380 (17), 269 (40), 216 (48), 203 (64), 190 (64), 75 (33), 71 (25).

3.1.16. 2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-2-methyl-cyclopent-2-enyl]-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (34). The reaction was carried out as described for compound **16**. Compound **34** was obtained as a colourless oil (two isomers, 5:1) in a quantitative yield of 4.2 g. IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2857, 1677, 1601, 1334, 1251, 1224; ^1H NMR (C_6D_6) δ: 0.13 (s, 6H), 0.94 (m) and 1.04 (*M*) (s, 9H), 1.20–1.50 (m, 1H), 1.55 (*M*) and 1.59 (m) (s, 3H), 1.60–1.85 (m, 2H), 2.05–2.32 (m, 3H), 2.38–2.63 (m, 3H), 3.33 (m) 3.34 (*M*) (s, 3H), 3.75–3.85 (*M*) and 3.85–3.98 (m) (m, 1H), 6.53 (d, $J=2.6$ Hz, 1H), 6.67 (dd, $J_1=2.6$ Hz, $J_2=8.7$ Hz, 1H), 8.32 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −4.1 (2q), 10.1 (*M*) and 12.0 (m) (q), 18.0 (s), 22.6 (*M*) and 23.9 (m) (t), 22.8 (*M*) and 25.0 (m) (t), 25.6 (3q), 29.7 (t), 33.3 (t), 43.4 (m) and 43.9 (*M*) (d), 49.6 (*M*) and 52.0 (m) (d), 54.5 (t), 112.7 (2d), 113.9 (s), 129.6 (*M*) and 129.8 (m) (d), 146.1 (m) and 146.4 (*M*) (s), 148.0 (s), 163.2 (s), 196.2 (m) and 197.2 (*M*) (s). HRMS: M^+, found 386.2274. $C_{23}H_{34}O_3Si$ requires 386.2277. MS *m/e* (%) 386 (M^+, 4), 233 (3), 211 (100), 176 (14), 97 (3), 75 (7), 73 (33).

3.1.17. 2-[2-(3-Ethoxy-3-phenyl-allyl)-2-methyl-3-oxo-cyclopentyl]-6-methoxy-3,4-dihydro-2*H*-naphthalen-1-one (35). The reaction was carried out as described for compound **18** on a 2 mmol scale. Compound **35** was obtained as a colourless oil as a mixture of isomers (5:1, NMR determination) in 93% yield. IR (CCl_4 sol.) cm^{-1}: 2976, 2937, 2840, 1737, 1679, 1602, 1249; ^1H NMR (C_6D_6) δ: 0.91 (*M*) and 0.97 (m) (s, 3H), 1.09 (t, $J=6.9$ Hz, 3H), 1.10–2.65 (m, 12H), 3.24 (m) and 3.26 (*M*) (s, 3H), 3.61 (q, $J=6.9$ Hz, 2H), 4.75 (*M*) and 5.21 (m) (t, $J=7.5$ Hz, 1H), 6.45 (*M*) and 6.49 (m) (d, $J=2.5$ Hz, 1H), 6.57 (m) and 6.61 (*M*) (dd, $J_1=2.5$ Hz, $J_2=8.7$ Hz, 1H), 6.95–7.25 (m, 3H), 7.35–7.55 (m, 2H), 8.17 (m) and 8.20 (*M*) (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 14.6 (*M*) and 15.3 (m) (q), 17.6 (*M*) and 17.8 (m) (q), 21.3 (*M*) and 23.3 (m) (t), 26.0 (*M*) and 27.4 (m) (t), 27.9 (m) and 28.8 (*M*) (t), 34.9 (t), 36.4 (*M*) and 36.7 (m) (t), 40.3 (*M*) and 42.9 (m) (d), 47.9 (*M*) and 49.0 (m) (d), 51.9 (*M*) and 52.4 (m) (s), 54.7 (q), 62.9 (*M*) and 63.0 (m) (t), 95.6 (M) and 96.6 (m) (d), 112.7 (d), 112.8 (d), 126.5 (m) and 127.9 (*M*) (2d), 126.8 (*M*) and 127.1 (m) (s), 128.1 (*M*) and 128.3 (m) (d), 129.2 (d), 129.4 (d), 129.9 (m) and 130.1 (*M*) (d), 136.8 (s), 145.6 (*M*) and 145.7 (m) (s), 156.7 (m) and 157.2 (*M*) (s), 163.3 (s), 163.5 (s), 196.6 (*M*) and 197.3 (m) (s), 219.7 (m) and 220.2 (*M*) (s). HRMS: M^+, found 432.2309. $C_{28}H_{32}O_4$ requires 432.2301. MS *m/e* (%) 432 (M^+, 2.5), 403 (1), 271 (3), 176 (8), 161 (100), 133 (25), 105 (9), 55 (10).

3.1.18. 6-Methoxy-2-[2-methyl-3-oxo-2-(3-phenyl-allyl)-cyclopentyl]-3,4-dihydro-2*H*-naphthalen-1-one (38). Silyl enol ether **34** (774 mg, 2 mmol) and 1-(4-methoxyphenyl)-prop-2-en-1-ol **37**[37] (164 mg, 1 mmol) were dissolved in CH_2Cl_2 (10 ml) and cooled to −5 °C. $ZnBr_2$ (a few crystals, approximately 60 mg) was added as the catalyst and the reaction mixture was stirred for 5 h at −5 to 0 °C, and then left to stand overnight at 4 °C. EtOAc (10 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution (10 ml) and brine (10 ml), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding compound **38** as a clear oil in 87% (363 mg), which solidified upon standing. IR (KBr) cm^{-1}: 2952, 2931, 2839, 1737, 1672, 1599, 1511, 1248, 1028; ^1H NMR (C_6D_6) δ: 0.75–1.15 (m, 1H), 1.17 (s, 3H), 1.50–2.95 (m, 11H), 3.31 (s, 3H), 3.35 (s, 3H), 5.80–6.10 (m, 2H), 6.50 (d, $J=2.5$ Hz, 1H), 6.67 (dd, $J_1=2.5$ Hz, $J_2=8.7$ Hz, 1H), 6.72 (d, $J=8.8$ Hz, 2H), 7.03 (d, $J=8.8$ Hz, 2H), 8.32 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 18.2 (q), 23.3 (t), 25.6 (t), 26.3 (t), 36.6 (t), 38.9 (d), 39.7 (t), 47.4 (d), 52.0 (s), 54.5 (q), 54.7 (q), 112.9 (d), 113.0 (d), 113.9 (2d), 123.5 (d), 126.7 (s), 127.3 92d), 130.4 (d), 130.5 (s), 133.3 (d), 145.5 (s), 159.2 (s), 163.5 (s), 197.8 (s), 220.3 (s). HRMS: M^+, found 418.2148. $C_{27}H_{30}O_4$ requires 418.2144. MS *m/e* (%) 418 (M^+, 16), 271 (5), 176 (16), 147 (100), 121 (5), 91 (4).

3.1.19. *tert*-Butyl-dimethyl-(2-methyl-cyclopent-1-enyloxy)-silane (39). To a solution of 2-methylcyclopentanone (5.2 g, 53.0 mmol) in acetonitrile (100 ml) were added triethyl amine (Et_3N, 11 ml, 80 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl, 12 g, 80 mmol) and NaI (12 g, 80 mmol) in this order. The reaction mixture was stirred overnight at room temperature, after which PE (50 ml) and saturated $NaHCO_3$ solution (50 ml) were added. The layers were separated and the combined acetonitrile–water phases were extracted with PE (3×50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography (PE/EtOAc/pyridine 98:1:1) and yielded compound **39** as a colourless oil in 95% yield (10.68 g). IR (CCl_4 sol.) cm^{-1}: 2956, 2931, 2361, 1690, 1550, 1472, 1333, 1253; ^1H NMR (C_6D_6) δ: 0.14 (s, 6H), 1.04 (s, 9H), 1.63–1.68 (m, 3H), 1.69–1.85 (m, 2H), 2.12–2.38 (m, 4H); ^{13}C NMR (C_6D_6) δ: −4.2 (q), −4.1 (q), 11.8 (q), 18.0 (s), 19.8 (t), 25.6 (3q), 33.5 (t), 33.7 (t), 111.9 (s), 146.6 (s). HRMS: M^+, found 212.1592. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%) 212 (M^+, 13), 197 (3), 155 (71), 75 (100), 59 (9).

3.1.20. 2-Methyl-3-ethenyl-*tert*-butyldimethylsilyloxy-cyclopent-1-ene (40). To a cooled (−40 °C) solution of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU, 3.84 g, 30 mmol) in THF (15 ml) cuprous bromide–dimethyl sulfide ($CuBr\cdot Me_2S$, 0.155 g, 0.75 mmol) was added, after which 22.5 ml of a 1 M solution of vinyl magnesium bromide in THF was added dropwise over a period of 1 h. The reaction mixture was stirred for a further 15 min and a mixture of 2-methyl-1-cyclopenten-1-one (1.40 g, 15 mmol) and TBDMSCl (3.40 g, 22.5 mmol) in THF (15 ml) was added dropwise over 30 min. The reaction mixture was stirred for 1 h, during which the temperature rose to −20 °C. Et_3N (4.15 ml, 30 mmol) was added and stirring was continued overnight at room temperature. A saturated NH_4Cl solution (75 ml) was added and the reaction mixture was extracted with *tert*-butyl dimethylether (*t*BuOMe, 3×75 ml). The organic layers were washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The crude product was purified by rapid column chromatography (PE/EtOAc/pyridine 98:1:1), yielding 1.93 g of **40** as a colourless oil (54%). IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2858, 2290, 1686, 1550, 1254; ^1H NMR (C_6D_6) δ: 0.13 (s, 6H), 0.89–1.00 (m, 1H), 1.03 (s, 9H) 1.48–1.66 (m, 1H), 1.67 (s, 3H), 1.90–2.45 (m, 3H), 2.93–3.14 (m, 1H), 4.79 (dd, $J_1=2.0$ Hz, $J_2=9.8$ Hz, 1H), 4.86 (dd, $J_1=2.0$ Hz, $J_2=17.0$ Hz, 1H), 5.51

(ddd, J_1=9.0 Hz, J_2=9.8 Hz, J_3=17.0 Hz, 1H); ^{13}C NMR (C_6D_6) δ: −4.3 (q), −4.2 (q), 10.4 (q), 17.9 (s), 25.6 (3q), 27.5 (t), 32.7 (t), 50.2 (d), 113.2 (t), 114.2 (s), 142.8 (d), 147.9 (s). HRMS: M^+, found 238.1746. $C_{14}H_{26}OSi$ requires 238.1753. MS *m/e* (%) 238 (M^+, 51), 223 (20), 211 (21), 182 (32), 181 (30), 75 (100), 73 (57).

3.1.21. (3-Isopropyl-2-methyl-cyclopent-1-enyloxy)-trimethyl-silane (41). The reaction was carried out as described for compound **40** on the same scale. Silyl enol ether **41** was obtained in 69% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2959, 2925, 2862, 2825, 1688, 1549, 1328, 1252, 1214; ^{1}H NMR (C_6D_6) δ: 0.13 (s, 9H), 0.73 (d, J=6.8 Hz, 3H), 0.88 (d, J=8.6 Hz, 3H), 1.36–2.05 (m, 3H), 1.56 (s, 3H), 2.13–2.29 (m, 2H), 2.35–2.52 (m, 1H); ^{13}C NMR (C_6D_6) δ: 0.3 (3q), 10.5 (q), 15.7 (q), 20.1 (t), 20.5 (q), 28.9 (d), 33.2 (t), 50.6 (d), 114.8 (s), 147.4 (s). HRMS: M^+, found 212.1597. $C_{12}H_{24}OSi$ requires 212.1596. MS *m/e* (%) 212 (M^+, 4), 197 (3), 169 (100), 84 (16), 75 (25), 73 (50).

3.1.22. 2-(2-Methyl-3-trimethylsilanyloxy-cyclopent-2-enyl)-propionic acid methyl ester (42). 2-Methyl-1-cyclopenten-1-one (0.96 g, 10 mmol) and 1-methoxy-1-(trimethylsiloxy) propene[56] (3.2 g, 20 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to −78 °C. A solution of $TrSbCl_6$ (290 mg, 0.5 mmol) in CH_2Cl_2 was added and the reaction mixture was stirred for 3 h at −78 °C. When all 2-methyl-1-cyclopenten-1-one had disappeared (TLC), pyridine (1 ml) was added to quench the catalyst and the reaction mixture was warmed to room temperature. *t*BuOMe (50 ml) and saturated $NaHCO_3$ solution were added, the layers were separated and the organic layer was washed with brine, dried (Na_2SO_4) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc/pyridine 98:1:1) yielding 96% of **42** (2.46 g, colourless oil) as a mixture of two isomers (7:5, GC determination). IR (CCl_4 sol.) cm^{-1}: 2954, 2906, 2850, 1738, 1688, 1549, 1253; ^{1}H NMR (C_6D_6) δ: 0.10 (s, 9H), 0.99 (*M*) and 1.06 (m) (d, J=7.0 Hz, 3H), 1.47 (*M*) and 1.64 (m) (s, 3H), 1.53–2.00 (m, 2H), 2.04–2.37 (m, 2H), 2.46–2.68 (m, 1H), 2.68–2.82 (m) and 2.97–3.12 (*M*) (m, 1H), 3.34 (m) and 3.37 (*M*) (s, 3H); ^{13}C NMR (C_6D_6) δ: 0.4 (3q), 9.9 (m) and 10.3 (*M*) (q), 10.7 (m) and 13.7 (*M*) (q), 21.5 (*M*) and 22.8 (m) (t), 33.6 (m) and 33.0 (*M*) (t), 40.6 (*M*) and 41.7 (m) (d), 47.1 (*M*) and 48.8 (m) (q), 50.7 (q), 112.9 (*M*) and 113.6 (m) (s), 148.5 (s), 175.1 (m) and 175.6 (*M*) (s). HRMS: M^+, found 256.1496. $C_{13}H_{24}O_3Si$ requires 256.1495. MS *m/e* (%) 256 (M^+, 5), 169 (100), 89 (28), 84 (31), 75 (63), 73 (62).

3.1.23. (2-Ethyl-3-vinyl-cyclopent-1-enyloxy)-trimethyl-silane (43). The reaction was carried out as described for compound **40** on the same scale. Silyl enol ether **43** was obtained in 77% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2963, 2940, 2851, 1678, 1549, 1344, 1252, 1204; ^{1}H NMR (C_6D_6) δ: 0.12 (s, 9H), 1.03 (t, J=7.5 Hz, 3H), 1.31–2.51 (m, 6H), 3.08–3.27 (m, 1H), 4.93 (dd, J_1=9.8 Hz, J_2=2.1 Hz, 1H), 5.02 (dd, J_1=16.9 Hz, J_2=2.1 Hz, 1H), 5.65 (ddd, J_1=9.0 Hz, J_2=9.8 Hz, J_3=16.9 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 0.2 (3q), 12.2 (q), 18.1 (t), 27.6 (t), 32.7 (t), 47.8 (d), 113.1 (t), 120.3 (s), 143.0 (d), 147.1 (s). HRMS: M^+, found 210.1440. $C_{12}H_{22}OSi$ requires 210.1440. MS *m/e* (%) 210 (M^+, 59), 195 (42), 181 (90), 129 (11), 75 (28), 73 (100).

3.1.24. *tert*-Butyl-dimethyl-(2-methyl-cyclohex-1-enyloxy)-silane (44). The reaction was carried out as described for compound **39** on the same scale. Silyl enol ether **44** was obtained in quantitative yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2931, 2858, 1686, 1550, 1254; ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 6H), 0.92 (s, 9H), 1.43–1.72 (m, 4H), 1.56 (s, 3H), 1.85–2.09 (m, 4H); ^{13}C NMR ($CDCl_3$) δ: −3.8 (2q), 16.4 (q), 18.1 (s), 22.9 (t), 23.8 (t), 25.7 (3q), 30.3 (t), 30.4 (t), 111.5 (s), 142.9 (s). HRMS: M^+, found 226.1759. $C_{13}H_{26}OSi$ requires 226.1753. MS *m/e* (%) 226 (M^+, 34), 221 (3), 169 (70), 84 (22), 75 (100).

3.1.25. *tert*-Butyl-dimethyl-(2-methyl-3-vinyl-cyclohex-1-enyloxy)-silane (45). The reaction was carried out as described for compound **40** on the same scale. Silyl enol ether **45** was obtained in 51% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2932, 2858, 1678, 1549, 1256, 1193; ^{1}H NMR (C_6D_6) δ: 0.12 (s, 6H), 1.03 (s, 9H), 1.29–1.68 (m, 4H), 1.71 (s, 3H), 1.91–2.05 (m, 2H), 2.54–2.69 (m, 1H), 4.97 (m, 1H), 5.04 (s, 1H), 5.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ: −3.8 (2q), 14.9 (q), 18.2 (s), 20.0 (t), 25.9 (3q), 29.1 (t), 30.5 (t), 44.3 (d), 112.6 (s), 114.3 (t), 142.1 (d), 144.7 (s). HRMS: M^+, found 252.1912. $C_{15}H_{28}OSi$ requires 252.1909. MS *m/e* (%) 252 (M^+, 44), 237 (44), 195 (67), 167 (14), 119 (39), 75 (100), 73 (46).

3.1.26. *tert*-Butyl-(5-isopropenyl-2,3-dimethyl-cyclohex-1-enyloxy)-dimethyl-silane (46). The reaction was carried out as described for compound **40** on the same scale. Silyl enol ether **46** was obtained in 64% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2960, 2930, 2859, 1682, 1645, 1193; ^{1}H NMR (C_6D_6) δ: 0.00 (s, 6H), 0.88–0.91 (m, 12H), 1.32–1.47 (m, 2H), 1.53 (s, 3H), 1.60 (t, J=1.6 Hz, 3H), 1.98–2.05 (m, 3H), 2.29–2.34 (m, 1H), 4.68 (s, 1H), 4.72 (s, 1H); ^{13}C NMR (C_6D_6) δ: −3.9 (q), −3.7 (q), 14.9 (q), 18.2 (s), 19.6 (q), 20.6 (q), 25.8 (3×q), 33.7 (d), 35.2 (t), 36.1 (t), 37.3 (d), 109.0 (t), 115.0 (s), 142.7 (s), 148.9 (s). HRMS: M^+, found 280.2226. $C_{17}H_{32}OSi$ requires 280.2222. MS *m/e* (%) 280 (M^+, 69), 265 (72), 237 (100), 223 (37), 179 (15), 155 (15), 149 (17), 129 (17), 75 (78), 73 (79).

3.1.27. *tert*-Butyl-(5-isopropenyl-2-methyl-3-vinyl-cyclohex-1-enyloxy)-dimethyl-silane (47). The reaction was carried out as described for compound **40** on the same scale. Silyl enol ether **47** was obtained in 82% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2959, 2930, 1859, 1682, 1644, 1256, 1192, 1179, 925; ^{1}H NMR (C_6D_6) δ: 0.01 (s, 6H), 0.89 (s, 9H), 1.23–1.57 (m, 2H), 1.55 (s, 3H), 1.61 (s, 3H), 1.90–2.12 (m, 2H), 2.21–2.45 (m, 1H), 2.48–2.62 (m, 1H), 4.604.70 (m, 2H), 4.80–5.00 (m, 2H), 5.64 (ddd, J=7.1, 10.4, 17.4 Hz, 1H); ^{13}C NMR (C_6D_6) δ: −3.8 (2q), 15.2 (q), 18.2 (s), 20.5 (q), 25.7 (3q), 33.4 (t), 35.9 (t), 37.2 (d), 43.8 (d), 109.1 (t), 111.4 (s), 114.6 (t), 141.3 (d), 144.5 (s), 148.7 (s). HRMS: M^+, found 292.2217. $C_{18}H_{32}OSi$ requires 292.2222. MS *m/e* (%) 292 (M^+, 14), 277 (52), 249 (100), 235 (17), 161 (20), 75 (96), 73 (79), 59 (16).

3.1.28. (5-Isopropenyl-3-isopropyl-2-methyl-cyclohex-1-enyloxy)-trimethyl-silane (48). The reaction was carried out as described for compound **40** on the same scale. Silyl

enol ether **48** was obtained in 95% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2960, 2871, 1677, 1644, 1447, 1252, 1182, 927; ^1H NMR (C_6D_6) δ: 0.17 (s, 9H), 0.82 (d, J= 6.6 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H), 1.31–2.23 (m, 6H), 1.65 (s, 3H), 1.68 (s, 3H), 2.33–2.53 (m, 1H), 4.80 (s, 1H), 4.85 (s, 1H); ^{13}C NMR (C_6D_6) δ: 0.5 (3q), 15.2 (q), 18.5 (q), 20.7 (q), 21.6 (q), 27.6 (t), 29.6 (d), 35.2 (t), 38.8 (d), 43.5 (d), 109.1 (t), 113.5 (s), 144.2 (s), 148.3 (s). HRMS: M^+, found 266.2068. $C_{16}H_{30}OSi$ requires 266.2066. MS *m/e* (%) 266 (M^+, 8), 251 (1.4), 223 (100), 195 (5), 181 (14), 165 (4), 75 (6), 73 (40).

3.1.29. (5-Isopropenyl-2-methyl-cyclohexa-1,3-dienyloxy)-trimethyl-silane (49). A solution of dry $FeCl_3$ in THF (50 ml) was cooled to −20 °C and a solution of MeMgBr in THF (75 mmol, 3 M in THF) was added dropwise over a period of 1 h. After complete addition the reaction mixture was stirred for 30 min at −20 °C and *R*-(−)-carvone (10 g, 66.7 mmol) in THF (100 ml) was then added by slow dropping over a period of 2 h. The temperature was kept at −20 °C during the complete addition and for 30 min more and then warmed to 0 °C. TMSCl (8.2 g, 75 mmol) was added, followed by EtN_3 (6 ml) and DMPU (6 ml). The reaction mixture was stirred overnight at room temperature. A saturated solution of $NaHCO_3$ (100 ml) was added and the resulting grey suspension was filtered over a plug of Hyflo and carefully washed with Et_2O. The filtrate layers were separated and the water layer was extracted with Et_2O (3×50 ml). The combined organic layers were washed with brine, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. Purification of the residue by column chromatography (PE/EA/pyridine 98:1:1) gave compound **49** as a colourless oil in 70% yield (10.3 g); ^1H NMR (C_6D_6) δ: 0.17 (s, 9H), 1.67 (s, 3H), 1.71 (s, 3H), 2.00–2.52 (m, 2H), 2.97–3.19 (m, 1H), 4.78 (s, 1H), 4.86 (s, 1H), 5.37 (dd, J_1=3.4 Hz, J_2=9.8 Hz, 1H), 5.86 (dd, J_1=2.4 Hz, J_2=9.3 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 0.3 (s, 3q), 20.4 (q), 20.5 (q), 34.3 (t), 43.7 (d), 110.4 (t), 121.8 (d), 129.8 (d), 145.4 (s), 146.9 (s), 148.8 (s).

3.1.30. 2-[3-(*tert*-Butyl-dimethyl-silanyloxy)-5-isopropenyl-2-methyl-cyclohex-2-enyl]-propionic acid methyl ester (50). The reaction was carried out as described for compound **42** on the same scale. Silyl enol ether **50** was obtained as two isomers (7:1, NMR determination) in 85% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2931, 2859, 1737, 1677, 1254, 1195; ^1H NMR ($CDCl_3$) δ: 0.07 (s, 6H), 0.91 (s, 9H), 1.02 (*M*) and 1.15 (m) (d, J=7.0 Hz, 3H), 1.10–2.90 (m, 7H), 1.52 (s, 3H), 1.63 (m) and 1.67 (*M*) (s, 3H), 3.59 (m) and 3.64 (*M*) (s, 3H), 4.65 (s, 1H), 4.69 (s, 3H); ^{13}C NMR ($CDCl_3$) δ: −3.8 (2q), 12.9 (*M*) and 16.2 (m) (q), 14.5 (*M*) and 16.6 (m) (q), 18.1 (s), 20.7 (q), 25.8 (3q), 28.9 (*M*) and 30.8 (m) (t), 34.9 (*M*) and 36.2 (m) (t), 37.5 (m) and 38.2 (*M*), 39.9 (m) and 40.7 (*M*) (d), 41.8 (*M*) and 42.8 (m) (d), 51.3 (q), 109.0 (t), 111.7 (*M*) and 112.4 (m) (s), 145.2 (s), 148.2 (*M*) and 148.5 (m) (s), 176.8 (s). HRMS: M^+, found 352.2428. $C_{20}H_{36}O_3Si$ requires 352.2434. MS *m/e* (%) 352 (M^+, 10), 265 (100), 223 (5), 73 (27), 59 (3).

3.1.31. 3-(*tert*-Butyl-dimethyl-silanyloxy)-5-isopropenyl-2-methyl-cyclohex-2-enecarbonitrile (51). The reaction was carried out as described for compound **39** on the same scale. Silyl enol ether **51** was obtained in 70% yield from cyanocarvone[57] as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2960, 2932, 2885, 2860, 2235, 1686, 1647, 1550, 1256, 1210; ^1H NMR (C_6D_6) δ: −0.01 (s, 6H), 0.92 (s, 9H), 1.11 (dt, J_1=5.6 Hz, J_2=12.8 Hz, 1H), 1.46 (s, 3H), 1.64 (s, 3H), 1.69–1.94 (m, 2H), 1.85 (dt, J_1=2.0 Hz, J_2=11.0 Hz, 1H), 2.04 (dd, J_1=5.2 Hz, J_2=16.5 Hz, 1H), 2.37–2.45 (m, 1H), 2.53 (dd, J_1=4.4 Hz, J_2=14.6 Hz, 1H); ^{13}C NMR (C_6D_6) δ: −4.0 (q), −3.9 (q), 14.7 (q), 18.0 (s), 20.3 (q), 25.6 (3×q), 30.8 (t), 32.0 (d), 35.2 (t), 38.8 (d), 104.9 (s), 109.8 (t), 120.9 (s), 146.7 (s), 146.9 (s). HRMS: M^+, found 291.2017. $C_{17}H_{29}NOSi$ requires 291.2018. MS *m/e* (%) 291 (M^+, 6), 248 (10), 234 (100), 179 (8), 166 (14), 165 (20), 75 (26), 73 (26).

3.1.32. 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (52). 6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol **11** (204 mg, 1 mmol) and 2-methyl-*tert*-butyldimethylsilyloxy-cyclopent-1-ene **39** (636 mg, 3 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to −20 °C. $ZnBr_2$ (a few crystals, approximately 60 mg) was added as the catalyst and the reaction mixture was stirred for 3 h at −15 to −10 °C. When all of compound **11** had disappeared (TLC), EtOAc (25 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding compound **52** as a colourless oil in 84% yield (238 mg), which crystallised upon standing (mp 53–55 °C, decomp. From *t*BuOMe). IR (CCl_4 sol.) cm^{-1}: 2959, 1738, 1550, 1255; ^1H NMR (C_6D_6) δ: 0.93 (s, 3H), 1.26–1.54 (m, 3H), 1.54–1.83 (m, 3H), 1.87–2.09 (m, 2H), 2.25 (d, J=7.7 Hz, 2H), 2.32 (t, J=6.1 Hz, 2H), 2.54 (t, J=6.1 Hz, 2H), 3.38 (s, 3H), 5.87 (t, J= 7.7 Hz, 1H), 6.57 (d, J=2.5 Hz, 1H), 6.71 (dd, J_1=2.5 Hz, J_2=8.7 Hz, 1H), 7.51 (d, J=8.7 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 18.8 (t), 21.9 (q), 23.4 (t), 26.8 (t), 30.8 (t), 35.1 (2t), 37.3 (t), 48.7 (s), 54.5 (q), 112.7 (d), 113.2 (d), 117.0 (d), 125.3 (d), 129.2 (s), 136.5 (s), 138.5 (s), 158.9 (s), 220.8 (s). HRMS: M^+, found 284.1779. $C_{19}H_{24}O_2$ requires 284.1776. MS *m/e* (%) 284 (M^+, 10), 187 (100), 148 (4), 146 (4), 128 (4), 115 (3).

3.1.33. 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclopentanone (53). The reaction was carried out as described for compound **52** on the same scale. Compounds **53** were obtained in 83% yield as a colourless oil and as a mixture of two isomers (2:1, NMR determination). IR (CCl_4 sol.) cm^{-1}: 2945, 2937, 2836, 1739, 1606, 1496, 1234; ^1H NMR (C_6D_6) δ: 0.78 (*M*) and 1.06 (m) (s, 3H), 1.15–2.61 (m, 13H), 3.32 (s, 3H), 4.88–5.07 (m, 2H), 5.52–5.84 (m, 1H), 5.89–6.11 (m, 1H), 6.58 (d, J=2.6 Hz, 1H), 6.70 (dd, J_1=2.6 Hz, J_2= 8.7 Hz, 1H), 7.53 (*M*) and 7.64 (m) (d, J=8.7 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 17.9 (*M*) and 20.8 (m) (q), 23.4 (m) and 23.5 (*M*) (t), 24.2 (m) and 24.6 (*M*) (t), 26.7 (*M*) and 26.8 (m) (t), 30.8 (*M*) and 30.9 (m) (t), 34.7 (*M*) and 35.7 (m) (t), 37.0 (t), 47.5 (*M*) and 51.9 (m) (d), 52.3 (s), 54.5 (q), 112.7 (m) and 112.7 (*M*) (d), 113.3 (*M*) and 113.4 (m) (d), 115.9 (m) and 115.9 (*M*) (t), 116.8 (m) and 117.3 (*M*) (d), 125.4 (d), 129.2 (s), 135.8 (m) and 136.4 (*M*) (s), 137.6 (m) and137.9 (*M*) (d), 138.5 (*M*) and 138.5 (m) (s), 159.0 (s), 219.0 (m) and 219.8 (*M*) (s). HRMS: M^+, found 310.1937. $C_{21}H_{26}O_2$

requires 310.1933. MS *m/e* (%) 310 (M^+, 15), 187 (100), 161 (4), 160 (4), 159 (8), 146 (5).

3.1.34. 3-Isopropyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (54). The reaction was carried out as described for compound **52** on the same scale. Compound **54** was obtained in 83% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2962, 2940, 2836, 1738, 1606, 1496, 1239; ^1H NMR (C_6D_6) δ: 0.66 (dd, $J_1=1.8$ Hz, $J_2=6.2$ Hz, 1H), 0.74 (d, $J=6.5$ Hz, 3H), 0.85 (s, 3H), 0.90 (d, $J=6.5$ Hz, 3H), 0.96–2.02 (m, 6H), 2.05 (dd, $J_1=8.2$ Hz, $J_2=18.4$ Hz, 1H), 2.29 (dd, $J_1=8.7$ Hz, $J_2=14.7$ Hz, 1H), 2.42 (t, $J=6.2$ Hz, 2H), 2.56 (t, $J=6.2$ Hz, 2H), 2.71 (dd, $J_1=6.5$ Hz, $J_2=13.4$ Hz, 1H), 3.34 (s, 3H), 5.84 (dd, $J_1=6.5$ Hz, $J_2=8.5$ Hz, 1H), 6.55 (d, $J=2.7$ Hz, 1H), 6.67 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.52 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 18.0 (q), 21.0 (q), 22.3 (q), 23.5 (t), 23.6 (t), 26.8 (t), 29.2 (d), 30.7 (t), 36.5 (t), 37.5 (t), 48.5 (d), 52.1 (s), 54.4 (q), 112.6 (d), 113.3 (d), 117.8 (d), 125.2 (d), 129.3 (s), 135.8 (s), 138.5 (s), 158.9 (s), 221.3 (s). HRMS: M^+, found 326.2248. $C_{22}H_{30}O_2$ requires 326.2246. MS *m/e* (%) 326 (M^+, 9), 187 (100), 161 (4), 159 (3), 146 (3), 131 (3), 69 (8).

3.1.35. 2-{2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-oxo-cyclopentyl}-propionic acid methyl ester (55). The reaction was carried out as described for compound **52** on the same scale. Compounds **55** were obtained in 57% yield as a colourless oil and as a 7:5 mixture of two isomers.

Main isomer. IR ($CHCl_3$ sol.) cm^{-1}: 2974, 2942, 2839, 1732, 1605, 1496, 1464, 1272, 1235, 1198, 1164; ^1H NMR (C_6D_6) δ: 0.84–1.08 (m, 1H), 0.96 (s, 3H), 1.02 (d, $J=6.7$ Hz, 3H), 1.45–2.82 (m, 12H), 2.84 (dd, $J_1=8.5$ Hz, $J_2=14.8$ Hz, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 6.16 (dd, $J_1=6.9$ Hz, $J_2=8.3$ Hz, 1H), 6.62 (d, $J=2.7$ Hz, 1H), 6.76 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.74 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 15.8 (q), 18.3 (q), 23.0 (t), 23.6 (t), 26.7 (t), 30.8 (t), 34.7 (t), 36.9 (t), 40.3 (d), 44.3 (d), 50.9 (s), 52.1 (q), 54.4 (q), 112.6 (d), 113.2 (d), 117.0 (d), 125.4 (d), 129.5 (s), 136.6 (s), 138.8 (s), 158.9 (s), 175.9 (s), 219.7 (s). HRMS: M^+, found 370.2149. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 11), 339 (1.5), 187 (100), 174 (2), 171 (2), 159 (5), 146 (3).

Minor isomer. IR (CCl_4 sol.) cm^{-1}: 2941, 2837, 1740, 1604, 1550, 1496, 1458, 1251, 1156; ^1H NMR (C_6D_6) δ: 0.86 (s, 3H), 0.90–1.04 (m, 1H), 1.19 (d, $J=6.7$ Hz, 3H), 1.25–2.65 (m, 12H), 2.72 (dd, $J_1=8.0$ Hz, $J_2=14.8$ Hz, 1H), 3.37 (s, 3H), 3.38 (s, 3H), 5.93 (dd, $J_1=6.9$ Hz, $J_2=8.4$ Hz, 1H), 6.62 (d, $J=2.7$ Hz, 1H), 6.76 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.74 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 16.7 (q), 17.7 (q), 23.5 (t), 23.8 (t), 26.8 (t), 30.7 (t), 36.3 (t), 37.2 (t), 41.3 (d), 45.6 (d), 50.7 (q), 51.7 (s), 54.4 (q), 112.6 (d), 113.3 (d), 116.9 (d), 125.3 (d), 129.1 (s), 136.6 (s), 138.5 (s), 159.0 (s), 175.4 (s), 219.9 (s). HRMS: M^+, found 370.2150. $C_{23}H_{30}O_4$ requires 370.2144. MS *m/e* (%) 370 (M^+, 7), 339 (2), 187 (100), 159 (3), 146 (3).

3.1.36. 2-Ethyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-3-vinyl-cyclopentanone (56). The reaction was carried out as described for compound **52** on the same scale. Compounds **56** were obtained in 64% yield as a colourless oil and as a 2:1 mixture of two isomers. IR (CCl_4 sol.) cm^{-1}: 2950, 2939, 2836, 1736, 1606, 1570, 1497, 1464, 1237, 1235; ^1H NMR (C_6D_6) δ: 0.78 (M) and 0.85 (m) (t, $J=7.3$ Hz, 3H), 1.23–2.76 (m, 16H), 3.33 (s, 3H), 4.97 (m, d, $J=11.1$ Hz) and 5.04 (*M*, d, $J=2.9$ Hz) (2H), 5.66–5.87 (m, 1H), 5.94 (m) and 6.07 (*M*) (m, 1H), 6.60 (d, $J=2.6$ Hz, 1H), 6.71 (dd, $J_1=2.6$ Hz, $J_2=8.7$ Hz, 1H), 7.55 (m) and 7.66 (*M*) (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 8.5 (m) and 8.7 (*M*) (q), 23.4 (*M*) and 23.5 (m) (t), 24.3 (m) and 24.4 (*M*) (t), 24.3 (m) and 26.5 (*M*) (t), 26.8 (*M*) and 26.9 (m) (t), 30.5 (m) and 30.8 (*M*) (t), 30.7 (*M*) and 31.7 (m) (t), 36.9 (m) and 37.1 (*M*) (t), 47.0 (*M*) and 47.9 (m) (d), 54.5 (q), 55.4 (m) and 55.7 (*M*) (s), 112.7 (d), 113.3 (m) and 113.4 (*M*) (d), 115.7 (m) and 115.8 (*M*) (t), 116.8 (*M*) and 117.5 (m) (d), 15.4 (d), 129.3 (s), 135.6 (*M*) and 136.3 (m) (s), 137.9 (m) and 138.0 (*M*) (d), 138.5 (s), 158.9 (s), 218.9 (s). HRMS: M^+, found 324.2093. $C_{22}H_{28}O_2$ requires 324.2089. MS *m/e* (%) 324 (M^+, 20), 187 (100), 186 (5), 174 (6), 171 (5), 159 (8).

3.1.37. 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone (57). The reaction was carried out as described for compound **52** on the same scale. Compound **57** were obtained in 72% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2936, 2866, 2856, 2281, 1708, 1606, 1550, 1496, 1237, 1234; ^1H NMR (C_6D_6) δ: 1.10 (s, 3H), 1.21–1.78 (m, 8H), 2.17–2.54 (m, 6H), 2.60 (t, $J=6.2$ Hz, 2H), 3.39 (s, 3H), 6.01 (t, $J=7.6$ Hz, 1H), 6.65 (d, $J=2.7$ Hz, 1H), 6.74 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.62 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 21.2 (t), 22.8 (q), 23.4 (t), 26.9 (t), 27.2 (t), 30.8 (t), 35.9 (t), 38.4 (t), 38.5 (t), 49.1 (s), 54.5 (q), 112.7 (d), 113.3 (d), 117.1 (d), 125.4 (d), 129.3 (s), 136.2 (s), 138.4 (s), 158.9 (s), 212.7 (s). HRMS: M^+, found 298.1935. $C_{20}H_{26}O_2$ requires 298.1933. MS *m/e* (%) 298 (M^+, 11), 187 (100), 159 (3), 146 (4), 128 (3), 115 (3).

3.1.38. 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclohexanone (58). The reaction was carried out as described for compound **52** on the same scale. Compounds **58** were obtained in 20% yield as a colourless oil and as a 2:1 mixture of two isomers (NMR determination). IR (CCl_4 sol.) cm^{-1}: 3079, 2936, 2867, 2836, 2360, 1708, 1606, 1550, 1496, 1464, 1233; ^1H NMR (C_6D_6) δ: 0.99 (*M*) and 1.28 (m) (s, 3H), 1.28–1.77 (m, 6H), 2.05–2.80 (m, 9H), 3.39 (s, 3H), 4.90–5.10 (m, 2H), 5.59–5.82 (m, 1H), 5.88 (m) and 6.19 (*M*) (m, 1H), 6.70 (d, $J=2.4$ Hz, 1H), 6.79 (dd, $J=2.4$, 8.7 Hz, 1H), 7.63 (m) and 7.69 (*M*) (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 19.6 (*M*) and 20.6 (m) (q), 23.4 (m) and 23.5 (*M*) (t), 24.1 (*M*) and 25.3 (m) (t), 26.9 (*M*) and 27.0 (m) (t), 27.0 (m) and 27.1 (*M*) (t), 30.7 (m) and 30.9 (*M*) (t), 31.3 (m) and 34.9 (*M*) (t), 38.1 (*M*) and 38.3 (m) (t), 49.1 (*M*) and 52.9 (m) (d), 52.1 (s), 54.5 (q), 112.6 (d), 113.3 (*M*) and 113.4 (m) (d), 116.0 (t), 116.2 (m) and 118.4 (*M*) (d), 125.5 (d), 129.1 (m) and 129.5 (*M*) (s), 135.4 (*M*) and 136.3 (m) (s), 138.1 (m) and 138.2 (*M*) (d), 138.3 (m) and 138.4 (*M*) (s), 158.9 (*M*) and 159.0 (m) (s), 212.0 (m) and 212.3 (*M*) (s). HRMS: M^+, found 324.2090. $C_{22}H_{28}O_2$ requires 324.2089. MS *m/e* (%) 324 (M^+, 14), 213 (3), 187 (100), 174 (6), 161 (4), 159 (4), 146 (4).

3.1.39. 5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2,3-dimethyl-cyclohexanone (59). The reaction was carried out as described for compound **52** on the same scale. Compound **59** was obtained in 47% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2936, 2836, 1706, 1606, 1496, 1234; ^1H NMR (C_6D_6) δ: 0.75 (d, $J=7.0$ Hz, 3H), 1.06 (s, 3H), 1.51 (s, 3H), 1.80–2.10 (m, 6H), 2.25–2.63 (m, 8H), 3.34 (s, 3H), 4.77 (s, 2H), 5.91 (t, $J=7.7$ Hz, 1H), 6.59 (d, $J=2.6$ Hz, 1H), 6.68 (dd, $J_1=2.6$ Hz, $J_2=8.7$ Hz, 1H), 7.57 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 16.0 (q), 19.3 (q), 20.7 (q), 23.4 (t), 26.9 (t), 30.8 (t), 32.9 (t), 35.8 (t), 36.6 (d), 40.4 (d), 42.7 (d), 52.3 (s), 54.5 (q), 110.3 (t), 112.6 (d), 113.4 (d), 117.0 (d), 125.4 (d), 129.2 (s), 136.6 (s), 138.4 (s), 147.5 (s), 158.9 (s), 212.9 (s). HRMS: M^+, found 352.2403. $C_{24}H_{32}O_2$ requires 352.2402. MS *m/e* (%) 352 (M^+, 4), 187 (100), 186 (11), 174 (6), 171 (3), 159 (5), 146 (4).

3.1.40. 5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-3-vinyl-cyclohexanone (60). The reaction was carried out as described for compound **52** on the same scale. Compound **60** was obtained in 14% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 3080, 2937, 2836, 1707, 1606, 1496, 1234; ^1H NMR (C_6D_6) δ: 0.88–1.12 (m, 1H), 1.08 (s, 3H), 1.49 (s, 3H), 1.50–1.98 (m, 4H), 2.32–2.61 (m, 9H), 3.34 (s, 3H), 4.79 (s, 2H), 4.84–4.92 (m, 1H), 5.03 (s, 1H), 5.55–5.78 (m, 1H), 5.96 (t, $J=7.2$ Hz, 1H), 6.60 (d, $J=2.7$ Hz, 1H), 6.69 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 20.3 (q), 20.8 (q), 23.4 (t), 27.0 (t), 30.8 (t), 31.5 (t), 35.7 (t), 40.6 (d), 42.6 (t), 47.2 (d), 51.4 (s), 54.5 (q), 110.7 (t), 112.6 (d), 113.4 (d), 116.0 (t), 116.9 (d), 125.4 (d), 129.2 (s), 136.0 (s), 138.4 (s), 138.5 (d), 147.3 (s), 158.9 (s), 212.3 (s). HRMS: M^+, found 364.2403. $C_{25}H_{32}O_2$ requires 364.2402. MS *m/e* (%) 364 (M^+, 3), 187 (100), 186 (3), 174 (5), 161 (4), 159 (4), 146 (5).

3.1.41. 5-Isopropenyl-3-isopropyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone (61). The reaction was carried out as described for compound **52** on the same scale. Compound **61** was obtained in 18% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2939, 2836, 1704, 1606, 1550, 1496, 1256; ^1H NMR (C_6D_6) δ: 0.76 (d, $J=5.5$ Hz, 3H), 0.79 (d, $J=5.5$ Hz, 3H), 1.00 (s, 3H), 1.50 (s, 3H), 1.35–1.85 (m, 7H), 2.23–2.48 (m, 5H), 2.56 (t, $J=6.3$ Hz, 2H), 2.84 (dd, $J_1=5.8$ Hz, $J_2=15.1$ Hz, 1H), 3.32 (s, 3H), 4.90 (s, 2H), 5.99 (m, 1H), 6.59 (d, $J=2.7$ Hz, 1H), 6.70 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.61 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 19.1 (q), 20.8 (q), 21.3 (q), 23.5 (t), 23.8 (t), 23.9 (q), 26.5 (d), 26.9 (t), 30.9 (t), 35.0 (t), 40.7 (d), 42.3 (t), 42.7 (d), 53.7 (s), 54.5 (q), 111.8 (t), 112.6 (d), 113.4 (d), 118.6 (d), 125.3 (d), 129.5 (s), 134.8 (s), 138.3 (s), 147.1 (s), 158.8 (s), 213.2 (s). HRMS: M^+, found 380.2709. $C_{26}H_{36}O_2$ requires 380.2715. MS *m/e* (%) 380 (M^+, 8), 187 (100), 186 (4), 174 (6), 172 (2), 161 (3), 159 (2), 146 (4).

3.1.42. 5-Isopropenyl-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohex-3-enone (62) and 5-isopropenyl-4-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohex-2-enone (63). The reaction was carried out as described for compound **52** on the same scale.

Compound **62** was obtained in 28% yield as a 5:1 mixture of two isomers as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2974, 2950, 2836, 1713, 1606, 1496, 1233; ^1H NMR (C_6D_6) δ: 1.18 (s, 3H), 1.47 (s, 3H), 1.64 (quint., $J=6.2$ Hz, 2H), 2.14 (dd, $J_1=6.9$ Hz, $J_2=14.2$ Hz, 1H), 2.21–2.63 (m, 6H), 2.71 (dd, $J=8.9$, 14.2 Hz, 1H), 2.79–2.95 (m 1H), 3.34 (s, 3H), 4.68 (*M*, br s, 2H) and 4.71 (m, s, 1H) +4.77 (m, s, 1H), 5.44 (m) and 5.49 (*M*) (m, 1H), 5.59 (dt, $J_1=3.7$ Hz, $J_2=9.9$ Hz, 1H), 5.95 (dd, $J_1=7.0$ Hz, $J_2=8.6$ Hz, 1H), 6.57 (d, $J=2.7$ Hz, 1H), 6.72 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.53 (m) and 7.55 (*M*) (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 19.8 (m) and 20.0 (*M*) (q), 23.4 (t), 24.6 (m) and 25.0 (*M*) (q), 26.8 (t), 30.8 (t), 38.3 (t), 42.1 (m) and 42.6 (*M*) (t), 44.6 (*M*) and 44.9 (m) (d), 48.9 (s), 54.5 (q), 111.2 (*M*) and 111.4 (m) (t), 112.8 (d), 113.3 (d), 117.0 (*M*) and 117.2 (m) (d), 125.3 (d), 128.5 (d), 129.2 (s), 135.4 (d), 136.2 (m) and 136.4 (*M*) (s), 138.7 (s), 146.4 (s), 159.0 (s), 211.4 (m) and 211.6 (*M*) (s). HRMS: M^+, found 336.2084. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 3.3), 187 (100), 159 (2.6), 146 (4.1), 145 (2.1), 128 (2.2), 115 (1.7).

Compound **62** was obtained in 26% yield as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2970, 2937, 2836, 1678, 1606, 1550, 1496, 1233; ^1H NMR (C_6D_6) δ: 1.26 (s, 3H), 1.26–1.60 (m, 1H), 1.68 (quint, $J=6.2$ Hz, 2H), 1.91 (s, 3H), 1.95–2.65 (m, 9H), 3.41 (s, 3H), 4.73 (s, 1H), 4.78 (s, 1H), 5.78–5.88 (m, 1H), 6.40 (br s, 1H), 6.67 (d, $J=2.8$ Hz, 1H), 6.85 (dd, $J_1=2.8$ Hz, $J_2=8.7$ Hz, 1H), 7.62 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 15.9 (q), 18.6 (q), 23.3 (t), 26.9 (t), 30.8 (2t), 39.6 (d), 43.0 (t), 48.9 (d), 54.5 (q), 112.8 (d), 112.9 (t), 113.3 (d), 118.5 (d), 125.2 (d), 128.9 (s), 134.9 (s), 136.1 (s), 138.6 (s), 145.3 (s), 147.3 (d), 159.0 (s), 197.5 (s). HRMS: M^+, found 336.2085. $C_{23}H_{28}O_2$ requires 336.2089. MS *m/e* (%) 336 (M^+, 10), 187 (100), 174 (7), 161 (3), 159 (3), 146 (5), 128 (2), 115 (2).

3.1.43. 3-Methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthrene (64). 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone **52** (100 mg, 0.35 mmol) was dissolved in benzene (5 ml) and a crystal of *para*-toluene sulfonic acid (*p*-TsOH) was added. The reaction mixture was stirred at 40 °C for 4 h, then diluted with Et_2O (15 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding **64** as white crystals in 87% (81 mg). Recrystallisation from MeOH gave white needles (mp 89–92 °C). IR ($CHCl_3$ sol.) cm^{-1}: 3000, 2929, 2840, 1603, 1562, 1497, 1465, 1431, 1304, 1286, 1261, 1243, 1041; ^1H NMR (C_6D_6) δ: 1.01 (s, 3H), 1.50–1.93 (m, 4H), 2.11–2.82 (m, 8H), 3.38 (s, 3H), 5.54 (br s, 1H), 6.78–6.81 (m, 2H), 1.79–7.24 (m, 1H); ^{13}C NMR (C_6D_6) δ: 21.5 (q), 23.9 (t), 24.2 (t), 28.8 (t), 30.2 (t), 36.1 (t), 40.8 (t), 43.0 (s), 54.0 (q), 111.2 (d), 113.5 (d), 120.5 (d), 124.2 (d), 126.0 (s), 129.0 (s), 129.7 (s), 138.0 (s), 148.8 (s), 158.9 (s). HRMS: M^+, found 266.1673. $C_{19}H_{22}O$ requires 266.1671. MS *m/e* (%) 266 (M^+, 100), 251 (11), 238 (7), 223 (6), 187 (7), 171 (5).

3.1.44. 3-Methoxy-13-methyl-17-vinyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta-[*a*]-phenanthrene (65). The reaction was carried out as described for compound **64** on the same scale. Compound **65** was obtained in 82% yield as

a 2:1 mixture of two isomers and as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 3077, 2929, 2839, 1730, 165, 1562, 1497, 1465, 1285, 1250, 1040; ^1H NMR (C_6D_6) δ: 0.87 (*M*) and 1.02 (m) (s, 3H), 0.78–2.98 (m, 11H), 3.39 (s, 3H), 4.86–5.17 (m, 2H), 5.46 (m) and 5.51 (*M*) (br s, 1H), 5.65–6.10 (m, 1H), 6.65–6.79 (m, 2H), 7.11–7.23 (m, 1H); ^{13}C NMR (C_6D_6) δ: 16.9 (*M*) and 23.3 (m) (q), 23.8 (t), 24.0 (*M*) and 24.2 (m) (t), 28.8 (t), 30.6 (m) and 34.6 (*M*) (t), 35.8 (*M*) and 37.3 (m) (t), 46.2 (*M*) and 46.5 (m) (s), 54.5 (q), 54.5 (*M*) and 56.4 (m) (d), 111.3 (d), 113.3 (m) and 115.3 (*M*) (t), 113.6 (d), 118.6 (m) and 119.3 (*M*) (d), 124.3 (d), 125.8 (*M*) and 126.1 (m) (s), 129.2 (s), 129.5 (s), 138.0 (s), 138.8 (*M*) and 141.0 (m) (d), 147.2 (m) and 149.2 (*M*) (s), 158.8 (s). MS *m/e* (%) 292 (M^+, 100), 277 (7), 264 (7), 263 (7), 187 (6).

3.1.45. 17-Isopropyl-3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta-[*a*]-phenanthrene (66). The reaction was carried out as described for compound **64** on the same scale. Compound **66** was obtained in 79% yield as white crystals (recrystallised from MeOH, mp 123–125). IR ($CHCl_3$ sol.) cm^{-1}: 2958, 2937, 2837, 1730, 1604, 1563, 1498, 1466, 1246, 1040; ^1H NMR (C_6D_6) δ: 0.91 (d, J=6.4 Hz, 3H), 0.94 (s, 3H), 0.98 (d, J=6.4 Hz, 3H), 1.43–1.87 (m, 3H), 2.03–2.80 (m, 9H), 3.39 (s, 3H), 5.55 (br s, 1H), 6.70–6.79 (m, 2H), 7.21 (d, J=8.1 Hz, 1H); ^{13}C NMR (C_6D_6) δ: 16.7 (q), 23.6 (t), 23.9 (t), 24.8 (t), 25.0 (t), 29.8 (t), 30.5 (d), 37.4 (2t), 46.2 (s), 55.5 (q), 60.1 (d), 112.2 (d), 114.5 (d), 120.6 (d), 125.1 (d), 126.9 (s), 129.5 (s), 130.5 (s), 138.9 (s), 150.9 (s), 159.7 (s). HRMS: M^+, found 308.2143. $C_{22}H_{28}O$ requires 308.2140. MS *m/e* (%) 308 (M^+, 100), 293 (4), 265 (11), 237 (4), 187 (7).

3.1.46. 2-(3-Methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-propionic acid methyl ester (67). The reaction was carried out as described for compound **64** on the same scale. Compounds **67** were obtained in 91% yield as a 7:5 mixture of two isomers and as a colourless oil.

Main isomer. IR (CCl_4 sol.) cm^{-1}: 2941, 2838, 1729, 1605, 1498, 1435, 1254, 1167, 1040; ^1H NMR (C_6D_6) δ: 0.83 (s, 3H), 0.96–1.14 (m, 1H), 1.20 (d, J=6.8 Hz, 3H), 1.46–1.69 (m, 1H), 1.82–2.02 (m, 1H), 2.02–2.83 (m, 9H), 3.38 (s, 3H), 3.39 (s, 3H), 5.47 (br s, 1H), 6.68–6.81 (m, 2H), 7.11–7.27 (m, 1H); ^{13}C NMR (C_6D_6) δ: 15.5 (q), 17.2 (q), 23.7 (t), 23.9 (t), 28.7 (t), 35.7 (t), 36.4 (t), 41.5 (d), 45.3 (s), 50.7 (q), 54.2 (d), 54.5 (q), 111.3 (d), 113.6 (d), 119.4 (d), 124.2 (d), 125.7 (s), 128.7 (s), 129.3 (s), 138.0 (s), 149.4 (s), 158.8 (s), 176.1 (s). MS *m/e* (%) 352 (M^+, 100), 265 (14), 264 (19), 263 (14), 249 (10), 187 (13), 171 (7), 110 (7).

Minor isomer. White crystals (recrystallised from MeOH, mp 152–155). IR (CCl_4 sol.) cm^{-1}: 2939, 2892, 2836, 1728, 1604, 1498, 1458, 1434, 1250, 1164, 1040; ^1H NMR (C_6D_6) δ: 1.03 (s, 3H), 1.09 (d, J=6.8 Hz, 3H), 1.55–1.76 (m, 1H), 1.83–2.78 (m, 11H), 3.37 (s, 3H), 3.40 (s, 3H), 5.43–5.52 (m, 1H), 6.64–6.78 (m, 2H), 7.12–7.23 (m, 1H); ^{13}C NMR (C_6D_6) δ: 16.0 (q), 17.3 (q), 23.7 (t), 23.9 (t), 28.7 (t), 34.9 (2t), 40.2 (d), 45.0 (s), 50.6 (q), 54.5 (d), 54.5 (q), 111.2 (d), 113.6 (d), 118.6 (d), 124.2 (d), 125.5 (s), 129.0 (s), 129.4 (s), 138.0 (s), 149.9 (s), 158.8 (s), 176.3 (s). MS *m/e* (%) 352 (M^+, 100), 264 (11), 187 (13), 184 (15), 171 (8), 161 (17).

3.1.47. 13-Ethyl-3-methoxy-17-vinyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta-[*a*]-phenanthrene (68). The reaction was carried out as described for compound **64** on the same scale. Compounds **68** were obtained in 87% yield as a 2:1 mixture of two isomers and as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2975, 2938, 2839, 1734, 1605, 1498, 1244; ^1H NMR (C_6D_6) δ: 0.86 (*M*) and 0.89 (m) (t, J=7.4 Hz, 3H), 1.13–1.86 (m, 5H), 1.98–2.90 (m, 8H), 3.38 (s, 3H), 4.88–5.18 (m, 2H), 5.47 (*M*) and 5.60 (m) (br s, 1H), 5.80 (*M*, dt, J_1=9.7 Hz, J_2=17.0 Hz) and 6.06 (m, ddd, J_1=7.3 Hz, J_2=10.3 Hz, J_3=17.2 Hz) (1H), 6.68–6.80 (m, 2H), 7.12–7.22 (m, 1H); ^{13}C NMR (C_6D_6) δ: 8.8 (*M*) and 9.5 (m) (q), 23.8 (t), 24.0 (t), 26.8 (t), 26.9 (t), 28.7 (*M*) and 33.8 (m) (t), 37.2 (m) and 37.7 (*M*) (t), 49.5 (*M*) and 56.7 (m) (d), 50.0 (s), 54.5 (q), 111.2 (d), 112.9 (*M*) and 114.9 (m) (t), 113.5 (d), 118.7 (*M*) and 119.6 (m) (d), 124.2 (d), 125.9 (s), 129.3 (s), 129.4 (s), 137.9 (s), 138.9 (m) and 141.2 (*M*) (d), 147.3 (s), 158.7 (s). MS *m/e* (%) 306 (M^+, 100), 278 (17), 277 (29), 249 (6), 169 (6), 165 (5).

3.1.48. 8-Methoxy-12a-methyl-1,2,3,5,6,11,12,12a-octahydro-chrysene (69). 2-[2-(6-Methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclohexanone **57** (110 mg, 0.37 mmol) was dissolved in CH_2Cl_2 (5 ml) and a catalytic amount of P_2O_5 (approximately 10 mg) was added. The reaction mixture was refluxed for 3 h, diluted with EtOAc (25 ml) and washed with water (10 ml), a saturated $NaHCO_3$ solution (10 ml) and brine (10 ml). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 4:1) yielding **69** as a slightly yellow oil in 88% yield (91 mg). IR (CCl_4 sol.) cm^{-1}: 2936, 2837, 1606, 1498, 1250, 1078, 1043; ^1H NMR ($CDCl_3$) δ: 1.01 (s, 3H), 1.26–1.92 (m, 6H), 2.04–2.37 (m, 3H), 2.45–2.85 (m, 5H), 3.80 (s, 3H), 5.81 (t, J=3.9 Hz, 1H), 6.70–6.77 (m, 2H), 7.24 (d, J=8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ: 18.1 (t), 22.9 (t), 23.4 (q), 23.7 (t), 26.6 (t), 29.0 (t), 32.0 (s), 37.2 (t), 38.3 (t), 55.3 (q), 110.9 (d), 113.1 (d), 120.5 (d), 123.7 (d), 127.0 (s), 128.7 (s), 129.8 (s), 138.0 (s), 141.6 (s), 158.0 (s). HRMS: M^+, found 280.1830. $C_{20}H_{24}O$ requires 280.1827. MS *m/e* (%) 280 (M^+, 100), 265 (9), 223 (5), 171 (4), 140 (4).

3.1.49. 8-Methoxy-12a-methyl-1-vinyl-1,2,3,5,6,11,12,12a-octahydro-chrysene (70). The reaction was carried out as described for compound **64** on the same scale. Compounds **70** were obtained in 75% yield as a 2:1 mixture of two isomers and as a colourless oil. IR (CCl_4 sol.) cm^{-1}: 2937, 2838, 1606, 1499, 1250, 1040; ^1H NMR (C_6D_6) δ: 1.00 (*M*) and 1.14 (m) (s, 3H), 1.30–2.75 (m, 13H), 3.44 (s, 3H), 5.00–5.21 (m, 2H), 5.72–6.49 (m, 2H), 6.77–6.86 (m, 2H), 7.25–7.30 (m, 1H); ^{13}C NMR (C_6D_6) δ: 18.3 (*M*) and 25.1 (m) (q), 22.9 (t), 23.3 (m) and 23.9 (*M*) (t), 23.5 (m) and 24.2 (*M*) (t), 24.8 (m) and 26.0 (*M*) (t), 29.1 (t), 33.5 (m) and 34.4 (*M*) (t), 34.1 (m) and 34.8 (*M*) (s), 49.8 (m) and 50.2 (*M*) (d), 54.5 (q), 111.2 (d), 113.2 (d), 114.6 (m) and 115.2 (*M*) (t), 119.5 (m) and 119.9 (*M*) (d), 124.1 (d), 124.1 (s), 129.8 (s), 137.9 (s), 139.4 (s), 140.3 (*M*) and 140.6 (m) (d), 141.8 (s), 158.6 (s). HRMS: M^+, found 306.1989. $C_{22}H_{26}O$ requires 306.1984. MS *m/e* (%) 306 (M^+, 100), 291 (5), 252 (8), 237 (6), 223 (5), 171 (4).

3.1.50. 17-Isopropyl-3-methoxy-13-methyl-7,11,12,13,14,15,16,17-octahydro-6*H*-cyclopenta-[*a*]-phenanthrene (71). A suspension of $Pd/CaCO_3$ (5 wt%, 50 mg) in benzene (2 ml) was stirred for 1 h at room temperature under an atmosphere of H_2. Compound **66** (154 mg, 0.5 mmol) in benzene (4 ml) was then added and stirring was continued for 3 h more. The reaction mixture was filtered over a short plug of Hyflo, which was carefully washed with Et_2O (25 ml). Evaporation of the solvent then yielded the pure product as white crystals (145 mg, 93%), which were recrystallised from MeOH (mp 114–116 °C). IR ($CHCl_3$ sol.) cm^{-1}: 2952, 2837, 1607, 1570, 1498, 1467, 1430, 1302, 1250, 1038; ^1H NMR (C_6D_6) δ: 0.69 (s, 3H), 0.89 (d, $J=6.4$ Hz, 3H), 1.00 (d, $J=6.4$ Hz, 3H), 0.84–2.85 (m, 15H), 3.41 (s, 3H), 6.71–6.83 (m, 2H), 7.02–7.15 (m, 1H). ^{13}C NMR (C_6D_6) δ: 11.4 (q), 22.5 (q), 23.1 (q), 23.3 (t), 24.6 (t), 25.4 (t), 28.9 (2t), 31.5 (d), 36.7 (t), 42.3 (s), 52.6 (d), 54.5 (q), 56.7 (d), 110.9 (d), 113.7 (d), 123.0 (d), 125.4 (s), 129.4 (s), 132.5 (s), 137.0 (s), 158.3 (s). HRMS: M^+, found 310.2297. $C_{22}H_{30}O$ requires 310.2297. MS *m/e* (%) 310 (M^+, 100), 308 (28), 267 (7), 225 (15), 174 (51), 173 (11), 171 (21), 93 (15).

3.1.51. 17-Isopropyl-3-methoxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthrene (72). Compound **71** (65 mg, 0.21 mmol) was dissolved in dry benzene (5 ml) and Et_3SiH (0.35 ml) and CF_3COOH (0.35 ml) were added. The reaction mixture was stirred for 12 h at room temperature, diluted with Et_2O (25 ml), washed with a saturated solution of NH_4Cl (10 ml) and brine (10 ml). The organic phase was dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding **72** as white crystals (56 mg, 86%), which could be recrystallised from MeOH (mp 112–114 °C). IR ($CHCl_3$ sol.) cm^{-1}: 2954, 2872, 1608, 1498, 1466, 1238, 1039; ^1H NMR (C_6D_6) δ: 0.60 (s, 3H), 0.90 (d, $J=6.6$ Hz, 3H), 0.97 (d, $J=6.6$ Hz, 3H), 0.98–2.27 (m, 15H), 2.68–2.84 (m, 2H), 3.41 (s, 3H), 6.69 (d, $J=2.7$ Hz, 1H), 6.79 (dd, $J_1=2.7$ Hz, $J_2=8.6$ Hz, 1H), 7.21 (d, $J=8.6$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 11.9 (q), 22.4 (q), 23.2 (q), 23.9 (t), 26.9 (t), 27.9 (t), 28.5 (t), 29.9 (t), 31.0 (d), 38.9 (d), 39.9 (t), 42.7 (s), 43.8 (d), 54.4 (q), 55.2 (d), 58.3 (d), 111.6 (d), 113.8 (d), 126.3 (d), 132.7 (s), 137.7 (s), 157.9 (s). HRMS: M^+, found 312.2458. $C_{22}H_{32}O$ requires 312.2453. MS *m/e* (%) 312 (M^+, 100), 227 (12), 199 (10), 186 (7), 174 (10), 173 (13), 160 (7), 147 (9).

Acknowledgements

The authors gratefully acknowledge financial support from the Dutch Technology Foundation (Grant CW/STW-project 790.35.215) and from Organon International. The authors thank B. van Lagen for NMR and IR spectroscopic data.

References and notes

1. Paulsen, H.; Antons, S.; Brandes, A.; Lögers, M.; Müller, S. N.; Naab, P.; Schmeck, C.; Schneider, S.; Stoltefuss, J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3373.
2. Hagiwara, H.; Yamada, Y.; Sakai, H.; Suzuki, T.; Ando, M. *Tetrahedron* **1998**, *54*, 10999.
3. Prowotorow, I.; Stepanenko, W.; Wicha, J. *Eur. J. Org. Chem.* **2002**, *5*, 2727.
4. Gorobets, E.; Miftakhov, M. S.; Valeev, F. A. *Russ. Chem. Rev.* **2000**, *69*, 1001.
5. Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1998**, *39*, 885.
6. Marczak, S.; Wicha, J. *Tetrahedron Lett.* **1993**, *34*, 6627.
7. Marczak, S.; Michalak, K.; Urbanczyk-Lipkowska, Z.; Wicha, J. *J. Org. Chem.* **1998**, *63*, 2218.
8. Grzywacz, P.; Marczak, S.; Wicha, J. *J. Org. Chem.* **1997**, *62*, 5293.
9. Mukaiyama, T.; Sagawa, Y.; Kobayashi, S. *Chem. Lett.* **1986**, 1821.
10. Hagiwara, H.; Okano, A.; Uda, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1047.
11. Posner, G. H.; Asirvatham, E. *Tetrahedron Lett.* **1986**, *27*, 663.
12. Posner, G. H.; Lu, S. B.; Asirvatham, E. *Tetrahedron Lett.* **1986**, *27*, 659.
13. Posner, G. H.; Lu, S. B.; Asirvatham, E.; Silversmith, E. F.; Shulman, E. M. *J. Am. Chem. Soc.* **1986**, *108*, 511.
14. Wakselman, C.; Mondon, M. *Tetrahedron Lett.* **1973**, *14*, 4285.
15. Sarabèr, F. C. E.; Drach, S.; Bosselaar, G.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2005**, *61* previous article.
16. Dratch, S.; Charnikhova, T.; Sarabèr, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287.
17. Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047.
18. Djuric, S.; Sarkar, T.; Magnus, P. *J. Am. Chem. Soc.* **1980**, *102*, 6886.
19. Duhamel, P.; Hennequin, L.; Poirier, J. M.; Tavel, G.; Vottero, C. *Tetrahedron* **1986**, *42*, 4777.
20. Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387.
21. Duhamel, P.; Deyine, A.; Dujardin, G.; Plé, G.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2103.
22. Ziegler, F. E.; Lim, H. *J. Org. Chem.* **1982**, *47*, 5230.
23. Posner, G. H. *Chem. Rev.* **1986**, *86*, 831.
24. Mikami, K.; Takahashi, K.; Nakai, T.; Uchimaru, T. *J. Am. Chem. Soc.* **1994**, *116*, 10948.
25. Mikami, K.; Takahashi, K.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 4035.
26. Saraber, F. C. E.; de Groot, A. *Tetrahedron Lett.* **2004**, *45*, 9431–9433.
27. Möller, R.; Engel, N.; Steglich, W. *Synthesis* **1978**, 620.
28. Grieco, P. A.; Collins, J. L.; Henry, K. J., Jr. *Tetrahedron Lett.* **1992**, *33*, 4735.
29. Ayerbe, M.; Cossio, F. P. *Tetrahedron Lett.* **1995**, *36*, 4447.
30. Pearson, W. H.; Schkeryantz, J. M. *J. Org. Chem.* **1992**, *57*, 2986.
31. The concentrations used here are lower than those used in the references cited.
32. Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178–3196.
33. Schank, K.; Weiter, M. *Helv. Chim. Acta* **2002**, *85*, 2105.
34. Keul, H.; Choi, H. S.; Kuczkowski, R. L. *J. Org. Chem.* **1985**, *50*, 3365.
35. Borowitz, I. J.; Rapp, R. D. *J. Org. Chem.* **1969**, *34*, 1370.
36. Gazzard, L. J.; Motherwell, W. B.; Sandham, D. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 979.
37. Laabs, S.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Tetrahedron* **2002**, *58*, 1317.

38. Krafft, M. E.; Holton, R. A. *J. Am. Chem. Soc.* **1984**, *106*, 7619.
39. Corey, E. J.; Huang, A. X. *J. Am. Chem. Soc.* **1999**, *121*, 710.
40. Sobolev, A.; Vos, M.; Zuilhof, H.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Arkivoc* **2005**, 29 part (xiv).
41. Ananchenko, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355.
42. Rao, G. S. R. S.; Banerjee, D. K.; Devi, L. U.; Sheriff, U. *Aust. J. Chem.* **1992**, *45*, 187.
43. Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460.
44. Blazejewski, J. C.; Dorme, R.; Wakselman, C. *J. Chem. Soc., Perkin Trans. 1* **1986**, 337.
45. Zhuang, Z. P.; Zhou, W. S. *Tetrahedron* **1985**, *41*, 3633.
46. Quinkert, G.; Del Grosso, M.; Döring, A.; Döring, W.; Schenkel, R. I.; Bauch, M.; Dambacher, G. T.; Bats, J. W.; Zimmermann, G.; Dürner, G. *Helv. Chim. Acta* **1995**, 78.
47. Broess, A. I. A.; van Vliet, N. P.; Groen, M. B.; Hamersma, H. *Steroids* **1992**, *57*, 514.
48. Rufer, C.; Schröder, E.; Gibian, H. *Liebigs Ann. Chem.* **1971**, *752*, 1.
49. Kurosawa, T.; Niistu, U.; Tohma, M. *Chem. Pharm. Bull.* **1987**, *35*, 585.
50. Künzer, H.; Sauer, G.; Wiechert, R. *Tetrahedron Lett.* **1991**, *32*, 743.
51. Bijoy, P.; Ramachandran, U.; Rao, G. S. R. S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2331.
52. Pillai, K. M. R.; Murray, W. V.; Shooshani, I.; Williams, D. L.; Gordon, D.; Wang, S. Y.; Johnson, F. *J. Med. Chem.* **1984**, *27*, 1131.
53. The all-trans configuration of compound **72** was confirmed by X-ray analysis. see: Kooijman, H.; Saraber, F. C. E.; de Groot, A.; Spek, A. L. *Acta Crystallogr., Sect. E* **2005**, *61*, 3908.
54. Cossi, M.; Barone, V.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1998**, *286*, 253.
55. Assignment according to ^{1}H NMR shifts of allylic proton due to influence of adjacent phenyl group.
56. RajanBabu, T. V. *J. Org. Chem.* **1984**, *49*, 2083.
57. Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10073.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1743–1748

Synthesis of a chiral steroid ring D precursor starting from carvone

Serghei Pogrebnoi,[a,b] Florence C. E. Sarabèr,[a] Ben J. M. Jansen[a] and Aede de Groot[a,*]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Institute of Chemistry, Academy str. 3, MD-2028 Kishinev, Republic of Moldova*

Received 20 May 2005; accepted 24 November 2005

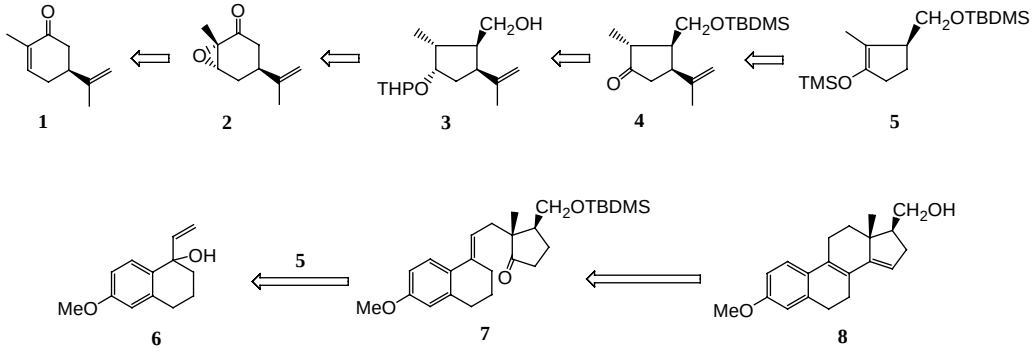
Available online 20 December 2005

Abstract—A chiral five-membered, silyl enol ether containing, steroid ring D precursor has been synthesized from carvone. This silyl enol ether has been applied in the synthesis of a chiral C17 functionalized steroid skeleton using the addition of a carbocation, generated with $ZnBr_2$ from a Torgov reagent, followed by cyclization of the adduct by treatment with acid.

1. Introduction

An ultimate goal in steroid synthesis is the development of short and efficient routes to enantiomerically pure compounds. The encouraging results obtained in the coupling reactions of the Torgov reagent **6** with silyl enol ether derivatives of five-membered ring D precursors,[1] seems to offer a good prospect for a chiral approach. On the other hand, suitably functionalised optically active five-membered ring ketones or their silyl enol ethers, with the right configuration for steroid synthesis, are not over-abundant. Most efforts were developed to obtain ring D precursors for the synthesis of vitamin D analogs[2–10] and some for steroids.[9–13] Three such routes starting from a chiral natural product have been published,[3,8–10,14,15] next to several routes using a chiral auxiliary during synthesis.[2,4,5,11,16–19] In one route a chiral starting material obtained through biotransformation has been applied.[6,7]

Compounds from the chiral pool seemed to offer good opportunities to access a chiral steroid ring D precursor and based on our experience it was decided to explore a synthesis starting from carvone (**1**). A sequence involving a ring contraction of carvone using a Favorskii rearrangement has been reported in the literature and leads, in five steps, to the selectively protected diol **3** in 36% overall yield.[20] Further transformation could lead in a few more steps to silyl enol ether **5** as the chiral steroid ring D precursor. Coupling with the Torgov reagent **6** and ring closure should lead to the chiral steroid skeleton **8** with a functionalised substituent at C17 (see Scheme 1). To obtain the correct stereochemistry at C17 in the final steroid skeleton, C5 in carvone **1** should have the *S* configuration.



Scheme 1.

Keywords: Mukaiyama–Michael addition; Carvone; Chiral silyl enol ethers; C,D-trans steroid synthesis.
* Corresponding author. Tel.: +31 317482370; fax: +31 317484914; e-mail: aede.degroot@wur.nl

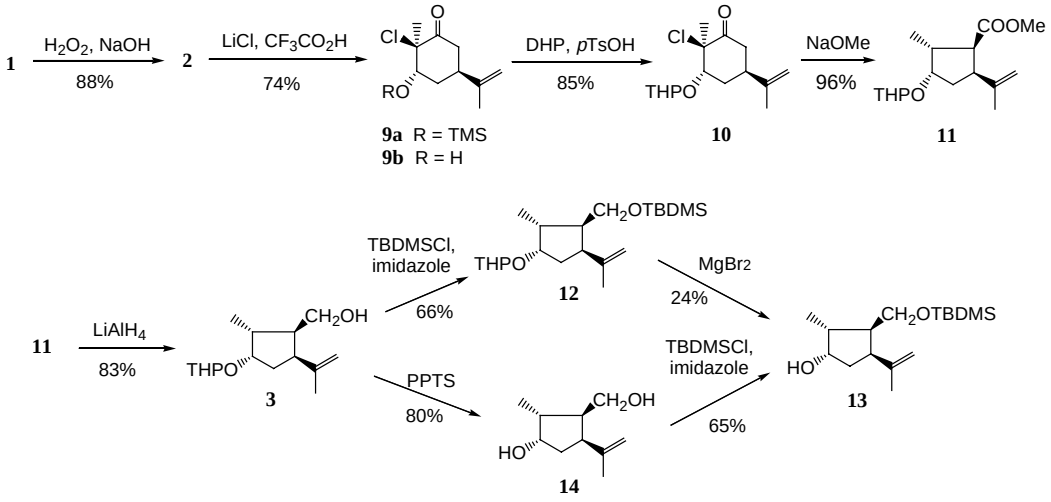
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.057

2. Results and discussion

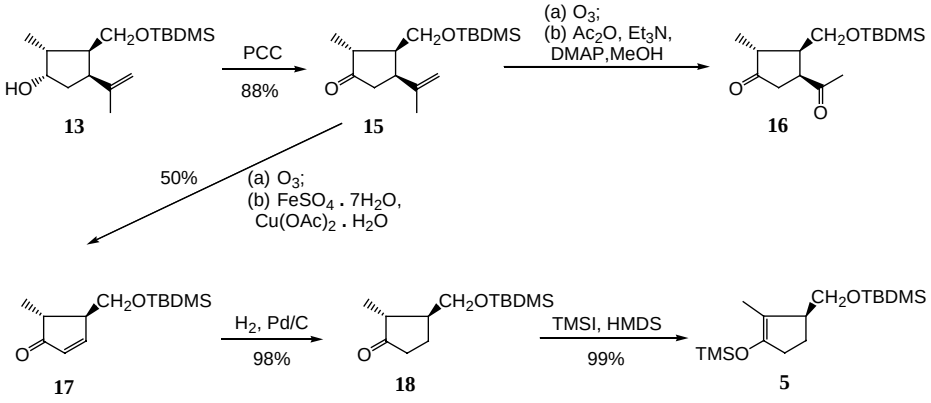
Epoxidation of the double bond of the enone in carvone using hydrogenperoxide in basic solution, leads to epoxide **2** in 88% yield, and in principle this epoxide should be a substrate for the required Favorskii rearrangement. Unfortunately, this rearrangement does not give only the desired ring contraction product, but also a regioisomer and opening of the epoxide.[20–23] For a more selective result, the epoxide ring has to be opened first stereoselectively to compound **9b** and then converted to THP ether **10** (Scheme 2). In the literature an opening of epoxide **2** to the silylated alcohol **9a** was reported using TMSCl.[20] In our hands better results were obtained using LiCl in combination with trifluoroacetic acid,[24] giving directly the free alcohol **9b**. Protection of the alcohol as a diastereomeric mixture of THP ethers **10** was necessary for complete stereo- and regioselectivity in the Favorskii rearrangement,[20,24] the use of silyl protecting groups on the alcohol moiety did not give as good results.[25] Coordination of the oxygen in the THP ring with the alcohol that donates its proton during the rearrangement could be a possible explanation for the desired regioselective opening of the cyclopropane ring.

Reduction of the rearranged ester **11** gave the selectively protected diol **3**.[24] Our attempts to first protect the primary alcohol in **3** and then selectively remove the THP group using $MgBr_2$[26] gave only 24% of **13**, and treatment with Et_2AlCl[27] failed completely. Diol **13**, with a protected primary hydroxyl group, was obtained in a better 65% yield via deprotection to diol **14**, followed by selective reprotection of the primary alcohol. Although this yield is still not very high, the remaining products consist of unreacted diol **14** (21%) and the double protected diol (12.5%), which can be separated easily from **13** and used again.

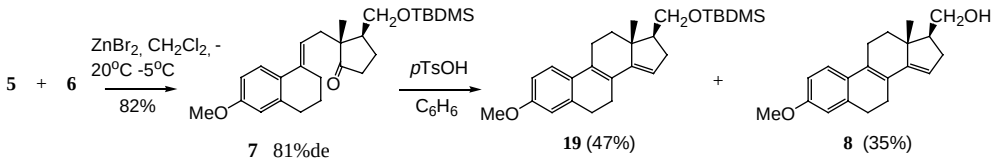
Oxidation of the secondary hydroxyl group in **13** opens up the possibility for regioselective elimination of the isopropenyl group to compound **17** (Scheme 3). Ozonolysis followed by Criegee rearrangement, using triethylamine, aceticanhydride and DMAP in methanol,[28,29] was troublesome in our hands and usually gave diketone **16**, in which normal ozonolysis of the double bond to the ketone had taken place. Only with the use of $FeSO_4$ and $CuSO_4$ salts for decomposition of the intermediate a fair yield (50%) of the desired enone **17** could be obtained.[30] Catalytic reduction of the double bond to **18** and regioselective formation of the silyl enol ether, both in near quantitative yields, finally led to the desired chiral steroid ring D precursor **5** in 10% overall yield starting from (*S*)-(+)-carvone.



Scheme 2.



Scheme 3.



Scheme 4.

Silyl enol ether **5** was put into reaction with the Torgov reagent **6**, which yielded secosteroid **7** in 82% yield as a mixture of two C13 diastereomers, with a diastereomeric excess of 81% (Scheme 4). No crystals could be obtained to prove the configuration of the main product using X-ray crystallography, and also NOE experiments failed to show any effect between the C13 methyl group or the C12 methylene group with the hydrogen atom on C17 or the methylene group bearing the OTBDMS group. However, based on experience with similar reactions,[1] it may be assumed that this main product has the desired *S*-configuration on C13.

Subsequent cyclisation of **7** gave the steroidal diene **19** in 47% yield, next to the deprotected compound **8**, in 35% yield. The protected diene **19** appeared to be unstable upon storage, decomposing to a complex mixture of products, even when kept at −18 °C. Better results were obtained with diene **8**, which remained stable upon storage and complete deprotection of the alcohol moiety in the side chain (e.g., using TBAF in THF) directly after the cyclisation, is therefore the best procedure. Selective reduction (e.g., using H_2, $Pd/CaCO_3$) then can be carried out to afford the C,D trans coupled steroid skeleton.

Although the overall yield of optically active steroid ring D precursor **5** from (*S*)-(+)-carvone is only 10% and requires 11 steps, the applicability of this approach for the preparation of enantiomerically pure steroid skeletons has been shown. The development of straightforward, easy and high yielding syntheses for chiral steroid ring D precursors is, however, essential to make this route to a good method for the synthesis of optically active steroid skeletons.

3. Experimental

3.1. General procedure. See[31]

3.1.1. 3-Hydroxymethyl-4-isopropenyl-2-methyl-cyclopentanol (14). To a cooled solution (at −15 °C) of (*S*)-(+)-carvone (10 g, 0.066 mol) in methanol (66 ml) and 22 ml of H_2O_2 (30%, 0.198 mol), 5 ml of 6.6 M NaOH solution in H_2O was added dropwise over a period of 5 min. During the addition the temperature was carefully kept below 0 °C. The mixture was stirred for 2 h at 0 °C and then the solution was allowed to warm to room temperature over a period of 1 h. The reaction mixture was poured in water (400 ml) and the water solution was extracted four times with diethyl ether (100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 9.8 g of crude product **2**, which was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 1.31 (s, 3H), 1.62 (s, 3H), 1.75–2.05 (m, 2H), 2.28 (br d, J=14.6 Hz, 1H), 2.38–2.75 (m, 2H), 3.37 (d, J=2.8 Hz, 1H), 4.63 (br s, 1H), 4.70 (br s, 1H); ^{13}C NMR (C_6D_6) δ: 15.2 (q), 20.5 (q), 28.6 (t), 34.9 (d), 41.7 (t), 58.6 (s), 61.2 (d), 110.4 (d), 146.3 (s), 205.3 (s).

To an ice-cooled solution of **2** (4.3 g, 26 mmol) in dry THF (100 ml), LiCl (1.8 g, 43 mmol) and CF_3COOH (4.9 g, 43 mmol) were added. The mixture was stirred for 20 min at 0 °C and during 2 h at room temperature. Water (500 ml) was added and the reaction mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were washed with a saturated solution of $NaHCO_3$ (100 ml), water (100 ml) and brine (100 ml), dried ($MgSO_4$) and evaporated under reduced pressure. The crude product (5.2 g) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 1.63 (s, 3H), 1.73 (s, 3H), 1.87 (ddt, J_1=2.1 Hz, J_2=3.6 Hz, J_3=14.2 Hz, 1H), 2.28–3.10 (m, 5H), 4.23 (dd, J_1=3.7 Hz, J_2=6.3 Hz, 1H), 4.75 (br s, 1H), 4.78 (br s, 1H); ^{13}C NMR (C_6D_6) δ: 20.3 (q), 22.1 (q), 32.8 (t), 38.9 (d), 41.1 (t), 67.9 (s), 76.8 (d), 110.6 (t), 146.4 (s), 205.3 (s).

A solution of product **9b** (5.2 g) from the former reaction in dry CH_2Cl_2 (100 ml) was cooled on ice and DHP (dihydropyran, 6.4 g, 76 mmol) was added, followed by a catalytic amount of *p*TsOH (50 mg). The mixture was stirred for 2 h during, which the temperature was allowed to rise to room temperature (the reaction mixture became green). After evaporation of CH_2Cl_2 under reduced pressure, the residue was dissolved in light petroleum and purified over a short plug of silica (5 g), yielding 4.7 g of crude product **10** as a mixture of diastereomers, which were used without any further purification in the next step.

To 20 ml of an ice-cooled solution of NaOMe (1.2 M) in methanol, 4.7 g of **10**, from the former experiment, in 10 ml of dry methanol was added drop wise over a period of 10 min. During the addition, a precipitate started to form and it appeared necessary to keep the temperature of the reaction below 15 °C. The reaction mixture was stirred for a further 15 min before water (300 ml) was added. The mixture was extracted with diethyl ether (3×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure, yielding 4.43 g of crude product **11** as a slightly yellow oil as a mixture of two diastereomers. The crude product was used without any further purification in the next step.

To an ice-cooled mixture of $LiAlH_4$ (1 g, 26 mmol) in dry diethyl ether (20 ml) was added drop wise a solution of **11** (4.43 g) in dry diethyl ether (10 ml), over a period of 10 min. The reaction mixture was stirred for a 2 h at room temperature. Then 1 ml of water was carefully added under cooling with ice, followed by 4 ml of a 4 M NaOH solution and again 4 ml of water. After stirring for 30 min

the reaction mixture was filtered to remove the inorganic precipitate, which was carefully washed with ether (20 ml). The filtrate was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product **3** (3.31 g, slightly yellow oil) was used without any further purification in the next step. ^{1}H NMR (C_6D_6) δ: 0.98 and 1.09 (2d, J= 6.6 Hz, 3H), 1.30–2.15 (m, 10H), 2.78–3.10 (m, 1H), 3.47 (q, J=5.5 Hz, 2H), 3.80–3.93 (m, 1H), 4.00–4.15 (m, 1H), m 4.52–4.67 (m, 1H), 4.76 (br s, 1H), 4.85 (br s, 1H).[24]

The crude product **3** from the former experiment (3.1 g) in 35 ml of methanol and a catalytic amount of pyridinium *para*-toluenesulfonic acid (PPTS, 10 mol%) were stirred at 50 °C during 2 h. After evaporation of the methanol under reduced pressure, the residue (2.35 g) was purified by rapid column chromatography (PE/EtOAc 10:1), yielding 1.5 g of pure **14** (32% overall yield from (*S*)-(+)-carvone). $[\alpha]_D^{20}$ 13.6 (*c* 12.0 in $CHCl_3$); IR (film) cm^{-1}: 3356 (br), 3081, 2957, 2932, 1646, 1453, 1375, 1080, 1041, 891; ^{1}H NMR ($CDCl_3$) δ: 1.01 (d, J=6, 7 Hz, 3H), 1.65–2.23 (m, 9H), 2.94–3.04 (m, 1H), 3.44 (d, J=5 Hz, 2H), 4.11 (m, 1H), 4.72 (s, 1H), 4.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 14.0 (q), 23.83 (q), 38.8 (t), 41.6 (d), 44.8 (d), 49.0 (d), 63.6 (t), 74.47 (d), 110.6 (t), 147.0 (s). HRMS: M^+, found 170.1308. $C_{10}H_{18}O_2$ requires 170.1307. MS *m/e* (%) 170 (M^+, <1), 155 (3), 152 (4), 121 (81), 99 (55), 81 (100), 72 (64), 71 (66), 55 (69), 43 (56).

3.1.2. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanol (13). A solution of **14** (3.8 g, 22 mmol) in dimethylformamide (DMF, 70 ml) was cooled to 5 °C and TBDMSCl (3.7 g, 24 mmol) in DMF (20 ml) was added by rapid dropping (5 min), followed by a solution of imidazole (3.8 g, 56 mmol) in DMF (10 ml). The reaction mixture was stirred for 20 min at 5 °C and then for 3 h at 30 °C. Water was added (500 ml) and the water layer was extracted with Et_2O (4×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EA 15:1), yielding 4.15 g of **13** (65%) as a colourless oil, 1.1 g of the diprotected compound (12.5%) as a colourless oil, and 0.46 g of unreacted material **14** (12%).

Compound **13**. $[\alpha]_D^{20}$ −3.1 (*c* 5.0 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 3631, 3491 (br), 3083, 2951, 2894, 2858, 1647, 1471, 1459, 1255, 1093, 1003, 889; ^{1}H NMR (C_6D_6) δ: 0.16 (s, 6H), 0.86 (s, 9H), 1.08 (d, J=6.9 Hz, 3H), 1.75 (s, 3H), 1.64–2.04 (m, 5H), 2.89–2.98 (m, 1H), 3.28 (dd, J_1= 7.6 Hz, J_2=10.1 Hz, 1H), 3.47 (dd, J_1=5.3 Hz, J_2= 10.1 Hz, 1H), 4.17 (dd, J_1=3.6 Hz, J_2=4.4 Hz, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) δ: −5.5 (2q), 14.7 (q), 18.2 (s), 23.8 (q), 25.9 (3q), 38.8 (t), 42.5 (d), 44.8 (d), 47.5 (d), 64.1 (t), 74.6 (d), 110.1 (t), 145.2 (s). HRMS: $[M-tBu]^+$, found 227.1470. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 251 ($[M-CH_3-H_2O]^+$, 2), 227 (32), 209 (76), 185 (20), 95 (18), 93 (14), 75 (100), 73 (29).

Diprotected compound. ^{1}H NMR (C_6D_6) δ: 0.07 (s, 6H), 0.09 (s, 6H), 0.89 (s, 18H), 1.02 (d, J=6.6 Hz, 3H), 1.60 (dd, J_1=6.4 Hz, J_2=12.4 Hz, 1H), 1.77 (s, 3H), 1.70–1.97 (m, 3H), 2.89–3.02 (m, 1H), 3.28 (dd, J_1=7.1 Hz, J_2= 10.0 Hz, 1H), 3.47 (dd, J_1=5.1 Hz, J_2=10.0 Hz, 1H), 4.09–4.13 (m, 1H), 4.62 (s, 1H), 4.77 (s, 1H); ^{13}C NMR (C_6D_6) δ: −5.4 (2q), −4.7 (q), −4.6 (q), 15.5 (q), 18.2 (s), 23.9 (q), 25.9 (6q), 39.5 (t), 43.2 (d), 43.7 (d), 47.5 (d), 64.2 (t), 74.8 (d), 109.7 (t), 145.7 (s).

3.1.3. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-4-isopropenyl-2-methyl-cyclopentanone (15). To a solution of **13** (4.1 g, 14.4 mmol) in dry CH_2Cl_2 (120 ml), to which 4 g of molecular sieves (3 Å) were added, 4.5 g of pyridinium chlorochromate (PCC, 21.6 mmol) was added in three portions over a period of 3 h. The reaction mixture was stirred for 2 h more, filtered over a short plug of silica and evaporated under reduced pressure. The residue was dissolved in Et_2O (200 ml) washed with water and brine, dried ($MgSO_4$) and evaporated again under reduced pressure. The crude product was purified by flash chromatography (PE/EtOAc 15:1), yielding 3.6 g of **15** (88%), next to some minor unidentified products. $[\alpha]_D^{20}$ 21.2 (*c* 1.25 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2958, 2931, 2859, 1743, 1471, 1254, 1091; ^{1}H NMR ($CDCl_3$) δ: 0.01 (s, 6H), 0.83 (s, 9H), 1.13 (d, J=7.5 Hz, 3H), 1.77 (s, 3H), 2.05–2.60 (m, 5H), 2.97 (br q, J=8.0 Hz, 1H), 3.57 (d, J=7.9 Hz, 2H), 4.69 (s, 1H), 4.88 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: −5.7 (2q), 15.9 (q), 18.1 (s), 22.6 (q), 25.7 (3q), 41.7 (t), 42.6 (d), 45.6 (d), 47.9 (d), 62.8 (t), 111.5 (t), 143.9 (s), 221.2 (s). HRMS: $[M-CH_3]^+$, found 267.1782. $C_{15}H_{27}O_2Si$ requires 267.1780. MS *m/e* (%) 282 (M^+, 0.03), 267 (2.7), 225 (100), 195 (8), 133 (20), 131 (15), 75 (59), 73 (22).

3.1.4. 4-(*tert*-Butyl-dimethyl-silanyloxymethyl)-5-methyl-cyclopent-2-enone (17). A stirred solution of **15** (1.0 g, 3.54 mmol) in CH_2Cl_2 (24 ml) and MeOH (20 ml) was cooled to −78 °C and purged with ozone until a pale blue colour appeared (~15 min). Nitrogen was then bubbled through for 30 min to remove the excess of ozone and $FeSO_4\cdot 7H_2O$ (0.98 g, 3.54 mmol) and $Cu(OAc)_2\cdot H_2O$ (1.4 g, 7.10 mmol) were added. The reaction mixture was allowed to warm to room temperature overnight, after which the solvents were evaporated under reduced pressure. The residue was dissolved in water and extracted with Et_2O (4×100 ml). The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 15:1), yielding 0.43 g of **17** (50%), next to some unidentified products and **16**. $[\alpha]_D^{20}$ 122.4 (*c* 6.6 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 0.02 (s, 6H), 0.75 (s, 9H), 1.17 (d, J=7.4 Hz, 3H), 2.09 (dq, J_1=2.5 Hz, J_2=7.5 Hz, 1H), 2.65 (m, 1H), 3.68 (m, 2H), 6.15 (dd, J_1= 2.0 Hz, J_2=5.8 Hz, 1H) 7.56 (dd, J_1=2.3 Hz, J_2=5.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ: −5.5 (2q), 14.9 (q), 18.9 (s), 25.8 (3q), 43.2 (d), 52.9 (d), 64.3 (t), 133.7 (d), 163.9 (d), 212.1 (s). HRMS: $[M-CH_3]^+$, found 225.1311. $C_{12}H_{21}O_2Si$ requires 225.1311. $[M-C_4H_9]^+$, found 183.00842, $C_9H_{15}O_2Si$ requires 183.0841. MS *m/e* (%) 225 ($M-CH_3^+$, 3), 210 (2), 183 ($M-C_4H_9^+$, 100), 153 (15), 139 (15), 126 (9), 75 (32).

3.1.5. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-cyclopentanone (18). To a solution of **17** (200 mg, 0.83 mmol) in *t*BuOMe (10 ml) was added Pd on C (10%, 20 mg) had the suspension was shaken under hydrogen atmosphere pressure (50 psi [3.45 bar]) during 1 h. The reaction mixture was filtered over a short plug of

Hyflo, which was then carefully washed with ether. The filtrate was dried ($MgSO_4$) and the solvent was removed under reduced pressure yielding pure **18** (198 mg, 98%), which needed no further purification. $[\alpha]_D^{20}$ −46.3 (*c* 1.7 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2957, 2925, 2876, 2858, 1743, 1470, 1255, 1107; ^1H NMR ($CDCl_3$) δ: 0.03 (s, 6H), 0.88 (s, 9H), 1.16 (d, $J=7$ Hz, 3H), 1.61–2.44 (m, 6H), 3.7 (m, 2H); ^{13}C NMR ($CDCl_3$) δ: −5.1 (2q), 12.8 (q), 23.6 (t), 25.8 (3q), 37.2 (t), 46.2 (d), 46.8 (d), 64.3 (t). HRMS: $[M-CH_3]^+$, found 227.1471. $C_{12}H_{23}O_2Si$ requires 227.1467. MS *m/e* (%) 227 ($[M-CH_3]^+$, 2.6), 185 (100), 141 (13), 129 (18), 75 (58), 73 (11).

3.1.6. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-methyl-1-trimethylsilanyloxy-cyclopentene (5). Compound **18** (174 mg, 0.72 mmol) was dissolved in CH_2Cl_2 (5 ml) and hexamethyl disilazane (HMDS, 0.550 ml, 2.6 mmol) was added, followed by TMSI (312 µl, 2.2 mmol). The reaction mixture was stirred overnight at room temperature, diluted with Et_2O (15 ml) and washed with a saturated solution of $NaHCO_3$ and brine. After drying (Na_2SO_4) the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE:Et_2O/Et_3N 98:1:1) giving 225 mg of pure product **5** (99%). $[\alpha]_D^{20}$ 15.4 (*c* 5.5 in *n*-C_6H_{12}); IR (CCl_4 sol.) cm^{-1}: 2958, 2924, 2898, 2857, 1685, 1329, 1253, 1205, 1107, 1065, 1006, 920; ^1H NMR (C_6D_6) δ: 0.03 (s, 6H), 0.14 (s, 9H), 0.97 (s, 9H), 1.67 (s, 3H), 1.64–1.93 (m, 2H), 2.15–2.34 (m, 2H), 2.50–2.67 (m, 1H), 3.44 (dd, $J_1=6.3$ Hz, $J_2=9.7$ Hz, 1H), 3.59 (dd, $J_1=4.8$ Hz, $J_2=9.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.4 (2q), 0.6 (3q), 10.8 (q), 18.4 (s), 24.0 (t), 26.0 (3q), 32.8 (t), 47.9 (d), 66.1 (t), 113.4 (s), 148.3 (s). HRMS: M^+, found 314.2095. $C_{16}H_{34}O_2Si_2$ requires 314.2097. MS *m/e* (%) 314 (M^+, 2), 299 (2), 257 (2), 169 (100), 147 (2), 73 (20).

3.1.7. 3-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2-[2-(6-methoxy-3,4-dihydro-2*H*-naphthalen-1-ylidene)-ethyl]-2-methyl-cyclopentanone (7). 6-Methoxy-1-vinyl-1,2,3,4-tetrahydro-naphthalen-1-ol (**6**, 68 mg, 0.33 mmol) and compound **5** (314 mg, 1 mmol) were dissolved in CH_2Cl_2 (20 ml) and cooled to −20 °C. $ZnBr_2$ (a few crystals, approx. 20 mg) was added as the catalyst and the reaction mixture was stirred for 4 h at −5 °C. When all of compound **6** had disappeared (TLC), EtOAc (25 ml) was added and the reaction mixture was washed with saturated $NaHCO_3$ solution and brine, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding compound **7** as a colourless oil in 82% yield (116 mg). $[\alpha]_D^{20}$ −16.5 (*c* 2.34 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2953, 2932, 2896, 2859, 1740, 1606, 1496, 1464, 1255, 1100; ^1H NMR (C_6D_6) δ: 0.02 (s, 6H), 0.94 (s, 9H), 0.97 (s, 3H), 1.10–1.34 (m, 1H), 1.60–1.95 (m, 4H), 2.05–2.26 (m, 2H), 2.30–2.64 (m, 6H), 3.33 (s, 3H), 3.35–3.62 (m, 2H), 6.00 (br t, $J=7.8$ Hz, 1H), 6.57 (d, $J=2.7$ Hz, 1H), 7.72 (dd, $J_1=2.7$ Hz, $J_2=8.7$ Hz, 1H), 7.60 (d, $J=8.7$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.7 (2q), 17.2 (q), 18.1 (s), 22.8 (t), 23.5 (t), 25.8 (q), 26.9 (t), 30.8 (t), 35.9 (t), 36.8 (t), 44.6 (d), 51.1 (s), 54.5 (q), 64.4 (t), 112.7 (d), 113.3 (d), 117.3 (d), 125.3 (d), 129.3 (s), 136.6 (s), 138.6 (s), 159.0 (s), 220.1 (s). HRMS: M^+, found 428.2755. $C_{26}H_{40}O_3Si$ requires 428.2747. MS *m/e* (%) 428 (M^+, 8.1), 187 (100), 174 (3.2), 161 (3.1), 159 (3.5), 75 (2.6), 73 (3.4).

3.1.8. *tert*-Butyl-(3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]-phenanthren-17-ylmethoxy)-dimethyl-silane (19) and (3-methoxy-13-methyl-7,11,12,13,16,17-hexahydro-6*H*-cyclopenta[*a*]phenanthren-17-yl)-methanol (8). Compound **7** (108 mg, 0.25 mmol) was dissolved in benzene (5 ml) and a crystal of *para*-toluene sulfonic acid (*p*TsOH) was added. The reaction mixture was stirred at 40 °C for 6 h, then the reaction mixture was diluted with Et_2O (15 ml) and washed with saturated $NaHCO_3$ solution and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc 9:1) yielding 47% of **19** (48 mg) and 35% of **8** (26 mg).

Compound **19**. $[\alpha]_D^{20}$ −9.3 (*c* 2.89 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2957, 2931, 2858, 1607, 1464, 1255; ^1H NMR (C_6D_6) δ: 0.10 (s, 6H), 1.00 (s, 3H), 1.02 (s, 9H), 1.20–1.38 (m, 1H), 1.55–1.78 (m, 2H), 2.10–2.80 (m, 8H), 3.38 (s, 3H), 3.65–3.88 (m, 2H), 5.53 (br s, 1H), 6.68–6.79 (m, 2H), 7.19 (d, $J=9.3$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: −5.5 (2q), 16.1 (q), 18.2 (s), 23.8 (t), 24.0 (t), 25.9 (3q), 28.8 (t), 33.8 (t), 36.1 (t), 44.9 (s), 53.6 (q), 54.5 (d), 63.7 (t), 111.2 (d), 113.6 (d), 119.3 (d), 124.2 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.0 (s), 149.8 (s), 158.8 (s). HRMS: M^+, found 410.2639. $C_{26}H_{38}O_2Si$ requires 410.2641. MS *m/e* (%) 410 (M^+, 100), 395 (4), 353 (8), 278 (43), 263 (33), 89 (9), 75 (17), 73 (23).

Compound **8**. $[\alpha]_D^{20}$ −34.0 (*c* 1.08 in $CHCl_3$); IR (CCl_4 sol.) cm^{-1}: 2933, 2835, 1606, 1561, 1498, 1248, 1216, 1044; ^1H NMR (C_6D_6) δ: 0.91 (s, 3H), 1.01 (br, 1H), 1.50–1.70 (m, 1H), 1.95–2.73 (m, 10H), 3.37 (s, 3H), 3.45–3.70 (m, 2H), 5.50 (br s, 1H), 6.68–6.75 (m, 2H), 7.17 (d, $J=9.8$ Hz, 1H); ^{13}C NMR (C_6D_6) δ: 16.1 (q), 23.8 (t), 24.0 (t), 28.8 (t), 34.1 (t), 35.9 (t), 44.8 (s), 53.7 (d), 54.5 (q), 63.2 (t), 111.3 (d), 113.6 (d), 119.3 (d), 124.3 (d), 125.7 (s), 129.1 (s), 129.5 (s), 138.1 (s), 149.7 (s), 158.8 (s). HRMS: M^+, found 296.1774. $C_{20}H_{24}O_2$ requires 296.1776. MS *m/e* (%) 296 (M^+, 100), 265 (7), 263 (9), 249 (3), 225 (3), 165 (4), 139 (3).

Acknowledgements

The authors gratefully acknowledge financial support from the Dutch Technology Foundation (Grant CW/STW-project 790.35.215), from Organon International and from WICC Wageningen. The authors thank B. van Lagen for NMR and IR spectroscopic data, and M.A. Posthumus for mass spectroscopic measurements.

References and notes

1. Saraber, F. C. E.; de Groot, A. *Tetrahedron Lett.* **2004**, *45*, 9431.
2. Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1473.
3. Daniewski, A. R.; Warchol, T. *Liebigs Ann. Chem.* **1992**, 965.

4. Nagasawa, K.; Matsuda, N.; Noguchi, Y.; Yamanashi, M.; Zako, Y.; Shimizu, I. *J. Org. Chem.* **1993**, *58*, 1483.
5. He, M.; Tanimori, S.; Ohira, S.; Nakayama, M. *Tetrahedron* **1997**, *53*, 13307.
6. Stepanenko, W.; Wicha, J. *Tetrahedron Lett.* **1998**, *39*, 885.
7. Gorobets, E.; Urbanczyk-Lipowska, Z.; Stepanenko, V.; Wicha, J. *Tetrahedron Lett.* **2001**, *42*, 1135.
8. Taber, D. F.; Malcolm, S. C. *J. Org. Chem.* **2001**, *66*, 944.
9. Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1988**, 724.
10. Suzuki, T.; Sato, E.; Unno, K. *Chem. Pharm. Bull.* **1993**, *41*, 244.
11. Quinkert, G.; Schwartz, U.; Stark, H.; Weber, W. D.; Adam, F.; Baier, H.; Frank, G.; Dürner, G. *Liebigs Ann. Chem.* **1982**, 1999.
12. Trudeau, S.; Deslongchamps, P. *J. Org. Chem.* **2004**, *69*, 832.
13. Jiang, X.; Covey, D. F. *J. Org. Chem.* **2002**, *67*, 4893.
14. Taber, D. F.; Raman, K. *J. Am. Chem. Soc.* **1983**, *105*, 5935.
15. Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2263.
16. Pan, L. R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, *33*, 1469.
17. Shimizu, I.; Matsuda, N.; Noguchi, Y.; Zako, Y.; Nagasawa, K. *Tetrahedron Lett.* **1990**, *31*, 4899.
18. Hanessian, S.; Gomtsyan, A.; Payne, A.; Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032.
19. Tanaka, K.; Ohta, Y.; Fuji, K. *J. Org. Chem.* **1995**, *60*, 8036.
20. Lee, E.; Yoon, C. H. *J. Chem. Soc., Chem. Commun.* **1994**, 479.
21. Kametani, T.; Suzuki, Y.; Ban, C.; Honda, T. *Heterocycles* **1987**, *26*, 1491.
22. Kametani, T.; Honda, T.; Ishizone, H.; Kanada, K.; Naito, K.; Suzuki, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 646.
23. Asaka, Y.; Kamikawa, T.; Kubota, T. *Tetrahedron* **1974**, *30*, 3257.
24. Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996.
25. A lower yield and selectivity was reported in the literature for the TBDPS-protected alcohol [Ref. 22]. In our case, the Favorskii rearrangement was also attempted with the TMS-protected alcohol, but this yielded a mixture of several products, which were not identified.
26. Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439.
27. Ogava, J.; Shibasaki, M. *Tetrahedron Lett.* **1984**, *25*, 663.
28. Schreiber, S. L.; Liew, W. F. *Tetrahedron Lett.* **1983**, *24*, 2363.
29. Daniewski, A. R.; Garofalo, L. M.; Hutchings, S. D.; Kabat, M. M.; Liu, W.; Okabe, M.; Radinov, R.; Yiannikouros, G. P. *J. Org. Chem.* **2002**, *67*, 1580.
30. Schreiber, S. L. *J. Am. Chem. Soc.* **1980**, *102*, 6165.
31. Sarabèr, F.C.E.; Drach, S.; Bosselaar, G.; Jansen, B.J.M.; de Groot, A. *Tetrahedron* **2005**, *62*, see doi: 10.1016/j.tet.2005.11.056.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1749–1755

1-Phenylthio-3-vinyl-3-cyclohexenol, a new reagent for bis-annelation of silyl enol ethers

Olga Konstantinova,[a,b] Florence C. E. Sarabèr,[a] Enrique Melguizo,[a,c] Ben J. M. Jansen[a] and Aede de Groot[a,*]

[a]*Laboratory of Organic Chemistry, Wageningen University, Dreijenplein 8, 6703 HB Wageningen, The Netherlands*
[b]*Institute of Bioorganic Chemistry, National Academy of Sciences of Belarus, Kuprevich str. 5/2, 220141, Minsk, Belarus*
[c]*Departamento de Quimica Organica, Facultad de Sciencias, Universidad de Granada, 18071, Granada, Spain*

Received 31 May 2005; accepted 24 November 2005

Available online 20 December 2005

Abstract—1-Phenylthio-3-vinyl-cyclohex-1-en-3-ol (**2**) has been synthesized and investigated as a new bis-annelation reagent for silyl enol ethers. Reagent **2** can be synthesized by a Grignard reaction of vinyl magnesium bromide with 3-phenylthiocyclohexenone. The reaction with silyl enol ethers takes place under Lewis acid catalysis and generally proceeds in good yields. The resulting phenylthiodienes can be hydrolyzed to enones, which have been cyclized in a homologous aldol reaction to polycyclic compounds.

1. Introduction

Bis-annelation usually refers to the attachment of two new fused six-membered rings in one reaction sequence and it is a valuable method for the synthesis of polycyclic natural products. In principle, bis-annelation can be achieved using two consecutive, but separate annelation reactions with methyl vinyl ketone (MVK) or an equivalent thereof.[1–16] A more efficient one pot annelation of two six-membered rings is possible using oct-7-ene-2,6-dione or its equivalents and several of such reagents have been developed.[6,10,17–19] Other possibilities are offered by precursors of oct-7-ene-2,6-dione like 6-methyl-2-vinylpyridine,[20–23] 2,6-dimethyl-4*H*-pyran-4-one[24] or the already partly cyclised bis-annelation reagent 3-vinylcyclohexenone. With these reagents, an extended (1,6) Michael addition followed by a vinylogous aldol condensation are the key reactions in the annelation of the two rings.[25–28]

In previous publications we have shown that additions of carbocations to silyl enol ethers can be a high yielding key step in short syntheses of polycyclic compounds and steroids.[29,30] A similar strategy can be possible for bis-annelations using a precursor for 3-vinylcyclohexenone from which a carbocationic intermediate could be generated under mild Lewis acid conditions. A consecutive reaction with a suitable silyl enol ether then should lead to intermediates of type **4**, which, after hydrolysis, should give the unsaturated diketones **5**. Vinylogous aldol condensation of compounds like **5** to polycyclic compound **6** has been mentioned in the literature. It was estimated that 1-phenylthio-3-vinyl-cyclohex-1-en-3-ol **2** could meet the requirements for a good starting material[31] (see Scheme 1).

2. Results and discussion

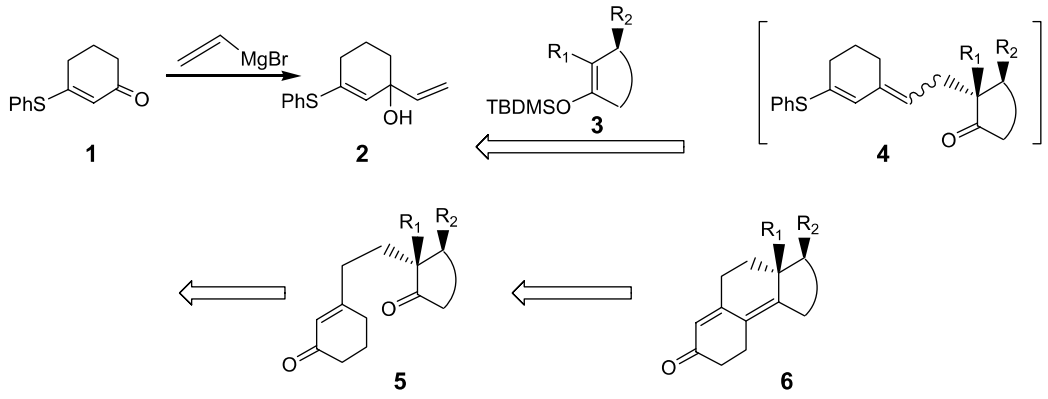
Reagent **2** was obtained from 3-phenylthiocyclohexenone **1**[32] by addition of vinyl magnesium bromide. Purification of reagent **2** on silica gel led to decomposition, but after a standard work up procedure, the compound could be used directly in the addition reactions with silyl enol ethers. Storage for some time was possible in a slightly basic solution.

To get information about the stability and reactivity of reagent **2**, its Lewis acid catalysed reaction with several silyl enol ethers has been investigated (see Table 1). The latter were selected to get an impression about the influence of steric hindrance and electronic factors on the reaction and about its stereoselectivity.

A moderate excess of silyl enol ether over reagent **2** was found to be favourable for the reaction yield. The Lewis acid used had to be powerful enough to generate a carbocation

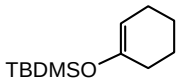
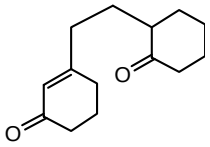
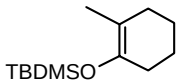
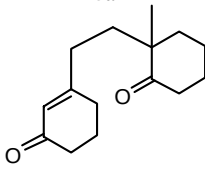
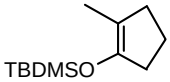
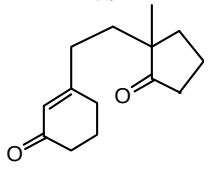
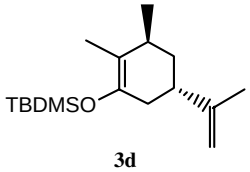
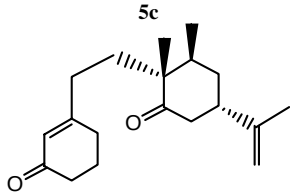
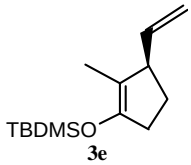
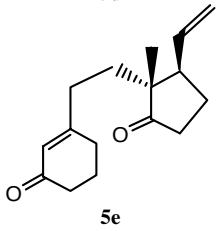
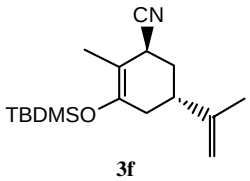
Keywords: 1-Phenylthio-3-vinyl-cyclohex-1-en-3-ol; Bis-annelation; Addition; Silyl enol ethers.
* Corresponding author. Tel.: +31 317482370; fax: +31 317484914; e-mail: aede.degroot@wur.nl

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.060



Scheme 1.

Table 1

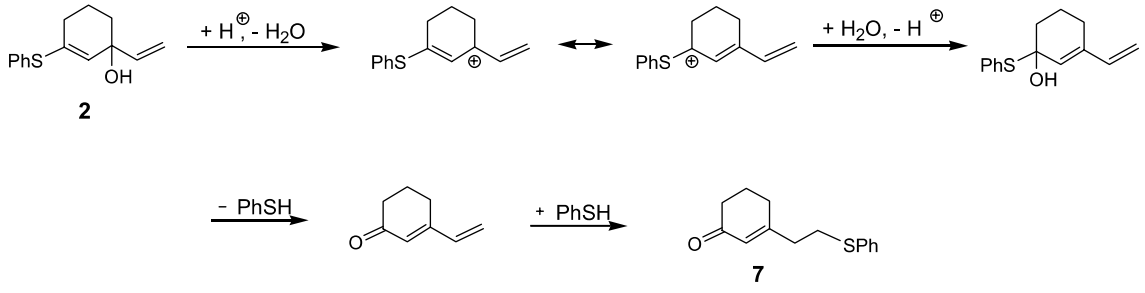
Entry	Silyl enol ethers	Reaction conditions	Coupling products	Yields (%)
1	 **3a**	a	 **5a**	54
2	 **3b**	a	 **5b**	55
3	 **3c**	b	 **5c**	65
4	 **3d**	c	 **5d**	44
5	 **3e**	d	 **5e**	28
6	 **3f**	e	No product	

(a) Silyl enol ether (1.5 equiv), 1 equiv of $ZnBr_2$, THF, −40 °C to room temperature. (b) Silyl enol ether (2 equiv), 1 equiv of $ZnBr_2$, THF/CH_2Cl_2, −40 °C to room temperature. (c) Silyl enol ether (1.5 equiv), 1 equiv of $ZnBr_2$, THF/CH_2Cl_2, −40 °C to room temperature. (d) Silyl enol ether (1.7 equiv), 1 equiv of $ZnBr_2$, THF/CH_2Cl_2, −40 °C to room temperature. (e) Silyl enol ether (1.4 equiv), 1 equiv of $ZnBr_2$, THF/CH_2Cl_2, −40 °C to room temperature.

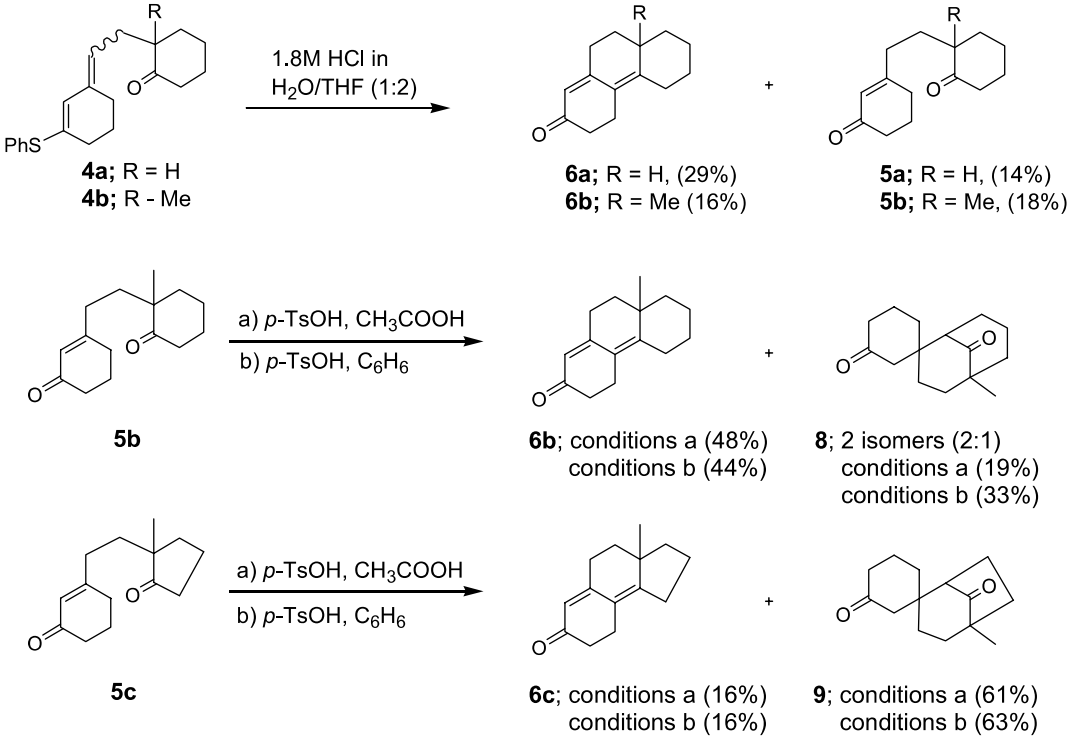
from **2**, but it should leave the silyl enol ether intact as long as possible and $ZnBr_2$ became our catalyst of choice. Usually a stoichiometric amount of $ZnBr_2$ was used, as applying a large excess of Lewis acid appeared to cause hydrolysis of the silyl enol ethers. Also the nature of the solvent influenced the rate and as a consequence also the yield of the reactions. Dichloromethane had given good results in the carbocation reactions performed before, but in this reaction the yields of coupled products were very low due to the instability of reagent **2** in this solvent. For the most reactive silyl enol ethers good results were obtained in tetrahydrofuran as solvent (Table 1, entries 1 and 2). As soon as the reactivity of the silyl enol ether was somewhat lowered, a mixture of tetrahydrofuran and dichloromethane gave the best results. The intermediate phenylthio dienes **4** are stable enough to allow isolation, but generally mixtures of stereoisomers were obtained, which were hydrolyzed immediately to the corresponding enones. Acidic conditions and $HgCl_2$ catalysis can be applied for unmasking these intermediate phenylthio dienes to the enones **5**. Mostly compound **7** was isolated as a sideproduct in a yield of about 30%. Formation of this product can be explained by the reaction sequence depicted in Scheme 2.

The reactions of reagent **2** with silyl enol ethers **3a–c** proceeded without problems and after hydrolysis of the intermediate phenylthiodienes, the corresponding enones **5a–c** were obtained in 54, 55 and 65% overall yields, respectively. The introduction of a methyl group on C2 in the silyl enol ether seemed to have a rate accelerating effect, determined by following the reactions on TLC, although in both cases reactions were left to stir overnight for complete conversion.

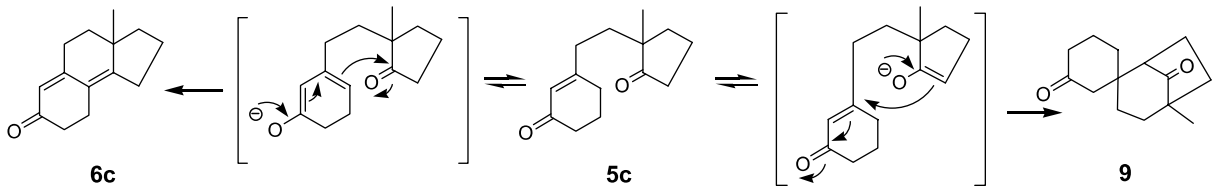
The stereoselectivity of the reaction was tested with silyl enol ether **3d**, which can be obtained from carvone.[33] The overall yield of enone **5d** was 44%, which is good for a two step reaction, and also the stereoselectivity was good. The reactions with the silyl enol ether **3e** gave a lower yield but here the stereoselectivity was complete when a mixture of dichloromethane and tetrahydrofuran was used as solvent. NOE measurements proved the enone **5e** to be the trans-coupled product. No reaction could be observed with silyl enol ether **5f**, which probably has to be attributed to the lower nucleophilicity of the silyl enol ether due to the negative inductive effect of the cyano group.[34,35]



Scheme 2.



Scheme 3.



Scheme 4.

Cyclisation was first attempted on the coupled thiophenol intermediates **4a** and **4b**, adding a solution of HCl in water to the reaction mixture in THF and omitting in this way the $HgCl_2$ deprotection step (see Scheme 3). For the cyclohexanone derivative **4a**, this gave a reasonable overall yield over four steps of 29% of compound **6a**, which means an average yield of 73% per step, together with 14% of non-cyclised compound **5a**. For compound **4b** the yield dropped to 16% of **6b**, which means an average of 63% per step, together with 18% of compound **5b**.

In the literature, good yields of 80–90%, were mentioned for the vinylogous aldol cyclisation of intermediates of type **5**, using *para*-toluenesulfonic acid (*p*-TsOH) in acetic acid under reflux conditions.[21–28,36] We therefore also investigated the cyclisation of compound **5b** using these conditions with a catalytic, equimolar or excess quantity of *p*-TsOH, which led to 40, 48 and 44% yield of **6b**, respectively. The use of equimolar amounts gave the best yield but, in our hands, the yields were not as good as in the literature and never exceeded those obtained with the HCl catalysed cyclisation. Besides compound **6b**, resulting from the expected vinylogous aldol cyclisation reaction, a second product was isolated in 19% yield as the result of a competing Michael addition, which led to spiro compound **8** as a 2:1 mixture of two stereoisomers. Moreover, when applying the *p*-TsOH–acetic acid conditions to the cyclisation of compound **5c**, the yield of the vinylogous aldol cyclisation dropped dramatically, giving only 16% of the cyclised product **6c**, next to starting material (22%) and a large amount (61%) of the spiro compound **9** again as a 2:1 mixture of two stereoisomers. The structure of spiro compound **9** was confirmed by 2D NMR measurements.

Also a solution of *p*-TsOH in benzene for the cyclisation of **5b** and **5c** did not improve the yield of the vinylogous aldol cyclisation products **6b** (44%) and **6c** (16%). Under these conditions the spiro cyclisation products **8** were obtained in 33% yield and compound **9** were obtained also in this case as the main products in 63% yield.

The formation of spiro compounds **8** and **9** has, to our knowledge, only been mentioned in literature twice for similar compounds,[28,37] but can easily be explained by enolisation of the non-conjugated carbonyl followed by a Michael reaction instead of the vinylogous aldol cyclisation (see Scheme 4).

In the five-membered ring compound **5c** the Michael reaction is the predominant one, leading to spiro compound **9**. In the six-membered ring compound **5b** the steric hindrance in the Michael adduct **8** is probably increased and the equilibrium of the cyclisation reaction is shifted more towards the side of the vinylogous aldol cyclisation product **6b**. The better yields, mentioned in the literature for vinylogous aldol cyclisations of compounds of type **5**, mostly concern substrates with an extra carbonyl group in the right upper ring. This second carbonyl group on the β position will enhance the reactivity of the first one for nucleophilic attack as is necessary for the vinylogous aldol condensation. Besides there are two carbonyl groups available for reaction in such compounds. No cyclisation experiments have been carried out with compounds **5c** and **5e** or their precursors.

3. Conclusions

The reactions of reagent **2** with silyl enol ethers **3** show that enones **5** can be obtained in good yields in two steps. Steric factors decrease the yield but improve the stereoselectivity of the reaction, which is in agreement with the reactions of silyl enol ethers with other carbocation precursors.[30] Cyclisation of the enones **5** to polycyclic compound **6** could be accomplished in good to moderate yields, with a spirocyclisation reaction as alternative.

4. Experimental

4.1. General procedure: see former paper

4.1.1. 3-Phenylthio-cyclohex-2-enone (1). 1,3-Cyclohexandione (5.0 g, 44 mmol) and thiophenol (5.5 ml, 53 mmol) were dissolved in benzene (100 ml) and stirred at reflux temperature for 6 h in a Dean–Stark apparatus. After cooling, the solution was diluted with saturated $NaHCO_3$ solution (50 ml), The layers were separated and the water layer was extracted with EtOAc (3×25 ml). The organic layers were combined, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc grad. 20:1–1:1) giving compound **1** in 71% yield (6.5 g).[32] Mp 43–44 °C (hexane–ethyl acetate).

IR (CCl_4 sol.) cm^{-1}: 2950, 1672, 1579, 1290; ^1H NMR ($CDCl_3$) δ: 1.94–2.07 (m, 2H), 2.34 (t, $J=6.2$ Hz, 2H), 2.49 (t, $J=6.1$ Hz, 2H), 5.44 (s, 1H), 7.36–7.47 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 22.89 (t), 30.18 (t), 37.20 (t), 120.71 (d), 127.47 (s), 129.51 (2d), 130.15 (d), 135.46 (2d), 166.95 (s), 196.12 (s). HRMS: M^+, found 204.0607. $C_{12}H_{12}OS$ requires 204.0609. MS *m/e* (%) 204 (M^+, 100), 187 (12), 176 (74), 171 (23), 148 (45), 147 (39), 127 (35), 110 (20), 67 (81).

4.1.2. 3-Phenylthio-1-vinyl-cyclohex-2-enol (2) (general procedure A). To a solution of ketone **1** (1.0 mmol) in tetrahydrofuran (4 ml) was added vinyl magnesium bromide

(1.5 mmol, 1 M solution in tetrahydrofuran) at 0 °C. After 10 min the cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 h. Then it was poured into a cold saturated solution of ammonium chloride and extracted with *tert*-butyl methyl ether. The combined organic fractions were dried over sodium sulfate and evaporated in vacuum to give alcohol **2**, which was used for reactions with the silyl enol ethers **3** without further purification. An NMR sample of alcohol **2** was prepared by flash column chromatography on silica gel.

^{1}H NMR (C_6D_6) δ: 1.34–1.68 (m, 4H), 2.01–2.11 (m, 2H), 4.97 (dd, $J_1=1.5$ Hz, $J_2=10.6$ Hz, 1H), 5.23 (dd, $J_1=1.5$ Hz, $J_2=17.4$ Hz, 1H), 5.76 (s, 1H), 5.83 (dd, $J_1=10.5$ Hz, $J_2=17.3$ Hz, 1H), 6.95–7.10 (m, 3H), 7.41–7.47 (m, 2H); ^{13}C NMR (C_6D_6) δ: 19.87 (t), 29.80 (t), 35.81 (t), 71.64 (s), 112.61 (t), 127.45 (d), 129.14 (2d), 131.24 (d), 132.50 (2d), 133.42 (s), 137.01 (s), 144.15 (d).

4.1.3. Coupling reaction of reagent 2 and silyl enol ethers 3 (general procedure B). A solution of silyl enol ether **3** (1.5–2 mmol) in tetrahydrofuran or dichloromethane (1 ml, choice used mentioned in procedure) was added to a suspension of $ZnBr_2$ (1 mmol) in tetrahydrofuran or dichloromethane (1 ml, as above, choice used mentioned in procedure) at −40 °C. Then to this mixture a solution of reagent **2** (obtained from 1 mmol of ketone **1**) in tetrahydrofuran (1.5 ml) was added dropwise. During the next 3–4 h the reaction mixture was warmed gradually to room temperature and left stirring overnight. Then the reaction mixture was mixed with cold brine and extracted with *tert*-butyl methyl ether. The combined organic fractions were dried over sodium sulfate and evaporated in vacuum to give phenylthiodiene **4** as a crude oil.

4.1.4. Hydrolysis of phenylthiodienes 4 to diketones 5 (general procedure C). To a solution of unpurified product **4** in ethanol (2 ml) was added dropwise a solution of mercury (II) chloride (2 mmol, calculated on the amount of used ketone **1**) in water (0.5 ml) and 37% hydrochloric acid (0.5 ml). The obtained mixture was stirred for 3 h at room temperature. The precipitate was filtered and washed with ethanol. The filtrate was mixed with pyridine (0.5 ml) and concentrated in vacuum. The residue was mixed with brine and extracted with dichloromethane. The combined organic fractions were washed with a saturated $NaHCO_3$ solution and a saturated NH_4Cl solution, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The obtained oil was purified by column chromatography (PE/EtOAc grad. 15:1⇒1:1) to give compound **5**, and usually some amount of compound **7**.

4.1.4.1. 3-(2-Phenylsulfanyl-ethyl)-cyclohex-2-enone (7). IR (CCl_4 sol.) cm^{-1}: 2930, 1678, 1628; ^{1}H NMR ($CDCl_3$) δ: 1.84–2.05 (m, 2H), 2.17–2.40 (m, 4H), 2.49 (t, $J=7.4$ Hz, 2H), 3.03 (t, $J=7.5$ Hz, 2H), 5.86 (s, 1H), 7.12–7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ: 22.5 (t), 29.4 (t), 31.1 (t), 37.2 (t), 37.4 (t), 126.5 (d), 126.7 (d), 129.0 (2d), 129.8 (2d), 135.4 (s), 163.4 (s), 199.5 (s). HRMS: M^+, found 232.0923. $C_{14}H_{20}O_2$ requires 232.0922. MS *m/e* (%) 232 (M^+, 63), 204 (4), 176 (4), 123 (100), 110 (6), 109 (5), 77 (10), 45 (16).

4.1.4.2. 3-[2-(2-Oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (5a). Obtained as a clear yellow oil, according to the general procedures A–C in 54% yield (245 mg) from ketone **1** (420 mg). Procedure B included the use of 1.5 equiv of silyl enol ether **3b**, 1 equiv of $ZnBr_2$ and tetrahydrofuran as solvent.

IR (CCl_4 sol.) cm^{-1}: 2938, 2866, 1713, 1674, 1627; ^{1}H NMR (C_6D_6) δ: 1.02–2.28 (m, 19H), 6.02 (s, 1H); ^{13}C NMR (C_6D_6) δ: 22.7 (t), 24.9 (t), 26.9 (t), 27.8 (t), 29.2 (t), 33.9 (t), 35.4 (t), 37.4 (t), 41.8 (t), 49.7 (d), 125.7 (d), 164.4 (s), 197.5 (s), 210.1 (s). HRMS: M^+, found 220.1463. $C_{14}H_{20}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 15), 123 (100), 110 (30), 98 (21), 55 (11).

4.1.4.3. 3-[2-(1-Methyl-2-oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (5b). Obtained as a clear yellow oil, according to the general procedures A–C in 55% yield (253 mg) from ketone **1** (400 mg). Procedure B included the use of 1.5 equiv of silyl ether **3b**, 1 equiv of $ZnBr_2$ and tetrahydrofuran as solvent.

IR ($CHCl_3$ sol.) cm^{-1}: 2939, 2869, 2356, 2252, 1702, 1664, 1623, 1455; ^{1}H NMR (C_6D_6) δ: 0.93 (s, 3H), 1.25–2.21 (m, 18H), 5.99 (s, 1H); ^{13}C NMR (C_6D_6) δ: 20.8 (t), 22.4 (q), 22.7 (t), 27.2 (t), 29.4 (t), 32.1 (t), 34.8 (t), 37.4 (t), 38.4 (t), 38.8 (t), 47.7 (s), 125.6 (d), 164.1 (s), 197.3 (s), 212.5 (s). HRMS: M^+, found 234.1615. $C_{15}H_{22}O_2$ requires 234.1620. MS *m/e* (%) 234 (M^+, 5), 123 (81), 112 (100), 110 (13), 97 (21), 55 (13).

4.1.4.4. 3-[2-(1-Methyl-2-oxo-cyclopentyl)-ethyl]-cyclohex-2-enone (5c). Obtained as a colourless oil, according to the general procedures A–C in 65% yield (211 mg) from ketone **1** (300 mg). Procedure B included the use of 2 equiv of silyl enol ether **7**–**40**, 1 equiv of $ZnBr_2$ and dichloromethane as solvent.

IR (CCl_4 sol.) cm^{-1}: 2960, 1738, 1674, 1628; ^{1}H NMR (C_6D_6) δ: 0.81 (s, 3H), 1.21–1.62 (m, 8H), 1.62–2.11 (m, 6H), 2.11–2.24 (m, 2H), 5.94 (s, 1H); ^{13}C NMR (C_6D_6) δ: 18.5 (t), 21.5 (q), 22.6 (t), 29.2 (t), 32.5 (t), 33.7 (t), 35.2 (t), 37.1 (t), 37.3 (t), 47.3 (s), 125.7 (d), 164.1 (s), 197.4 (s), 220.1 (s). HRMS: M^+, found 220.1463. $C_{14}H_{20}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 7), 123 (100), 110 (7), 98 (48), 83 (6), 67 (4), 55 (14).

4.1.4.5. 3-[2-(4-Isopropenyl-1,2-dimethyl-6-oxo-cyclohexyl)-ethyl]-cyclohex-2-enone (5d). Obtained as a slightly yellow oil, according to the general procedures A–C in 44% yield (91 mg) from ketone **1** (146 mg). Procedure B included the use of 1.5 equiv of silyl enol ether **3d**, 1 equiv of $ZnBr_2$ and dichloromethane as solvent. $[\alpha]_D^{25}$ −30.4 (*c* 2.70 in $CHCl_3$); IR ($CHCl_3$ sol.) cm^{-1}: 3088, 2938, 2889, 2252, 1699, 1666, 1626, 1456, 1428, 1257; ^{1}H NMR (C_6D_6) δ: 0.69 (d, $J=7.0$ Hz, 3H), 0.88 (s, 3H), 1.55 (s, 3H), 2.16 (t, $J=6.3$ Hz, 2H), 2.37 (s, 2H), 4.77 (s, 1H), 4.82 (s, 1H), 6.00 (s, 1H); ^{13}C NMR (C_6D_6) δ: 15.5 (q), 18.8 (q), 20.9 (q), 22.7 (t), 29.3 (t), 32.2 (t), 32.3 (t), 33.9 (t), 35.0 (d), 37.3 (t), 40.3 (d), 42.4 (t), 51.1 (s), 110.8 (t), 125.7 (d), 147.3 (s), 163.9 (s), 197.3 (s), 212.6 (s). HRMS: M^+, found 288.2086. $C_{19}H_{28}O_2$ requires 288.2089. MS *m/e*

(%) 288 (M^+, 4), 166 (18), 151 (8), 123 (100), 110 (15), 97 (9), 69 (11), 67 (9), 41 (17).

4.1.4.6. 3-[2-(1-Methyl-2-oxo-5-vinyl-cyclopentyl)-ethyl]-cyclohex-2-enone (5e). Mixture of cis–trans (1/3), obtained according to the general procedures A–C in 16% yield (24 mg) from ketone **1** (126 mg). Procedure B included the use of 1.7 equiv of silyl enol ether **3e**,[30] 2.2 equiv of $ZnBr_2$ and tetrahydrofuran as solvent. Data of the cis–trans mixture: ^{1}H NMR (C_6D_6) δ: 0.66 and 0.93 (s, s, 3H), 0.85–2.37 (m, 15H), 4.85–5.10 (m, 2H), 5.41–5.65 (m, 1H), 5.96 and 6.01 (s, s, 1H); ^{13}C NMR-cis isomer (C_6D_6) δ: 19.8 (q), 22.6 (t), 23.7 (t), 28.5 (t), 29.5 (t), 31.6 (t), 35.4 (t), 37.3 (t), 50.4 (s), 52.0 (d), 116.3 (t), 125.4 (d), 136.8 (d), 164.0 (s), 197.5 (s), 218.7 (s).

Trans-isomer, obtained as a slightly yellow oil, according to the general procedures A–C in 28% yield (62 mg) from ketone **1** (182 mg). Procedure B included the use of 1.7 equiv of silyl enol ether **3e**, 1 equiv of $ZnBr_2$ and dichloromethane as solvent.

IR (CCl_4 sol.) cm^{-1}: 2964, 1740, 1674, 1628; ^{1}H NMR (C_6D_6) δ: 0.65 (s, 3H), 0.81–2.31 (m, 15H), 4.92 (d, J= 17.1 Hz, 1H), 5.00 (d, J=10.3 Hz, 1H), 5.46 (ddd, J_1= 7.8 Hz, J_2=10.3, 17.1 Hz, 1H), 6.00 (s, 1H); ^{13}C NMR (C_6D_6) δ: 17.5 (q), 22.6 (t), 24.2 (t), 29.1 (t), 32.5 (t), 32.7 (t), 36.5 (t), 37.3 (t), 47.4 (d), 50.7 (s), 116.3 (t), 125.9 (d), 137.2 (d), 163.8 (s), 197.3 (s), 219.3 (s). HRMS: M^+, found 246.1618. $C_{16}H_{22}O_2$ requires 246.1620. MS *m/e* (%) 246 (M^+, 3.5), 124 (80), 123 (100), 110 (7), 109 (12, 95 (6), 81 (7).

4.1.4.7. 4,5,6,7,8,8a,9,10-Octahydro-3*H*-phenanthren-2-one (6a). After having performed procedures A and B starting from 0.86 mmol **1**, the crude reaction mixture was cooled on ice to 5 °C and 1 ml of concentrated HCl (37%) was added drop wise. The colour of the reaction mixture immediately turned red. The temperature was kept at 5 °C for 30 min, after which the mixture was allowed to warm to room temperature and 5 ml of water, followed again by 1 ml of concentrated HCl (37%), was added. The mixture was left to stir overnight, diluted with a saturated Na_2CO_3 solution and extracted with *tert*-butyl methyl ether (3× 15 ml). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude product was purified by column chromatography (PE/EtOAc grad. 20:1–1:1) yielding 29% of compound **6a** (50 mg) as a colourless oil, next to 14% of compound **5a** (26 mg, for data see above).

^{1}H NMR ($CDCl_3$) δ: 1.10–2.85 (m, 17H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 25.4 (t), 26.1 (t), 27.6 (t), 29.3 (t), 30.3 (2t), 35.4 (t), 37.2 (t), 39.5 (d), 122.1 (d), 124.3 (s), 147.2 (s), 158.1 (s), 200.1 (s). Data are in accordance with literature data.[20]

4.1.5. Cyclisation of 5b using *p*-TsOH in AcOH. Compound **5b** (200 mg, 0.86 mmol) was dissolved in acetic acid (AcOH, 6 ml) and *p*-TsOH was added in catalytic, equimolar and excess amounts. The reaction mixture was stirred during 1 h at reflux, then cooled and neutralised with a saturated $NaHCO_3$ solution (50 ml). The mixture was extracted with CH_2Cl_2 (3×50 ml) and the organic fractions were combined and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the resulting crude oil was purified by column chromatography (PE/EtOAc grad. 20:1–2:1), yielding compound **6b** in 40, 48 and 44%, respectively, as a thick slightly yellow oil, next to some amount of compound **8** (19%) as a mixture of two isomers (1:1).

4.1.6. Cyclisation of 5b using *p*-TsOH in benzene. Compound **5b** (115 mg, 0.49 mmol) was dissolved in benzene (15 ml) and *p*-TsOH (190 mg, 0.49 mmol) was added. The reaction mixture was stirred under N_2 during 5 h at 60 °C, then cooled and neutralised with a saturated $NaHCO_3$ solution (50 ml). The mixture was extracted with CH_2Cl_2 (3×50 ml) and the organic fractions were combined and dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the resulting crude oil was purified by column chromatography (PE/EtOAc grad. 20:1–2:1), yielding compound **6b** (47 mg, 44%) as a thick slightly yellow oil, next to some amount of compound **8** (33%) as a mixture of two isomers (2:1).

4.1.6.1. 8a-Methyl-4,5,6,7,8,8a,9,10-octahydro-3*H*-phenanthren-2-one (6b). IR (CCl_4 sol.) cm^{-1}: 2932, 1669, 1606, 1448, 1381, 1340, 1271, 1219; ^{1}H NMR (C_6D_6) δ: 0.89 (s, 3H), 0.92–2.45 (m, 16H), 5.86 (s, 1H); ^{13}C NMR (C_6D_6) δ: 22.2 (t), 23.4 (d), 25.7 (t), 26.3 (t), 27.7 (t), 28.1 (t), 36.6 (s), 37.6 (t), 38.6 (t), 42.3 (t), 123.0 (d), 124.5 (s), 148.8 (s), 155.5 (s), 197.5 (s). HRMS: M^+, found 216.1516. $C_{15}H_{20}O$ requires 216.1514. MS *m/e* (%) 216 (M^+, 67), 201 (100), 187 (7), 173 (9), 160 (11), 159 (15), 148 (10), 131 (11), 117 (10), 91 (11). Data are in accordance with literature data.[38]

Compound **8**. IR (CCl_4 sol.) cm^{-1}: 2937, 1716, 1455, 1381, 1313, 1231; ^{1}H NMR ($CDCl_3$) δ: 0.92 (s, 3H), 1.43–2.34 (m, 21H); ^{13}C NMR ($CDCl_3$) δ: 21.2 (*M*) and 21.3 (*m*) (t), 21.8 (*M*) and 21.9 (*m*) (t), 24.6 (q), 29.8 (*m*) and 30.2 (*M*) (t), 31.2 (*M*) and 31.5 (*m*) (t), 34.0 (*m*) and 35.3 (*M*) (t), 37.4 (*M*) and 37.7 (*m*) (t), 41.2 (*M*) and 41.3 (*m*) (t), 43.1 (*M*) and 43.2 (*m*) (t), 46.3 (s), 47.9 (s), 51.5 (*M*) and 52.3 (*m*) (t), 56.5 (*m*) and 57.6 (*M*) (d), 210.6 (*M*) and 211.0 (*m*) (s), 219.4 (*M*) and 219.8 (*m*) (s). HRMS: M^+, found 234.1622. $C_{15}H_{20}O$ requires 234.1620. MS *m/e* (%) 234 (M^+, 33), 123 (100), 112 (30), 111 (53), 95 (7), 93 (7), 79 (7), 67 (9), 55 (15), 41 (11).

4.1.7. Cyclisation of 5c using *p*-TsOH in AcOH.

4.1.7.1. 3a-Methyl-1,2,3,3a,4,5,8,9-octahydro-cyclopenta[*a*]naphthalen-7-one (6c). The method and scale as described for the cyclisation of **5b** was used. Compound **6c** was obtained in 16% yield as a slightly yellow oil.

IR (CCl_4 sol.) cm^{-1}: 2931, 1742, 1667, 1634, 1582, 1440, 1261, 1233, 1024; ^{1}H NMR ($CDCl_3$) δ: 0.97 (s, 3H), 0.92–2.77 (m, 14H), 5.66 (s, 1H); ^{13}C NMR ($CDCl_3$) δ: 21.7 (t), 23.1 (q), 25.5 (t), 29.4 (t), 30.1 (t), 35.9 (t), 37.1 (t), 42.0 (t), 43.3 (s), 121.9 (d), 123.2 (s), 156.5 (s), 158.0 (s), 200.1 (s). HRMS: M^+, found 202.1358. $C_{14}H_{18}O$ requires 202.1358. MS *m/e* (%) 202 (M^+, 45), 187 (100), 174 (10), 160 (12), 159 (10), 145 (11), 131 (11), 117 (12), 91 (15).

Compound **9** was obtained in 61% yield as a slightly yellow oily mixture of two isomers, ratio 2:1.

IR (CCl_4 sol.) cm^{-1}: 2939, 2875, 1747, 1716, 1452, 1319, 1230; ^1H NMR ($CDCl_3$) δ: 0.91 (s, 3H), 0.90–2.27 (m, 19H); ^{13}C NMR ($CDCl_3$) δ: 18.2 (*m*) and 18.6 (*M*) (t), 19.1 (q), 21.8 (*M*) and 21.9 (*m*) (t), 27.7 (*M*) and 29.5 (*m*) (t), 29.9 (*M*) and 30.0 (*m*) (t), 32.2 (*m*) and 35.8 (*M*) (t), 38.7 (*m*) and 38.9 (*M*) (t), 41.3 (*M*) and 41.4 (*m*) (t), 45.7 (s), 49.2 (*M*) and 52.2 (*m*) (t), 49.7 (s), 53.2 (*m*) and 55.8 (*M*) (d), 210.8 (*M*) and 210.9 (*m*) (s), 219.2 (*M*) and 219.4 (*m*) (s). HRMS: M^+, found 220.1467. $C_{14}H_{22}O_2$ requires 220.1463. MS *m/e* (%) 220 (M^+, 60), 192 (7), 123 (100), 110 (10), 97 (65), 55 (12).

4.1.8. Cyclisation of 5c using *p*-TsOH in benzene.

4.1.8.1. 3a-Methyl-1,2,3,3a,4,5,8,9-octahydro-cyclopenta[*a*]naphthalen-7-one (6c). The method and scale as described for the cyclisation of **5b** was used. Compound **6c** was obtained in 16% yield as a slightly yellow oil. Compound **9** was obtained in 63% yield as a slightly yellow oil and as a mixture of two stereoisomers, ratio 2:1.

Acknowledgements

The authors gratefully acknowledge financial support from Organon International. The authors thank B. van Lagen for NMR and IR spectroscopic data, and M.A. Posthumus for mass spectroscopic measurements.

References and notes

1. Rapson, W. S.; Robinson, R. *J. Am. Chem. Soc.* **1935**, *57*, 1285.
2. duFeu, E. C.; McQuillin, F. J.; Robinson, R. *J. Chem. Soc., Chem. commun.* **1937**, 53.
3. Wichterle, O.; Prochaska, J.; Hoffman, J. *Collect. Czech. Chem. Commun.* **1948**, *13*, 300.
4. Stork, G. *Pure Appl. Chem.* **1964**, *9*, 131 and references cited therein.
5. Marshall, J. A.; Schoeffer, D. J. *J. Org. Chem.* **1965**, *30*, 3642.
6. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5459.
7. Caine, D.; Tuller, F. N. *J. Org. Chem.* **1969**, *34*, 222.
8. Green, M. J.; Abraham, N. A.; Fleischer, E. B.; Case, J.; Fried, J. *J. Chem. Soc., Chem. Commun.* **1970**, 234.
9. Heathcock, C. H.; Ellis, J. E.; McMurray, J. E.; Coppolino, A. *Tetrahedron Lett.* **1971**, 4995.
10. Stork, G.; Ganem, B. *J. Am. Chem. Soc.* **1973**, *95*, 6152.
11. Stork, G.; Jung, M. E. *J. Am. Chem. Soc.* **1974**, *96*, 3682.
12. Stork, G.; Jung, M. E.; Colvin, E.; Noel, Y. *J. Am. Chem. Soc.* **1974**, *96*, 3684.
13. Stotter, P.; Hill, K. A. *J. Am. Chem. Soc.* **1974**, *96*, 6524.
14. Boeckman, R., Jr.,; Blum, D. M.; Ganem, B.; Halvey, N. *Org. Synth.* **1978**, *58*, 152.
15. Boeckman, R., Jr. *Tetrahedron* **1983**, *39*, 925.
16. Duhamel, P.; Dujardin, G.; Hennequin, L.; Poirier, J. M. *J. Chem. Soc., Perkin Trans. 1* **1992**, 387.
17. Ireland, R. E.; Hengartner, U. *J. Am. Chem. Soc.* **1972**, *94*, 3652.
18. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5463.
19. Stork, G.; McMurry, J. E. *J. Am. Chem. Soc.* **1967**, *89*, 5464.
20. Danishefsky, S.; Cavanaugh, R. *J. Am. Chem. Soc.* **1968**, *90*, 520.
21. Danishefsky, S.; Nagel, A. *J. Chem. Soc., Chem. Commun.* **1972**, 372.
22. Danishefsky, S.; Peterson, D. *J. Chem. Soc., Chem. Commun.* **1972**, 374.
23. Danishefsky, S.; Cain, P.; Nagel, A. *J. Am. Chem. Soc.* **1975**, *97*, 380.
24. Yamamoto, M.; Iwasa, S.; Takatsuki, K.; Yamada, K. *J. Org. Chem.* **1986**, *51*, 346.
25. Eschenmoser, A.; Schreiber, J.; Julia, S. A. *Helv. Chim. Acta* **1953**, *36*, 482.
26. Panouse, J. J.; Sannie, C. *Bull. Soc. Chim. Fr.* **1956**, 1429.
27. Panouse, J. J.; Sannie, C. *Bull. Soc. Chim. Fr.* **1956**, 1435.
28. Sakai, K.; Amemiya, S. *Chem. Pharm. Bull.* **1970**, *18*, 641.
29. Drach, S.; Charnikhova, T.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **2003**, *59*, 4287.
30. Saraber, F. C. E.; de Groot, A. *Tetrahedron Lett.* **2004**, *45*, 9431–9433.
31. Grieco et al. have shown that phenylthio enol stabilized carbocations are capable to react with silyl enol ethers in good yields. Grieco, P. A.; May, S. A.; Kaufman, M. D. *Tetrahedron Lett.* **1998**, *39*, 7047.
32. Trost, B. M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* **1989**, *111*, 7487.
33. Verstegen-Haaksma, A. A.; Swarts, H. J.; Jansen, B. J. M.; de Groot, A. *Tetrahedron* **1994**, *50*, 10037.
34. Sobolev, A.; Vos, M.; Zuilhof, H.; Saraber, F. C. E.; Jansen, B. J. M.; de Groot, A. *Arkivoc* **2005**, part (xiv), 29.
35. Saraber, F. C. E.; Baranovsky, A.; Jansen, B. J. M.; Posthumus, M. A.; de Groot, A. *Tetrahedron* **2005**, *62*, proceding paper. doi:10.1016/j.tet.2005.11.056.
36. Sannie, C.; Panouse, J. J. *Bull. Soc. Chim. Fr.* **1956**, 1435.
37. Brown, R. F. C.; Burge, G. L.; Collins, D. J. *Aust. J. Chem.* **1984**, *37*, 2305.
38. Hickmott, P. W.; Simpson, R. *J. Chem. Soc., Perkin Trans. 1* **1992**, *3*, 357.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1756–1763
Tetrahedron

Use of zinc enolate, free from other metals, in enantioselective palladium-catalyzed allylic alkylation

Naosumi Kinoshita,[a] Takeo Kawabata,[b,*] Kazunori Tsubaki,[b] Masahiko Bando[a] and Kaoru Fuji[c,*]

[a]*Medicinal Chemistry Research Institute, Otsuka Pharmaceutical Company, Ltd, 463-10 Kagasuno, Kawauchi-cho, Tokushima 771-0192, Japan*
[b]*Institute for Chemical Research, Kyoto University, Uji, Kyoto 611-0011, Japan*
[c]*Faculty of Pharmaceutical Sciences, Hiroshima International University, 5-1-1 Hirokoshingai, Kure, Hiroshima 737-0112, Japan*

Received 12 September 2005; revised 21 November 2005; accepted 22 November 2005

Available online 27 December 2005

This paper is dedicated to the memory of the late Professor Kiyoshi Tanaka.

Abstract—Zinc enolate, free from other metal cations directly prepared from malonate and diethylzinc, was proven to be an excellent nucleophile for enantioselective palladium-catalyzed allylic alkylation, particularly for the allylic cation bearing aromatic rings at the 1- and 3-positions.

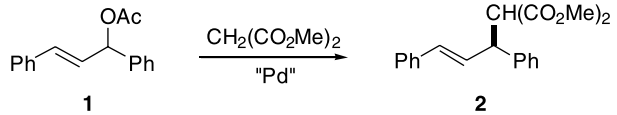
1. Introduction

Diethylzinc is a weak nucleophile used for the nucleophilic addition to aldehydes,[1] 1,4-addition to α,β-unsaturated carbonyl compounds,[2–4] the Simmons–Smith reaction,[5] and the umpolung of π-allylpalladium compounds.[6] It is also known that diethylzinc is a weak Lewis acid coordinating to oxygen, nitrogen, and halogens.[7] Diethylzinc has been rarely used as a base to generate enolates from carbonyl compounds, although limited examples have been reported for the preparation of enolates from dialkyl malonates,[8] and chiral phosphonate anions for the asymmetric Horner–Wadsworth–Emmons reaction.[9] The usefulness of zinc malonate free from other metals has also been reported in iridium-catalyzed allylic alkylation.[10]

Zinc enolates are routinely prepared in situ by metal–metal exchange with other metal enolates.[11] Since the other metals coexist with zinc in the reaction medium, the nature must be quite different from that of the zinc enolate free from other metals, which may affect the stereochemical outcome of the reactions. We have reported a remarkable enhancement of the enantiomeric excess (ee) in a palladium-catalyzed allylic alkylation with (*R*)-BINAP as a chiral ligand using zinc enolates, free from other metals, and generated with diethylzinc as a base.[12] Here, we report a full account of palladium-catalyzed asymmetric allylic alkylation using diethylzinc as a base.

2. Results and discussion

Control of the regio- and stereochemistry of palladium-catalyzed allylic alkylations relies upon the chiral ligand, the structure of a nucleophile and an electrophile, and the nature of counter cations. We have chosen 1,3-diphenylprop-2-enyl acetate (**1**) as a starting material, which gives symmetrical allylic cation, to avoid the ambiguity arising from unsymmetrical allylic cation (Scheme 1). The test reactions were performed with the zinc enolate of dimethyl malonate using triphenylphosphine as a ligand and the



1 **2**

Scheme 1.

Keywords: Enantioselective allylic alkylation; Zinc enolate; Chiral ligand.
* Corresponding authors. Tel.: +81 823 73 8936; fax: +81 823 73 8981; e-mail address: fuji@ps.hirokoku-u.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.053

Table 1. Palladium-catalyzed allylic alkylation of racemic 1,3-diphenylprop-2-enyl acetate (**1**) with dimethyl malonate using Et_2Zn as a base[a]

Entry	Pd source	Pd (mol%)	PPh_3 (mol%)	Solvent	Reaction time (h)	Yield (%)
1	$Pd(OAc)_2$	5	20	THF	20	6
2	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	20	THF	19	4
3	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	5	20	CH_2Cl_2	17	79
4	$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$	2	8	CH_2Cl_2	4	74

[a] Two equivalents of dimethyl malonate and Et_2Zn were used.

Table 2. Palladium-catalyzed enantioselective allylic alkylation[a] of racemic 1,3-diphenylprop-2-enyl acetate (**1**) with Et_2Zn[b] as a base using (*R*)-BINAP[c] as a ligand giving (*S*)-**2**

Entry	Solvent	Temperature (°C)	Reaction time (h)	Product **2**		Recovered **1** yield (%)
				Yield (%)	ee (%)	
1	CH_2Cl_2	0	88	67	14	18
2	CH_3CN	0	65	14	89	53
3	Et_2O	0 to rt	76	26	79	33
4	Toluene	0	45	63	77	13
5	Toluene	rt	17	71	22	0
6	THF	0	39	46	98	36
7	THF	0 to rt	47	73	96	0
8	THF	rt	20	84	99	0
9	THF	Reflux	0.5	90	97	0
10[d]	THF	0 to rt	35	57	88	0
11[e]	THF	rt	134	52	72	10

[a] $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%) was used for all reactions.
[b] Two equivalents for each reaction.
[c] Eight mol% for each reaction.
[d] $Pd_2(dba)_3 \cdot CHCl_3$ was used.
[e] $Pd_2(dba)_3$ was used.

results are shown in Table 1. The alkylated product **2** was obtained in low yields in THF. Change of the solvent to CH_2Cl_2 increased the yield dramatically (entry 3) even with decreased amount of the catalyst (entry 4). Thus, the possible use of diethylzinc was demonstrated for palladium-catalyzed allylic alkylation.

We chose the conditions in entry 4, involving the acetate **1** (1 equiv), dimethyl malonate (2 equiv), diethylzinc (2 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and the ligand (8 mol%), as a standard procedure for the asymmetric version. The results with (*R*)-BINAP as a chiral ligand are listed in Table 2. All reactions gave (*S*)-**2**, which was confirmed by the comparison of an $[\alpha]_D$ value with that reported by Hayashi[13] and the ee was determined by chiral HPLC analysis. All solvents tested except for CH_2Cl_2 gave moderate to high ee at 0 °C, though the chemical yield was unsatisfactory. Increase in the reaction temperature decreased ee in toluene (entries 4 and 5), while the high ee was kept in THF even under refluxing conditions (entries 6–9). Change of the catalyst to $Pd_2(dba)_3$ was less effective (entries 10 and 11).

We examined the effect of counter cations (Table 3) since their importance for enantioselectivity is well demonstrated in the allylic alkylations,[14,15] The use of NaH decreased the

Table 3. Effects of counter cations in enantioselective allylic alkylation of racemic **1** with dimethyl malonate[a]

Entry	Base	Additive	Temperature (°C)	Reaction time (h)	Yield (%)	ee (%)
1	NaH	None	rt	18	75	35
2	NaH	$ZnCl_2$	rt	48	19 (58)[b]	57
3	KH	None	rt	5	77	59
4	LiH	None	rt	64	68 (89)[b]	72
5	LDA	None	rt	2	87	76
6	LDA	$ZnCl_2$	rt	68	60 (71)[b]	87
7	*n*-BuLi	None	rt	24	91	56
8	*n*-BuLi	$ZnCl_2$	rt	42	19	53
9	Et_2Zn	LiCl	rt	42	67	82
10	Et_2Zn	LiCl	Reflux	1	82	14
11	*t*-Bu–P_4-base	None	rt	3	82	84
12	MeMgBr	None	rt	192	16 (44)[b]	0
13	MeMgBr	None	Reflux	1	81	2
14	MeMgI	None	rt	72	26 (36)[b]	0

[a] Under the standard conditions with (*R*)-BINAP (8 mol%) in THF.
[b] The numbers in the parenthesis are the yields based on the recovered starting material.

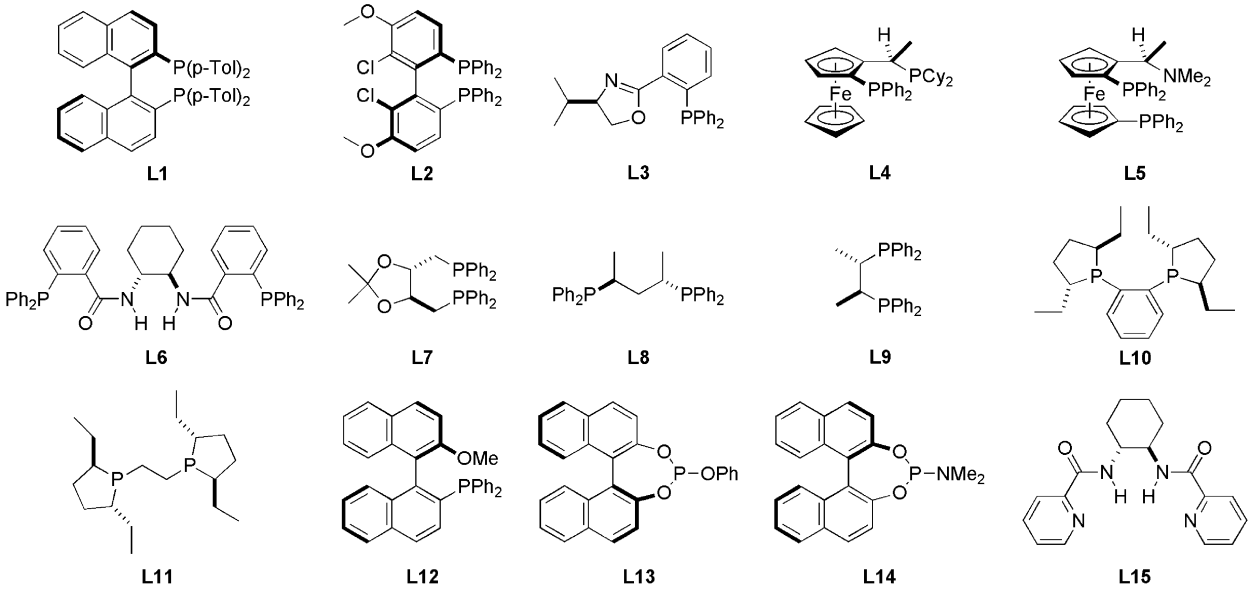
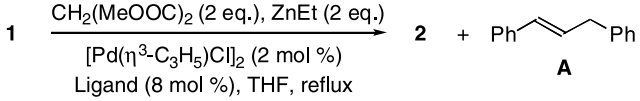


Figure 1. List of ligands tested.

ee to 35% (entry 1).[16] Zinc enolate prepared by the addition of zinc chloride to the sodium enolate gave a higher ee but with a lower yield (entry 2). No significant effect of counter cations was observed under these reaction conditions (entries 3–8). Adding lithium chloride to the pure zinc enolate slightly lowered both the ee and the yield (compare entry 8 in Table 2 with entry 9 in Table 3). The ee was remarkably decreased at refluxing temperature in the presence of lithium chloride (entries 9 vs 10), while decrease in ee was not observed in the absence of lithium chloride at the same temperature (Table 2, entries 8 vs 9). This could be ascribed to the difference in the aggregate structure of the enolate in the former conditions from the latter. The phosphazene base P_4–*t*-Bu, known to generate a metal-free enolate, gave a fairly good yield and ee (entry 11). Magnesium enolate afforded racemic **2** (entries 12–14). The results in Tables 2 and 3 show the advantage of using the zinc enolate, free from other metals, in enantioselective allylic alkylations with (*R*)-BINAP.

The results of applying the standard conditions at refluxing temperature to other chiral ligands are listed in Figure 1 and Table 4. The advantage of the zinc enolate free from other metals was not observed with other chiral

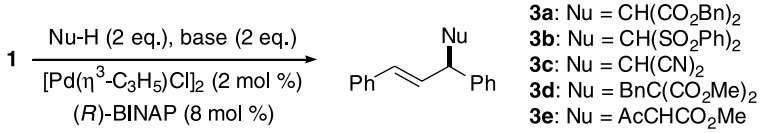
Table 4. Assessment of chiral ligands for the enantioselective allylic alkylation of racemic **1** using Et_2Zn as a base



Entry	Ligand[a]	Reaction time (h)	Yield (%)[b]		ee of **2** (%)[c]
			2	**A**[d]	
1	**L1**:(*R*)-Tol-BINAP	0.5	89	—	91 (*S*)
2	**L2**:(*R*)-Cl-MeO-BIPHEP	0.5	91	—	98 (*S*)
3	**L3**:(*R*)-PHOX	3	72	—	96 (*R*)
4	**L4**:(*R*)-(*S*)-JOSIPHOS	0.5	86	—	84 (*S*)
5	**L5**:(*R*)-(*S*)-BPPFA	0.5	86	—	54 (*S*)
6	**L6**:(*R*,*R*)-Trost ligand	0.5	(3)[e]	—	—
7	**L7**:(*S*,*S*)-DIOP	0.5	86	—	11 (*S*)
8	**L8**:(*S*,*S*)-BDPP	0.5	88	—	36 (*R*)
9	**L9**:(*S*,*S*)-CHIRAPHOS	0.5	0	—	—
10	**L10**:(*R*)-(*R*)-Et-DUPHOS	3	28	—	77 (*S*)
11	**L11**:(*R*)-(*R*)-Et-BPE	3	(10)[e]	—	—
12	**L12**:(*R*)-MeO-MOP	0.5	—	84	—
13	**L13**	1	33	52	34 (*S*)
14	**L14**:(*R*)-MonoPhos	0.5	(5)[e]	—	—
15	**L15**	0.5	—	—	—

[a] Structures of chiral ligands are listed in Figure 1.
[b] Isolated yield.
[c] Determined by HPLC on CHIRALCEL OJ-R (MeOH/H^2O=80:20).
[d] Similar reduction of allyl acetates with alkyl zinc/Pd (0) system has been reported, see Ref. 21.
[e] The number in parenthesis indicates the yield determined by ^1H NMR of crude product.

Table 5. Palladium-catalyzed enantioselective allylic alkylation of the racemic acetate **1** with various nucleophiles (Nu-H) in THF



Entry	Nu-H	Base	Temperature (°C)	Reaction time (h)	Product[a]	Yield (%)[b]	ee (%)
1	$CH_2(CO_2Bn)_2$	Et_2Zn	rt	20	**3a**[c]	81	92[d]
2	$CH_2(CO_2Bn)_2$	Et_2Zn	Reflux	1	**3a**	78	95[d]
3	$CH_2(CO_2Bn)_2$	NaH	rt	2	**3a**	83	0[d]
4	$CH_2(CO_2Bn)_2$	*n*-BuLi	rt	18	**3a**	88	67[d]
5	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**[e]	24 (44)	92[f]
6[g]	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**	43	91[f]
7	$CH_2(SO_2Ph)_2$	Et_2Zn	Reflux	2	**3b**	70	39[f]
8[h]	$CH_2(SO_2Ph)_2$	Et_2Zn	rt	72	**3b**	62 (76)	88[f]
9	$CH_2(SO_2Ph)_2$	NaH	rt	45	**3b**	36 (60)	88[f]
10	$CH_2(CN)_2$	Et_2Zn	rt	48	**3c**[i]	48	85[j]
11	$CH_2(CN)_2$	Et_2Zn	Reflux	1.5	**3c**	89	7[j]
12	$CH_2(CN)_2$	NaH	rt	48	**3c**	33 (62)	75[j]
13	$BnCH(CO_2Me)_2$	Et_2Zn	rt	168	**3d**[k]	47 (53)	70[l]
14	$BnCH(CO_2Me)_2$	Et_2Zn	Reflux	3	**3d**	92	76[l]
15[h]	$BnCH(CO_2Me)_2$	Et_2Zn	rt	168	**3d**	55 (65)	84[l]
16[m]	$BnCH(CO_2Me)_2$	NaH	rt	211	**3d**	45	0[l]
17	$AcCH_2CO_2Me$	Et_2Zn	rt	20	**3e**[n]	13 (76)	96[o]
18	$AcCH_2CO_2Me$	Et_2Zn	Reflux	3	**3e**	70	97[o]
19	$AcCH_2CO_2Me$	NaH	rt	3	**3e**	86	57[o]

[a] The absolute configuration was determined by comparison of the $[\alpha]^D$ value with that in the literature.
[b] The number in parenthesis indicates the yield based on the consumed starting material.
[c] New compound. The absolute configuration was not confirmed.
[d] Determined by HPLC on CHIRALPAK AD (hexane/2-propanol=9:1).
[e] Known; see Ref. 17.
[f] Determined by HPLC on CHIRALCEL OJ-R (MeOH).
[g] $CH^2(SO_2Ph)_2$ (10 equiv), base (10 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and (*R*)-BINAP (8 mol%) were used.
[h] DMF as a solvent.
[i] Known; see Ref. 18.
[j] Determined by HPLC on CHIRALCEL OJ (hexane/2-propanol=9:1).
[k] Known; see Ref. 16; where the absolute configuration was assigned without evidence. Absolute configuration was postulated from the optical rotation of the corresponding diethyl ester. See Ref. 19.
[l] Determined by HPLC on CHIRALPAK AD (hexane/2-propanol=92:8).
[m] Taken from Ref. 16, where $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (0.5 mol%), and (*S*)-BINAP (1.2 mol%) were used.
[n] Known; see Ref. 13.
[o] Determined by ^1H NMR with $Eu(hfc)_3$.

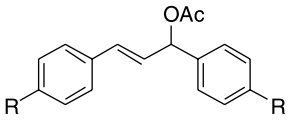
ligands, although modified BINAP analogues (L1 and L2) gave good results comparable to (*R*)-BINAP (entries 1 and 2). Since the combination of (*R*)-BINAP as a chiral ligand and diethylzinc for the generation of enolate was shown to be the best for allylic alkylation, we applied this system to other nucleophiles. The results, together with those with NaH, are compiled in Table 5. The standard conditions were shown to be applicable to other nucleophiles to give high ee's, though yields are sometimes low (entries 5, 10, 13, and 17). The close inspection of Table 5 reveals that the reaction time was remarkably shortened at refluxing temperature without decrease in the ee with the nucleophiles stabilized by carbonyl groups (compare entries 1 and 2, 13 and 14, 17 and 18). Use of NaH dramatically decreased the ee, with these nucleophiles (entries 3, 16, and 19), while nucleophiles stabilized by the sulfonyl or the cyano group gave comparable ee's (compare entries 5 and 9, 10 and 12). Another characteristic disposition of the latter nucleophiles includes low ee's at refluxing temperature (entries 7 and 11). These findings suggest that the structure and/or the aggregation state of the enolates generated from malonate is quite different from those generated from the active methylene compounds with sulfonyl and cyano groups.

The results of enantioselective allylic alkylation of racemic acetates **4**–**7** and **12** with dimethyl malonate are listed in Table 6. All of the starting material except for the nitro substituted compound **7** showed characteristic features associated with a combination of a malonate and diethylzinc, in which the high ee's were kept under refluxing conditions (entries 2, 6, 10, and 17). The (*S*)-configuration of the carbon center, newly created in **9**, was determined by X-ray crystallography (Fig. 2). The same absolute configurations for other products **8**, **10**, **11**, and **13** can be postulated by the reaction mechanism, though direct evidence is lacking. The advantage of diethylzinc as a base was not observed with 1,3-dialkylallylic esters **14**, **15**, and **17**–**19** (Table 7).

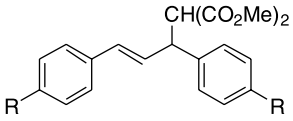
3. Conclusion

Zinc enolate free from other metal cations, directly prepared from malonate, was proven to be a good

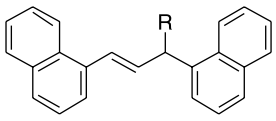
Table 6. Palladium-catalyzed enantioselective allylic alkylation of the racemic acetate **4**–**7** and **12** with dimethyl malonate in THF[a]



4: R = Cl
5: R = Br
6: R = Me
7: R = NO_2



8: R = Cl
9: R = Br
10: R = Me
11: R = NO_2



12: R = OAc
13: R = $CH(CO_2Me)_2$

Entry	Substrate	Base	Temperature (°C)	Reaction time (h)	Product	Yield (%)	ee (%)
1	**4**	Et_2Zn	rt	20	**8**	92	97
2	**4**	Et_2Zn	Reflux	0.5	**8**	95	96
3	**4**	NaH	rt	4	**8**	88	30
4[b]	**4**	NaH	rt	1	**8**	91	0
5	**5**	Et_2Zn	rt	40	**9**	60[c]	97
6	**5**	Et_2Zn	Reflux	1	**9**	40	97
7	**5**	NaH	rt	4	**9**	90	34
8[b]	**5**	NaH	rt	1	**9**	84	0
9	**6**	Et_2Zn	rt	72	**10**	73	78
10	**6**	Et_2Zn	Reflux	1	**10**	91	80
11	**6**	NaH	rt	4	**10**	78	19
12[b]	**6**	NaH	rt	1	**10**	83	0
13	**7**	Et_2Zn	rt	72	**11**	21	32
14	**7**	NaH	rt	24	**11**	44	36
15[b]	**7**	NaH	rt	0.5	**11**	75	0
16	**12**	Et_2Zn	rt	48	**13**	73	88
17	**12**	Et_2Zn	Reflux	2	**13**	95	90
18	**12**	NaH	rt	8	**13**	88	67
19[b]	**12**	NaH	rt	10	**13**	83	0

[a] Unless otherwise stated, dimethyl malonate (2 equiv), base (2 equiv), $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (2 mol%), and (*R*)-BINAP (8 mol%) were used for all of the reactions.
[b] PPh^3 was used as a ligand.
[c] A 7% of starting material was recovered.

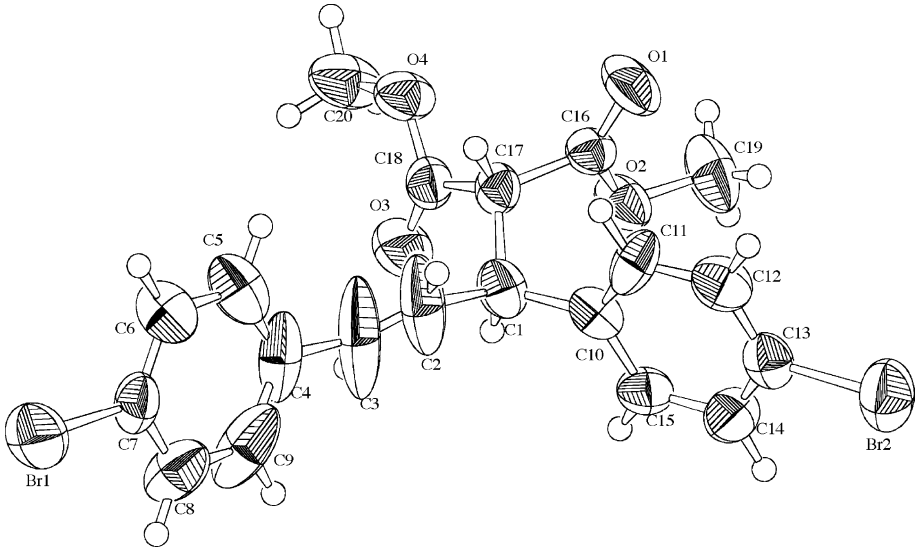
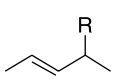


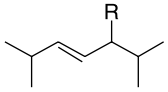
Figure 2.

nucleophile for palladium-catalyzed allylic alkylation to give a product with good yield and high ee. In particular, the allylic cation bearing aromatic rings at the 1- and 3-positions gave excellent results with BINAP or modified BINAP analogues. Advantage to use zinc enolates free from other metals involves marked decrease in the reaction time by using refluxing conditions without any loss of the ee. The present results may suggest that the use of zinc enolates free from other metals is the method of choice to increase ee's and/or chemical yields in other types of enantioselective reactions involving enolates.

Table 7. Enantioselective allylic alkylation of the racemic 1,3-dialkyl allyl ester derivatives **14**, **15**, and **17–19** under the standerd conditions



14: R = OAc
15: R = OCO_2Me
16: R = $CH(CO_2Me)_2$



17: R = OAc
18: R = OCO_2Me
19: R = $OPO(OEt)_2$
20: R = $CH(CO_2Me)_2$

Entry	Substrate	Solvent	Temperature (°C)	Reaction time (h)	Product	Yield (%)[a]	ee (%)[b]
1	**14**	THF	Reflux	0.5	**16**	54	41
2	**14**	THF	rt	6	**16**	21	63
3	**14**	THF	rt	24	**16**	40	45
4	**15**	THF	rt	24	**16**	63	41
5	**15**	DMF	rt	24	**16**	27	28
6	**17**	THF	Reflux	16	**20**	62	66
7	**17**	DMF	70	36	**20**	31	77
8[c]	**17**	THF	Reflux	1	**20**	88	68
9	**18**	THF	rt	360	**20**	0	—
10	**18**	THF	Reflux	4	**20**	16	82
11	**18**	DMF	70	8	**20**	23	78
12	**19**	THF	Reflux	8	**20**	67	78

[a] Isolated yield.
[b] Determined by GLC (Chirasil-DXE CB) for **16**[20] and ^{1}H NMR with Eu(hfc)$_3$ for **20**.[20]
[c] NaH was used as a base.

4. Experimental

4.1. Standard procedure of allylic alkylation (entry 9 in Table 2)

$[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (1.82 mg, 0.005 mmol, 2 mol%), and (*R*)-BINAP (12.5 mg, 0.02 mmol, 8 mol%) were dissolved in THF (0.5 ml) and stirred for 1 h at room temperature. After cooling to 0 °C, 1,3-diphenylprop-2-enyl acetate (1.59 mg, 0.25 mmol) in THF (0.5 ml) was added to prepare the solution A. Diethylzinc (1.0 M in hexane, 0.5 ml, 0.5 mmol) was added to a solution of dimethyl malonate (67 mg, 0.5 mmol) in THF (1.5 ml) and stirred for 1 h at room temperature, to which the solution A was introduced via Teflon tube. After the mixture was stirred at refluxing temperature for 30 min, it was diluted with 1 N HCl followed by the extraction with AcOEt. Organic layer was successively washed with aq $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent gave an oil, which was purified by PTLC over silica gel (AcOEt/hexane=1:7).

4.1.1. Dibenzyl[(1,3-diphenyl)prop-2-enyl]malonate (3a). The crude product obtained through the standard procedure was purified by PTLC over silica gel (Et_2O/CH_2Cl_2/hexane=1:1:5). Oil (95% ee, determined by CHIRALPAC AD, hexane/2-propanol=9:1, flow rate 0.5 ml/min., detection at 254 nm, t_R 47 and 59 min), $[\alpha]_D^{20}$ −7.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.04 (d, J=10.9 Hz, 1H), 4.30 (dd, J=10.8, 8.5 Hz, 1H), 4.93 (dd, J=17.5, 12.3 Hz, 2H), 5.11 (dd, J=16.3, 12.2 Hz, 2H), 6.31 (dd, J=15.7, 8.5 Hz, 1H), 6.41 (d, J=15.8 Hz, 1H), 7.04–7.06 (m, 2H), 7.20–7.28 (m, 18H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 49.3, 57.8, 67.1, 67.4, 126.4, 127.2, 127.5, 127.9, 128.1, 128.2, 128.3, 128.4, 128.4, 128.5, 128.7, 129.0, 131.9, 135.1, 135.1, 136.7, 140.1, 167.2, 167.6. IR (neat) cm^{-1}: 1758, 1773, 1469, 1455, 1375, 1257, 1216, 1150, 966, 744, 695. MS *m*/*z*: 476 (M^+), 385, 341, 91 (base peak). HRMS *m*/*z*: Calcd for $C_{32}H_{28}O_4$ (M^+): 476.1988. Found: 476.1996. Anal. Calcd for $C_{32}H_{28}O_4$: C, 80.65; H, 5.92. Found C, 80.72; H, 5.96.

4.1.2. (*E*)-1,3-Bis(4-methylphenyl)prop-2-enyl acetate (6). To a suspension of (*E*)-1,3-bis(4-methylphenyl)propenone (1.18 g, 5.0 mmol) and $CeCl_3\cdot 7H_2O$ (1.86 g, 5.0 mmol) in MeOH was added $NaBH_4$ (0.19 g, 5.0 mmol) portionwise under ice-cooling and the mixture was stirred for 30 min. Usual extractive work-up with Et_2O afforded (*E*)-1,3-bis(4-methylphenyl)prop-2-en-1-ol (1.1 g, 94%). To a solution of (*E*)-1,3-bis(4-methylphenyl)prop-2-en-1-ol (0.55 g, 2.3 mmol) and DMAP (2.8 mg, 0.01 equiv) in CH_2Cl_2 (2 ml) was successively added Et_3N (0.38 ml, 2.7 mmol) and Ac_2O (0.24 ml, 2.5 mmol) under ice-cooling and the mixture was stirred for 1 h. Extractive work-up with Et_2O afforded **6** (0.61 g, 95%) as an oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.11 (s, 3H), 2.32 (s, 3H), 2.35 (s, 3H), 6.29 (dd, J=15.8, 6.8 Hz, 1H), 6.40 (d, J=6.9 Hz, 1H), 6.58 (d, J=15.8 Hz, 1H), 7.10 (d, J=8.0 Hz, 2H), 7.18 (d, J=8.0 Hz, 2H), 7.26–7.31 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.2, 21.2, 21.4, 76.2, 126.6, 127.1, 129.2, 129.3, 132.3, 133.4, 136.4, 137.9, 137.9, 170.1. IR (neat) cm^{-1}: 1738, 1513, 1369, 1233, 1017, 965, 818, 800. MS *m*/*z*: 280 (M^+), 238, 220 (base peak), 205, 129, 119. HRMS *m*/*z*: Calcd for $C_{19}H_{20}O_2$ (M^+): 280.1463. Found: 280.1452. Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.40; H, 7.19. Found: C, 81.60; H, 7.24.

4.1.3. (*E*)-1,3-Bis(4-nitrophenyl)prop-2-enyl acetate (7). To a suspension of (*E*)-1,3-bis(4-nitrophenyl)propenone (2.98 g, 10.0 mmol) and $CeCl_3\cdot 7H_2O$ (3.73 g, 10.0 mmol) in MeOH was added $NaBH_4$ (0.38 g, 10.0 mmol) portionwise under ice-cooling and the mixture was stirred for 2 h. Usual extractive work-up with Et_2O afforded (*E*)-1,3-bis(4-nitrophenyl)prop-2-en-1-ol (2.2 g, 75%) after column chromatography over silica gel (AcOEt/hexane=35:65). To a solution of (*E*)-1,3-bis(4-nitrophenyl)prop-2-en-1-ol (2.18 g, 7.26 mmol) and DMAP (9 mg, 0.01 equiv) in CH_2Cl_2 (15 ml) was successively added Et_3N (1.21 ml,

8.71 mmol) and Ac_2O (0.82 ml, 8.71 mmol) under ice-cooling and the mixture was stirred for 30 min. Extractive work-up with Et_2O followed by column chromatography over silica gel (AcOEt/hexane=20:80) afforded **7** (1.76 g, 71%) as yellow needles, mp 127–129 °C (from AcOEt–hexane). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.20 (s, 3H), 6.46 (dd, J=15.7, 6.6 Hz, 1H), 6.52 (d, J=6.8 Hz, 1H), 6.74 (d, J=15.7 Hz, 1H), 7.51–7.53 (m, 2H), 7.59–7.60 (m, 2H), 8.18–8.19 (m, 2H), 8.26 (dd, J=6.9, 1.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.1, 74.5, 124.0, 124.1, 127.4, 127.8, 130.7, 131.4, 141.9, 145.4, 147.5, 147.8, 169.6. IR (KBr) cm^{-1}: 1736, 1600, 1516, 1346, 1233, 859. MS *m/z*: 342 (M^+), 300 (base peak), 282, 271, 236, 189, 178. HRMS *m/z*: Calcd for $C_{17}H_{14}N_2O_6$ (M^+): 342.0852. Found: 342.0874. Anal. Calcd for $C_{17}H_{14}N_2O_6$: C, 59.65; H, 4.12. Found: C, 59.69; H, 4.09.

4.2. Products in Table 6

All reactions were performed with the same ratio of the substrate and reagents as those of described in standard procedure and under the conditions in Table 6.

4.2.1. Dimethyl [1,3-bis(4-chlorophenyl)prop-2-enyl]malonate (8) in entry 1. An oil, purified by PTLC (silica gel, AcOEt/hexane=1:6), 97% ee, determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=15:85, flow rate 0.8 ml/min, detection at 254 nm, t_R 19, 25 min), $[\alpha]_D^{20}$ −3.1 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.55 (s, 3H), 3.70 (s, 3H), 3.89 (d, J=10.7 Hz, 1H), 4.26 (dd, J=10.6, 8.7 Hz, 1H), 6.26 (dd, J=15.7, 8.5 Hz, 1H), 6.40 (d, J=15.8 Hz, 1H), 7.21–7.26 (m, 6H), 7.28–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.4, 52.6, 52.7, 57.4, 127.6, 128.7, 129.0, 129.2, 129.3, 131.1, 133.1, 133.4, 135.1, 138.5, 167.5, 167.9. IR (neat) cm^{-1}: 1758, 1739, 1491, 1435, 1255, 1159, 1093. MS *m/z*: 394 (M^+), 392 (M^+), 263, 261 (base peak), 226, 191, 149. HRMS *m/z*: Calcd for $C_{20}H_{18}O_4Cl_2$ (M^+): 394.0553, 392.0582. Found: 394.0541, 392.0604. Anal. Calcd for $C_{20}H_{18}O_4Cl_2$: C, 61.08; H, 4.61. Found: C, 61.36; H, 4.57.

4.2.2. Dimethyl [1,3-bis(4-bromophenyl)prop-2-enyl]malonate (9) in entry 5. An oil, purified by PTLC (silica gel, AcOEt/hexane=1:7), 97% ee, determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=20:80, flow rate 0.6 ml/min, detection at 254 nm, t_R((*R*)-**9**) 25 min, t_R((*S*)-**9**) 35 min), $[\alpha]_D^{20}$ +3.1 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.55 (s, 3H), 3.70 (s, 3H), 3.89 (d, J=10.7 Hz, 1H), 4.22 (dd, J=10.6, 8.7 Hz, 1H), 6.27 (dd, J=15.7, 8.4 Hz, 1H), 6.39 (d, J=15.8 Hz, 1H), 7.16 (d, J=8.2 Hz, 4H), 7.39 (d, J=8.4 Hz, 2H), 7.44 (d, J=8.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.5, 52.6, 52.7, 57.3, 121.2, 121.6, 127.9, 129.3, 129.6, 131.2, 131.7, 131.9, 135.5, 139.0, 167.5, 167.9. IR (neat) cm^{-1}: 1758, 1738, 1487, 1434, 1255, 1161, 1072, 1010, 757. MS *m/z*: 484 (M^+), 482 (M^+), 480 (M^+), 353, 351, 349, 272, 270, 191 (base peak), 189. HRMS *m/z*: Calcd for $C_{20}H_{18}O_4Br_2$ (M^+): 483.9531, 481.9552, 479.9572. Found: 483.9534, 481.9573, 479.9546. Anal. Calcd for $C_{20}H_{18}O_4Br_2$: C, 49.82; H, 3.76. Found: C, 49.98; H, 3.74.

A crystal for the X-ray analysis was obtained from MeOH, mp 78–80 °C. X-ray crystallographic data: $C_{20}H_{18}O_4Br_2$, Mr=482.17, orthorhombic, space group $P2_12_12_1$, a=13.655 (3) Å, b=25.107 (5) Å, c=5.796 Å, α=90°, β=90°, γ=90°, V=1987 (2) Å^3, Z=4, D_c=1.612 g/cm^3, $F(000)$=960 and μ=41.128 cm^{-1}. The structure was refined to R=0.200, Rw=0.114. Crystallographic data (excluding structure factors) for the structure in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication number CCDC 282742. 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].

4.2.3. Dimethyl[1,3-bis(4-methylphenyl)prop-2-enyl]malonate (10) in entry 10. Purified by PTLC (silica gel, AcOEt/hexane=1:6), 80% ee determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=6:94, flow rate 0.5 ml/min, detection at 254 nm, t_R 29, 40 min), $[\alpha]_D^{20}$ −13.4 (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.30 (s, 6H), 3.53 (s, 3H), 3.69 (s, 3H), 3.92 (d, J=10.9 Hz, 1H), 4.21 (dd, J=10.7, 8.8 Hz, 1H), 6.25 (dd, J=15.7, 8.7 Hz, 1H), 6.42 (d, J=15.7 Hz, 1H), 7.07 (d, J=8.0 Hz, 2H), 7.11 (d, J=7.9 Hz, 2H), 7.18 (dd, J=13.6, 8.1 Hz, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 21.0, 21.1, 48.9, 52.4, 52.6, 57.8, 126.3, 127.7, 128.3, 129.1, 129.4, 131.5, 134.1, 136.7, 137.3, 137.3, 167.9, 168.3. IR (neat) cm^{-1}: 1760, 1739, 1513, 1434, 1321, 1256, 1159. MS *m/z*: 352 (M^+), 221 (base peak), 129. HRMS *m/z*: Calcd for $C_{22}H_{24}O_4$ (M^+): 352.1675. Found: 352.1689. Anal. Calcd for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.75; H, 6.74.

4.2.4. Dimethyl[1,3-bis(4-nitrophenyl)prop-2-enyl]malonate (11) in entry 14. An oil, purified by PTLC (Silica gel, AcOEt/hexane=1:2), 36% ee determined by HPLC (CHIRALCEL OJ-R, MeOH/H_2O=85:15, flow rate 0.4 ml/min, detection at 300 nm, t_R 79, 87 min), $[\alpha]_D^{20}$ −127.7 (c 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.58 (s, 3H), 3.74 (s, 3H), 3.99 (d, J=10.5 Hz, 1H), 4.44 (dd, J=10.4, 8.1 Hz, 1H), 6.50 (dd, J=15.8, 8.1 Hz, 1H), 6.57 (d, J=15.8 Hz, 1H), 7.45–7.50 (m, 4H), 8.15–8.17 (m, 2H), 8.20–8.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 48.7, 52.9, 53.0, 56.7, 124.0, 124.2, 127.1, 128.9, 131.3, 132.2, 142.5, 146.9, 147.3, 167.1, 167.5. IR (neat) cm^{-1}: 1755, 1738, 1597, 1520, 1346, 858, 756. MS *m/z*: 414 (M^+, base peak), 354, 295, 283, 249, 237, 203, 191. HRMS *m/z*: Calcd for $C_{20}H_{18}N_2O_8$ (M^+): 414.1063. Found: 414.1078. Anal. Calcd for $C_{20}H_{18}N_2O_8$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.90; H, 4.40; N, 6.82.

4.2.5. Dimethyl(1,3-di-naphthalen-1-ylprop-2-enyl)malonate (13) in entry 17. Purified by PTLC (silica gel, AcOEt/hexane=2:9). The sample for $[\alpha]_D$ measurement was obtained by recycling preparative HPLC followed by recrystallization from Et_2O–hexane, mp 82–85 °C, 94% ee determined by HPLC (CHIRALPAK AD, 2-propanol/hexane=10:90, flow rate 1.0 ml/min, detection at 295 nm, t_R 10, 22 min), $[\alpha]_D^{20}$ −37.5 (c 0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 3.45 (s, 3H), 3.75 (s, 3H), 4.31 (d, J=10.7 Hz, 1H), 5.30–5.34 (m, 1H), 6.43 (dd, J=15.5, 8.6 Hz, 1H), 7.30 (d, J=15.5 Hz, 1H), 7.34–7.60 (m, 8H), 7.72 (d, J=8.1 Hz, 1H), 7.77–7.81 (m, 2H), 7.87 (d, J=8.1 Hz, 1H), 7.95–7.97 (m, 1H), 8.39 (d, J=8.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 44.2, 52.5, 52.7, 57.4, 123.4, 123.8,

124.0, 124.3, 125.4, 125.5, 125.7, 125.8, 126.0, 126.4, 127.9, 127.9, 128.4, 129.0, 130.0, 131.1, 131.4, 132.3, 133.5, 134.2, 134.7, 136.3, 167.8, 168.6. IR (neat) cm^{-1}: 1760, 1733, 1432, 1252, 1158, 797, 778, 757. MS *m/z*: 424 (M^+), 293, 165 (base peak), 141. HRMS *m/z*: Calcd for $C_{28}H_{24}O_4$ (M^+): 424.1675. Found: 424.1653. Anal. Calcd for $C_{28}H_{24}O_4$: C, 79.22; H, 5.70. Found: C, 79.27; H, 5.71.

References and notes

1. Kitamura, M.; Oka, H.; Suga, S.; Noyori, R. *Org. Synth.* **2003**, *79*, 139–145.
2. Kitamura, M.; Miki, T.; Nakano, K.; Noyori, R. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 999–1014.
3. Liang, L.; Au-Yeng, T. T. L.; Chan, A. S. C. *Org. Lett.* **2002**, *4*, 3799–3801.
4. Alexakis, A.; Polet, D.; Rosset, S.; March, S. *J. Org. Chem.* **2004**, *69*, 5660–5667.
5. Takahashi, H.; Yoshioka, M.; Shibasaki, M.; Ohno, M.; Imai, N.; Kobayashi, S. *Tetrahedron* **1995**, *51*, 12013–12026.
6. Kimura, M.; Ogawa, Y.; Shimidu, M.; Sueishi, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 6903–6906.
7. For example; see: Ozaki, H.; Hirano, A.; Nakahara, S. *Macromol. Chem. Phys.* **1995**, *196*, 2099–2111.
8. Kawakami, Y.; Tsuruta, T. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 247–257.
9. (a) Tanaka, K.; Watanabe, T.; Shimamoto, K.; Sahakitpichan, P.; Fuji, K. *Tetrahedron Lett.* **1999**, *40*, 6599–6602. (b) Yamazaki, J.; Bedekar, A. V.; Watanabe, T.; Tanaka, K.; Fuji, K. *Tetrahedron: Asymmetry* **2002**, *13*, 729–734.
10. Kinoshita, N.; Marx, K. H.; Tanaka, K.; Tsubaki, K.; Kawabata, T.; Yoshikai, N.; Nakamura, E.; Fuji, K. *J. Org. Chem.* **2004**, *69*, 7960–7964.
11. Zinc enolates of ketones free from other metals were generated from α-iodoketones or α-iodoaldehydes with diethylzinc; see: Ito, S.; Shinokubo, H.; Oshima, K. *Tetrahedron Lett.* **1998**, *39*, 5253–5256.
12. Fuji, K.; Kinoshita, N.; Tanaka, K. *Chem. Commun.* **1999**, 1895–1896.
13. Hayashi, T.; Yamamoto, A.; Hagihara, T.; Ito, Y. *Tetrahedron Lett.* **1986**, *27*, 191–194.
14. Trost, B. M.; Bunt, R. C. *J. Am. Chem. Soc.* **1994**, *116*, 4089–4090.
15. O'Donnell, M. J.; Chen, N.; Zhou, C.; Murray, A.; Kubiak, C. P.; Yang, F.; Stanley, G. G. *J. Org. Chem.* **1997**, *62*, 3962–3975.
16. (*R*)-**2** was obtained in 30% ee under the similar conditions with (*S*)-BINAP. See: Yamaguchi, M.; Shima, T.; Yamagishi, T.; Hida, M. *Tetrahedron: Asymmetry* **1991**, *2*, 663–666.
17. Kubota, H.; Koga, K. *Heterocycles* **1996**, *42*, 543–547.
18. Martin, C. J.; Rawson, D. J.; Williams, J. M. J. *Tetrahedron: Asymmetry* **1998**, *9*, 3723–3730.
19. Chen, X.; Guo, R.; Li, Y.; Chen, G.; Yeung, C.-H.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2004**, *15*, 213–217.
20. Evans, D. A.; Campos, K. R.; Tedrow, J. S.; Michael, F. E.; Gagné, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 7905–7920.
21. Matsushita, H.; Negishi, E. *J. Org. Chem.* **1982**, *47*, 4161–4165.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1764–1771
Tetrahedron

Regioselective arylation of 2′-deoxyribonucleosides on amido or imino sites by copper(II)-mediated direct coupling with arylboronic acids

Qing Dai, Chongzhao Ran and Ronald G. Harvey*

The Ben May institute for Cancer Research, The University of Chicago, IL 60637, USA

Received 16 August 2005; revised 21 November 2005; accepted 22 November 2005

Available online 20 December 2005

Abstract—N^1-Aryl derivatives of 2′-deoxyguanosine (dG) were synthesized by copper(II)-mediated coupling of dG with arylboronic acids. Analogous aryl derivatives of 2′-deoxyinosine (dIn), 2′-deoxyuridine (dU), thymidine (T), 2′-deoxyadenosine (dA), and 2′-deoxycytidine (dC) were also conveniently synthesized by this method. Arylation took place preferentially on the amido functions in dG and dIn and the imino functions in dU or T. Remarkably, the nucleosides themselves served as internal ligands as well as reactants.

1. Introduction

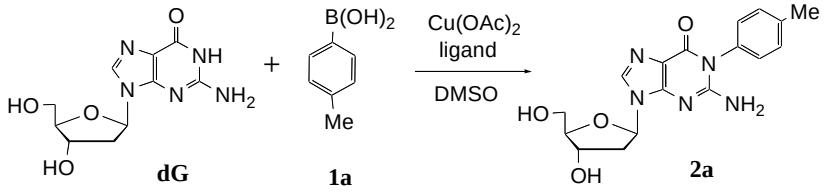
Aryl derivatives of purines and purine nucleosides are the focus of considerable research interest deriving from their diverse biological activities.[1] Aryl purine nucleoside derivatives also play an important role as key mutagenic and carcinogenic intermediates formed by reaction of the active metabolites of carcinogenic arylamines[2] and polycyclic aromatic hydrocarbons (PAHs) with DNA.[3,4]

Methods for the syntheses of aryl derivatives of purines and purine nucleosides have been extensively investigated, and convenient syntheses of the 2-, 6-, 8-, and 9-aryl derivatives of purines and purine nucleosides have been reported.[1a,5] Practical syntheses of the adducts formed by the active metabolites of benzo[*a*]pyrene and other PAH carcinogens with dA and dG have also been described.[6,7] In contrast, the N^1-aryl derivatives of dG, dA, and other nucleosides have been relatively neglected, and satisfactory methods for their synthesis are lacking.[8]

We now report a convenient method for regioselective N^1-arylation of 2′-deoxyguanosine (dG) and analogous arylation of other 2′-deoxyribonucleosides. The synthetic approach entails direct copper(II)-catalyzed coupling of unprotected 2′-deoxyribonucleosides with arylboronic acids under mild conditions.

2. Results and discussion

Initial exploratory experiments were conducted with dG, *p*-tolylboronic acid (**1a**), $Cu(OAc)_2$, and 1,10-phenanthroline in anhydrous DMSO (Scheme 1). The conditions employed in these initial studies were based on those reported previously for *N*-arylation of arylamines, amides,



Scheme 1.

Keywords: N^1-Aryl-2′-deoxyguanosine; Arylation of nucleosides; Arylboronic acids; Copper-mediated coupling of amides and imides.
* Corresponding author. Tel.: +1 773 702 6998; fax: +1 773 702 6260; e-mail: rharvey@ben-may.bsd.uchicago.edu

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.072

and other nitrogen-containing compounds.[9,10] Although CH_2Cl_2 is commonly employed as the solvent for copper-catalyzed coupling of arylboronic acids, the poor solubility of dG in this medium made necessary the choice of a different solvent. DMSO was selected because of the excellent solubility of all reactants in this medium. To a solution of dG (1 mmol) and **1a** (2 mmol) in DMSO (2 mL) were added anhydrous $Cu(OAc)_2$ (1 mmol), 1,10-phenanthroline (2 mmol), and 4 Å molecular sieves (50 mg), and the mixture was heated overnight at 60 °C. Reaction took place smoothly and regioselectively to afford an N^1-monoarylated-dG product (**2a**) (64%) accompanied by a small amount (~5%) of a diarylated-dG byproduct with a second aryl group attached to the 2-amino group. No products of arylation at other sites in dG were detected.

The structure of **2a** was assigned on the basis of its ^{1}H NMR spectrum in DMSO-d_6 and other data as N^1-*p*-tolyl-2′-deoxyguanosine. The presence of the *p*-tolyl group was clearly shown by the methyl signal at δ 2.36 (3H) in the ^{1}H NMR spectrum and the characteristic pair of doublets at δ 7.32 (2H) and 7.12 (2H) for the aromatic protons. The absence of an N^1-proton resonance, found at δ 10.7 in the spectrum of dG in DMSO-d_6, suggested that arylation had taken place at the N^1-position. This was also consistent with other spectral features. Thus, substitution at C^8 was ruled out by retention of the singlet at δ 7.9 (1H) assigned to the C^8 proton, and substitution on the 2-amino group of dG was excluded by the presence of a broad peak at δ 6.3 (2H) (exchangeable with D_2O) for the two protons of the amino group. Similarly, reaction on the 3′-OH or 5′-OH groups was ruled out by the presence of two broad peaks (exchangeable with D_2O) at δ 5.3 (1H) and δ 4.9 (1H), assigned to 3′-OH and 5′-OH, respectively. Finally, the presence of a carbonyl band at ~1690 cm^{-1} in the IR spectrum, the close similarity of the UV spectrum to that of dG, and the absence of significant shifts in the C-6 resonances of the purine component in the ^{13}C NMR spectrum ruled out O^6 as the site of reaction. These observations provide strong evidence for N^1 as the principal site of arylation of dG and for **2a** as the structure of the major product.

Preferential reaction of **1a** at the N^1-position of dG is surprising in view of prior reports that copper-catalyzed coupling of arylboronic acids with arylamines, amino-pyrimidines, and amino-purines, takes place predominantly on the amino functions.[5d,9a] A minor amount (<5%) of an N^1,N^2-diarylated byproduct was also formed. Evidently arylation of the N^2-amino of dG is much less favorable than arylation of the N^1-amido function under the conditions employed.

In order to optimize conditions, a series of reactions of dG with **1a** were conducted with various nitrogen-containing ligands and different ratios of $Cu(OAc)_2$ and **1a** (Table 1). Of the ligands tested, Et_3N afforded a somewhat better yield (71%) than those obtained with 1,10-phenanthroline, 2,2′-bipyridyl, pyridine, or *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) (55–64%). When $Cu(OAc)_2$ was omitted, no reaction occurred, indicating that $Cu(OAc)_2$ is an essential requirement for these reactions. The ratio of $Cu(OAc)_2$ was also important. With 0.1 equiv of $Cu(OAc)_2$, the yield of **2a** was 25%. When the amount of the copper catalyst was increased to 0.5 equiv, the yield of **2a** increased to 55%. The yield was also dependent upon the ratio of **1a** to **dG**, with 1:2 being optimal. With a ratio of 1:1, the yield decreased to 40%; and with an even larger ratio (3 or 4 equiv), the yields decreased to less than those obtained with 2 equiv of **1a**. This is likely due to increased formation of the diarylated byproduct. These reactions were insensitive to moisture, furnishing virtually identical yields in the presence or absence of molecular sieves as a drying agent. Also, substitution of dG hydrate for anhydrous dG or $Cu(OAc)_2$ hydrate for anhydrous $Cu(OAc)_2$ had minimal effect on the yield. The reactions were also relatively insensitive to air, affording similar yields when conducted in an open flask or under argon.

Table 1. $Cu(OAc)_2$-mediated coupling of dG with *p*-tolylboronic acid (**1a**)[a]

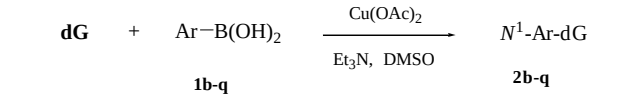
Entry	$Cu(OAc)_2$ (equiv)	Ligand	Boronic acid **1a** (equiv)	Yield of **2a** (%)
1	1	1,10-Phenanthroline	2	64
2	1	2,2′-Bipyridyl	2	61
3	1	Pyridine	2	60
4	1	TMEDA	2	55
5	1	Et_3N	2	71
6	None	Et_3N	2	0
7	0.1	Et_3N	2	25
8	0.5	Et_3N	2	55
9	1	Et_3N	1	40
10	1	Et_3N	3	62
11	1	Et_3N	4	56

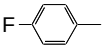
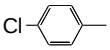
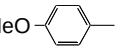
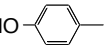
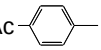
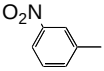
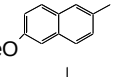
[a] Conditions: dG (1 mmol), **1a** (2 equiv), $Cu(OAc)_2$ (1 equiv), ligand (2 equiv), DMSO (2 mL), 60 °C, 16 h.

In order to assess the scope of the method, reactions of dG with a series of arylboronic acids (**1b–q**) were investigated (Table 2). Reactions were conducted in DMSO in the presence of $Cu(OAc)_2$ and Et_3N at 60 °C, and the principal products were the N^1-arylated dG derivatives (**2b–o**). Minimal dependence on the electronic nature of substituents on the arylboronic acid was observed. Moderately good yields of N^1-arylated-dG adducts were obtained from arylboronic acids bearing either electron-withdrawing or electron-donating groups. Halo, acetyl, hydroxyl, and nitro groups were all well tolerated.

In cases where the arylboronic acid contained a halogen atom capable of entering into competitive reaction, for example, 4-bromophenylboronic acid (**1e**) or 4-iodophenylboronic acid (**1f**), reactions occurred chemospecifically at the site of the boronic acid group. The position of substitution (*para* or *meta*) had minimal effect on the facility of reaction in the examples studied (entries 1–10). In contrast, the *ortho* methyl-substituted boronic acid **1l** gave a significantly lower yield than the *para* or *meta* substituted analogues, even with a large excess (10 equiv) of *o*-tolylboronic acid. The relatively low reactivity of **1l** is likely due to steric crowding at the site of substitution. The *ortho* fluoro-substituted arylboronic acid (**1q**) also failed to afford the expected products of reaction with dG, but this may be a consequence of the instability of **1q**, which results in its decomposition before reaction can take place.

Table 2. $Cu(OAc)_2$-promoted N^1-arylation of dG with arylboronic acids (**1b–q**)[a]



Entry	Ar-B(OH)$_2$	Ar-B(OH)$_2$ (equiv)	Ar	Product	Yield (%)
1	**1b**	2		**2b**	70
2	**1c**	2		**2c**	44
3	**1d**	4		**2d**	43
4	**1e**	4		**2e**	52
5	**1f**	2		**2f**	63
6	**1g**	2		**2g**	61
7	**1h**	3		**2h**	42
8	**1i**	2		**2i**	70
9	**1j**	2		**2j**	57
10	**1k**	3		**2k**	46
11	**1l**	10[b]		**2l**	38
12	**1m**	3		**2m**	50
13	**1n**	10[b]		**2n**	20
14	**1o**	10[b]		**2o**	36
15	**1p**	10[b]		**2p**	0
16	**1q**	10[b]		**2q**	0

[a] Conditions: dG (1 mmol), boronic acid (2 equiv), $Cu(OAc)_2$ (1 equiv), Et_3N (2 equiv), DMSO (2 mL), 60 °C, 16 h, unless otherwise stated.
[b] Boronic acid (10 equiv), 48 h.

Some examples of larger PAHs were also studied in order to assess the feasibility of the method for synthesis of adducts of PAH carcinogen metabolites with deoxyribonucleosides. 6-Methoxy-naphthylboronic acid (**1m**) reacted readily with dG to furnish an N^1-arylated adduct (**2m**) in moderate yield, and 1-pyrenylboronic acid (**1n**) reacted with dG to provide an N^1-arylated product (**2n**) in lower yield (20%). Two heterocyclic arylboronic acids were also investigated. 3-Thienylboronic acid (**1o**) reacted readily with dG to furnish an N^1-arylated product (**2o**), but 3-pyridinylboronic acid (**1p**) failed to react with dG under similar conditions. The apparent unreactivity of **1p** may be due, as in the case of **1q**, to its relatively facile decomposition.

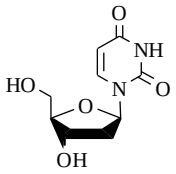
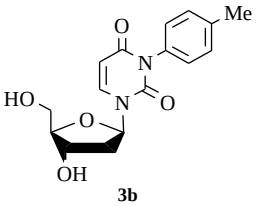
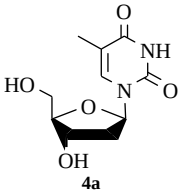
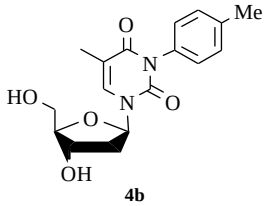
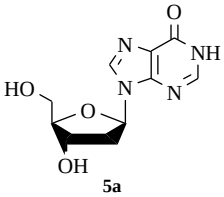
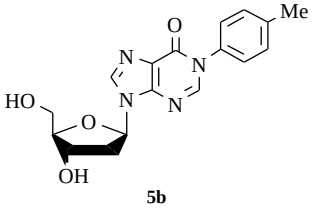
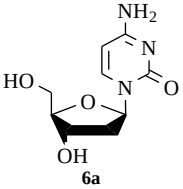
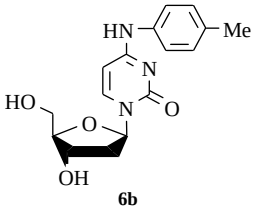
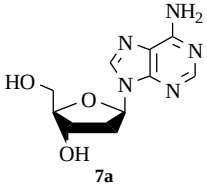
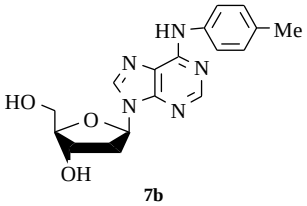
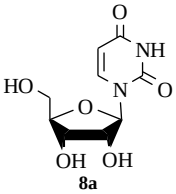
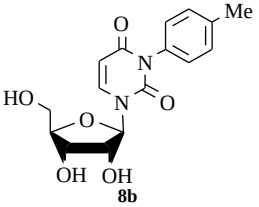
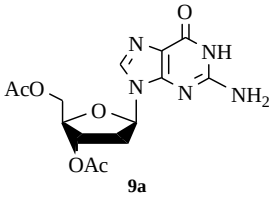
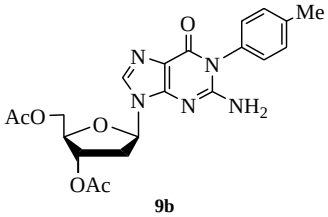
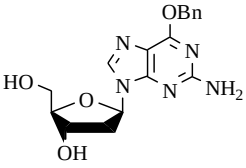
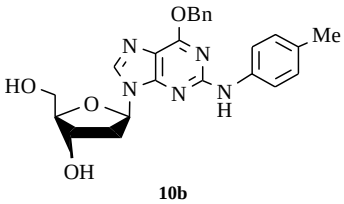
Extension of this methodology to synthesis of aryl derivatives of other purine and pyrimidine nucleosides was also examined (Table 3). Initial studies were conducted with *p*-tolylboronic acid (**1a**) and $Cu(OAc)_2$ in the presence of various ligands (Et_3N, pyridine, 2,2′-bipyridyl, TMEDA, and 1,10-phenanthroline) reported to facilitate copper-catalyzed *N*-arylation by arylboronic acids.[9,10] 2′-Deoxyuridine (**3a**) and thymidine (**4a**) reacted with *p*-tolylboronic acid (**1a**) in the presence of $Cu(OAc)_2$ to furnish N^3-*p*-tolyl-2′-deoxyuridine (**3b**) and N^3-tolylthymidine (**4b**), respectively. Yields of **3b** and **4b** were dependent upon the ligands used, with pyridine affording the highest yield. Similar reaction of 2′-deoxyinosine (**5a**) with **1a** and Et_3N provided N^1-*p*-tolyl-2′-deoxy-inosine (**5b**) (86%). In contrast, analogous reactions of 2′-deoxycytidine (**6a**), and 2′-deoxyadenosine (**7a**), both of which possess an exocyclic amino group but lack an imino or amido function, furnished products of arylation of the amino groups (**6b** and **7b**). However, the yields were significantly lower than those obtained in the examples where arylation took place on an amido or imino function (**3b**, **4b**, **5b**), and they also depended on the ligand employed. The yield of **6b** was lowest with pyridine and Et_3N (12–15%) and maximum with TMEDA (46%). The yield of **7b** was low (<10%) with pyridine, Et_3N, or TMEDA and highest (45–48%) with 1,10-phenanthroline or 2,2′-bipyridyl as ligands. It is worthy of note that **6a** and **7a** were not completely consumed, even with use of a large excess of **1a** (10 equiv), nor were the yields enhanced by longer reaction time.

Application of this method to *N*-arylation of ribonucleosides was also explored. Reaction of uridine (**8a**) with **1a** and $Cu(OAc)_2$ and pyridine gave N^3-*p*-tolyluridine (**8b**) as the principal product. Pyridine was the most effective ligands tested, providing **8b** in moderate yield (42%). 1,10-Phenanthroline gave a lower yield of **8b** (20%), and still lower yields (<10%) were obtained with other ligands. Uridine was incompletely consumed, even with a large excess of **1a** (10 equiv).

As already shown, reaction of **1a** with dG in the presence of $Cu(OAc)_2$ and various ligands took place preferentially on the N^1-amido group rather than the N^2-amino group (Scheme 1, Table 1). The diacetate derivative of dG (**9a**) underwent similar reaction with **1a** to afford the analogous product of N^1-arylation (**9b**). In the former example, the optimum yield (71%) was obtained with Et_3N as ligand, whereas with **9a** the optimum yield (88%) was obtained with TMEDA as ligand. On the other hand, the benzyl ether derivative of dG (**10a**), which has an amino group but no amido group, failed to react with **1a** in the presence of $Cu(OAc)_2$ and various ligands. The apparent unreactivity of **10a** is surprising in view of the observed facilities of reaction of **6a** and **7a** to provide the products of arylation on the exocyclic amino groups coupled with the prior findings that copper-mediated reactions of arylboronic acids with aminopurines and aminopyrimidines under similar, though not identical conditions, take place with facility on the amino functions.[11]

It is interesting to compare these findings with results of earlier studies where it was shown that CuI-catalyzed reactions of 2′-deoxyadenosine with aryl bromides or iodides in the presence of DMEDA and K_3PO_4 in DMSO

Table 3. $Cu(OAc)_2$,-promoted arylation of nucleosides by **1a** with various ligands[a]

Entry	Nucleoside	Ligand	Product	Yield (%)
1	 **3a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **3b**	55 62 92 86 78
2	 **4a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **4b**	52 58 88 85 72
3	 **5a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **5b**	50 78 84 86 82
4	 **6a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **6b**	30 24 15 12 46
5	 **7a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **7b**	45 48 <10 <10 <10
6	 **8a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **8b**	20 <5 42 <10 <10
7	 **9a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **9b**	55 62 82 58 88
8	 **10a**	1,10-Phenanthroline 2,2′-Bipyridyl Pyridine Et_3N TMEDA	 **10b**	0 0 0 0 0

[a] Conditions: same as Table 2.

provided products of arylation on the N^6-amino group.[5a] The benzyl ether derivative of dG (**10a**), which lacks an amido group, underwent CuI-catalyzed arylation on the N^2-amino group. The reasons for the striking differences observed in the relative reactivities of amido groups versus amino groups for these two copper-catalyzed arylation reactions are not obvious. In any case, selective application of these two methods allows regioselective arylation of nucleosides at either amido or amino sites.

The most effective ligand for these coupling reactions was highly dependent on the substrate employed (Table 3). 1,10-Phenanthroline was previously reported to afford better yields of arylated products than other ligands tested (Et_3N, pyridine, TMEDA, 2,2′-dipyridyl) in the copper-catalyzed reaction of arylboronic acids with purine derivatives.[1b] However, in the present studies 1,10-phenanthroline generally provided lower yields of arylated products than several of the other ligands tested (Table 3). It provided better yields only in the cases of **6a** and **7a** where arylation took place on the amino groups. Pyridine furnished superior yields in the N^1-arylation of dU (**3a**), thymidine (**4a**), and uridine (**8a**). Et_3N was almost as effective as pyridine as a ligand for N^1 arylation of **3a** and **4a**, but it was much less effective for arylation of **8a**.

Surprisingly, the yields of *N*-arylated nucleoside products were in most cases significantly improved by omission of ligands (Table 4). The principal exception was dA (**7a**), arylation of which took place on the amino group. Reaction of **7a** with **1a** in the presence of 2,2′-bipyridyl or 1,10-phenanthroline (Table 3) furnished higher yields of the dA adduct (**7b**) (48 and 45%, respectively) than were obtained without a ligand (<10%). The reactions of all other nucleosides listed in Table 4, except for **6a**, took place regioselectively on the amido or imino groups.

Table 4. $Cu(OAc)_2$-promoted arylation of nucleosides by **1a** in the absence of ligands[a]

Entry	Nucleoside	Product	Yield (%)
1	**3a**	**3b**	95
2	**4a**	**4b**	92
3	**5a**	**5b**	93
4	**6a**	**6b**	48
5	**7a**	**7b**	<10
6	**8a**	**8b**	45
7	**9a**	**9b**	92

[a] Conditions: same as Table 2.

The nature of the coordination complexes formed by the nucleosides with $Cu(OAc)_2$ is not known. However, in view of the fact that all the 2′-deoxyribonucleosides in Table 4, except **9a**, possess 3′- and 5′-hydroxyl groups, it is reasonable to suggest that these oxygen atoms coordinate with the copper ion to form a six-membered ring. Interaction of the chelated copper ion with N^1 of the same or another nucleoside molecule may be expected to result in formation of a copper amidate that may then react with the arylboronic acid to produce an N^1-arylated adduct.[12] This mechanism is consistent with the finding that ethylene glycol and other diols are good ligands for copper-mediate amination of aryl iodides.[13]

3. Summary and conclusions

In summary, we report a convenient method for regioselective arylation of dG and other 2′-deoxyribonucleosides on the amido or imino groups of the purine or pyrimidine bases via direct copper-mediated coupling with arylboronic acids. A remarkable feature of the method is that the nucleosides are able to serve as internal ligands that facilitate their own reactions. Reaction of dG, which possesses an N^1-amido and an exocyclic 2-amino group, takes place regiospecifically on the former. Although practical methods for syntheses of the 2-, 6-, 8-, and 9-aryl derivatives of dG and other nucleosides have been reported, a method for selective introduction of aryl groups into amido positions, such as the N^1 of dG, has until now been lacking. Analogous aryl derivatives of 2′-deoxyuridine, thymidine, 2′-deoxycytidine, and 2′-deoxyadenosine, 2′-deoxyinosine, and uridine were also readily prepared by appropriate modification of this method. This method has the practical advantages that protection of the hydroxyl groups of the sugar components and addition of external ligands are not necessary. The scope of the method appears to be relatively broad. Arylboronic acids with either electron-withdrawing or electron-donating substituents may be used, and a wide range of functional groups (halo, acetyl, nitro, hydroxyl etc.) are tolerated. Exclusion of air and moisture are also not necessary. The broad scope and relative convenience of the method suggests that it may find useful applications in medicinal chemistry.

4. Experimental

4.1. Materials and methods

All reactions using air sensitive or moisture sensitive reagents were carried out under an argon atmosphere. ^1H and ^{13}C NMR spectra were recorded on Bruker 500 or Bruker 400 MHz NMR spectrometers. ^1H chemical shifts are reported in δ (ppm) relative to tetramethylsilane. High-resolution mass spectra were obtained from the Department of Chemistry, University of California at Riverside. Merck silica gel (9385 grade, 230–400 mesh, 60A, Aldrich) was used for column chromatography. Silica gel on glass with fluorescent indicator (Sigma) was used for TLC.

4.2. Typical procedure for N^1-arylation of 2′-deoxyribonucleosides. Preparation of N^1-aryl-2′-deoxyguanosine (2a–o)

To a 100 mL flask was added dG (1 mmol), *p*-tolylboronic acid (**1a**) (2 mmol), Et_3N (2 mmol), anhydrous $Cu(OAc)_2$ (1 mmol), and DMSO (2 mL). The mixture was heated at 60 °C overnight, then cooled to room temperature, and concentrated to dryness. The residue was purified by chromatography on a silica gel column eluted with 8–14% MeOH in CH_2Cl_2 to yield N^1-aryl-2′-deoxyguanosine (**2**).

4.2.1. N^1-*p*-Tolyl-2′-deoxyguanosine (2a). ^1H NMR (500.1 MHz) (DMSO-d_6) δ: 7.94 (s, 1H), 7.32 (m, 2H), 7.12 (m, 2H), 6.30 (br, 2H), 6.14 (m, 1H), 5.28 (br, 1H), 4.91 (br, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 3.55 (m, 2H), 2.51

(m, 1H), 2.36 (s, 3H), 2.20 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 157.1, 154.2, 149.9, 138.8, 135.8, 133.5, 130.8, 129.1, 116.5, 88.0, 82.8, 71.2, 62.1, 2′-*C* is buried in DMSO-d_6 peaks, 21.2. HRMS calcd for $C_{17}H_{19}N_5O_4$, $[MH]^+$358.1515 (calcd), 358.1531 (found).

4.2.2. N^1-Phenyl-2′-deoxyguanosine (2b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.96 (s, 1H), 7.52 (m, 2H), 7.47 (t, 1H), 7.25 (m, 2H), 6.33 (br, 2H), 6.15 (m, 1H), 5.30 (br, 1H), 4.92 (br, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 3.55 (m, 2H), 2.51 (m, 2H), 2.20 (m, 2H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 157.1, 154.1, 150.0, 136.2, 135.9, 130.3, 129.5, 129.4, 116.5, 88.0, 82.8, 71.2, 62.1, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{17}N_5O_4$, $[MH]^+$344.1359 (calcd), 344.1357 (found).

4.2.3. N^1-*p*-Fluorophenyl-2′-deoxyguanosine (2c). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.95 (s, 1H), 7.33 (m, 4H), 6.45 (br, 2H), 6.14 (m, 1H), 5.29 (br, 1H), 4.95 (br, 1H), 4.33 (m, 1H), 3.79 (m, 1H), 3.50 (m, 2H), 2.48 (m, 1H), 2.20 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 161.3, 156.8, 153.9, 149.7, 135.5, 132.0, 131.4 (d, J=8.4 Hz), 116.8 (d, J=26.0 Hz), 116.1, 87.6, 82.4, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{16}FN_5O_4$, $[MH]^+$362.1265 (calcd), 362.1258 (found).

4.2.4. N^1-*p*-Chlorophenyl-2′-deoxyguanosine (2d). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.96 (s, 1H), 7.57 (d, J=7.7 Hz, 2H), 7.30 (m, 2H), 6.49 (br, 2H), 6.13 (m, 1H), 5.27 (br, 1H), 4.93 (br, 1H), 4.32 (m, 1H), 3.80 (m, 1H), 3.52 (m, 2H), 2.52 (m, 1H), 2.18 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 156.7, 153.7, 149.8, 135.6, 134.8, 133.7, 131.2, 130.0, 116.0, 87.6, 82.4, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{16}ClN_5O_4$, 378.0969 $[MH]^+$ (calcd), 378.0950 (found).

4.2.5. N^1-*p*-Bromophenyl-2′-deoxyguanosine (2e). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.95 (s, 1H), 7.57 (d, J=8.6 Hz, 2H), 7.30 (m, 2H), 6.50 (br, 2H), 6.13 (m, 1H), 5.28 (br, 1H), 4.94 (br, 1H), 4.32 (m, 1H), 3.79 (m, 1H), 3.51 (m, 2H), 2.48 (m, 1H), 2.20 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 156.6, 153.6, 149.8, 135.6, 135.2, 133.0, 131.5, 122.4, 116.0, 87.6, 82.4, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{16}BrN_5O_4$, $[MH]^+$422.0464 (calcd), 422.0444 (found).

4.2.6. N^1-*p*-Iodophenyl-2′-deoxyguanosine (2f). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.96 (s, 1H), 7.86 (d, J= 8.2 Hz, 2H), 7.07 (m, 2H), 6.49 (br, 2H), 6.13 (m, 1H), 5.27 (br, 1H), 4.93 (br, 1H), 4.33 (m, 1H), 3.79 (m, 1H), 3.51 (m, 2H), 2.48 (m, 1H), 2.19 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 156.6, 153.6, 138.8, 135.7, 131.6, 131.5, 116.1, 95.8, 87.6, 82.4, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{16}IN_5O_4$, $[MH]^+$470.0325 (calcd), 470.0312 (found).

4.2.7. N^1-*p*-Methoxyphenyl-2′-deoxyguanosine (2g). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.97 (s, 1H), 7.18 (m, 2H), 7.08 (m, 2H), 6.36 (br, 2H), 6.16 (m, 1H), 5.30 (br, 1H), 4.96 (br, 1H), 4.36 (m, 1H), 3.83 (s, 3H), 3.80 (m, 1H), 3.55 (m, 2H), 2.53 (m, 1H), 2.23 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 159.8, 157.3, 154.5, 149.9, 135.8, 130.5, 128.5, 116.5, 115.5, 88.0, 82.8, 71.2, 62.1, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{17}H_{19}N_5O_5$, $[MH]^+$374.1464 (calcd), 374.1473 (found).

4.2.8. N^1-*p*-Hydroxyphenyl-2′-deoxyguanosine (2h). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 9.88 (br, 1H), 7.93 (s, 1H), 7.01 (m, 2H), 6.86 (m, 2H), 6.28 (br, 2H), 6.13 (m, 1H), 5.30 (br, 1H), 4.95 (br, 1H), 4.33 (m, 1H), 3.80 (s, 3H), 3.80 (m, 1H), 3.53 (m, 2H), 2.51 (m, 1H), 2.18 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 157.8, 157.0, 154.3, 149.5, 135.4, 130.0, 126.6, 116.5, 116.2, 87.6, 82.4, 70.9, 62.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{17}N_5O_5$, $[MH]^+$360.1308 (calcd), 360.1309 (found).

4.2.9. N^1-*p*-Acetylphenyl-2′-deoxyguanosine (2i). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.08 (m, 2H), 7.99 (s, 1H), 7.43 (m, 2H), 6.48 (br, 2H), 6.15 (m, 1H), 5.28 (br, 1H), 4.93 (br, 1H), 4.33 (m, 1H), 3.81 (m, 1H), 3.51 (m, 2H), 2.51 (m, 1H), 2.46 (s, 3H), 2.20 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 197.6, 161.3, 156.6, 153.5, 140.1, 137.2, 129.9, 129.8, 129.7, 87.6, 82.5, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks, 27.0. HRMS calcd for $C_{18}H_{19}N_5O_5$, $[MH]^+$386.1464 (calcd), 386.1444 (found).

4.2.10. N^1-*m*-Tolylphenyl-2′-deoxyguanosine (2j). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.95 (s, 1H), 7.41 (m, 2H), 7.28 (d, J=7.6 Hz, 1H), 7.05 (m, 2H), 6.31 (br, 2H), 6.14 (m, 1H), 5.29 (br, 1H), 4.95 (br, 1H), 4.34 (m, 1H), 3.80 (m, 1H), 3.53 (m, 2H), 2.52 (m, 1H), 2.34 (s, 3H), 2.21 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 157.1, 154.1, 150.0, 139.8, 136.0, 135.9, 130.1, 129.8, 126.3, 116.5, 88.0, 82.8, 71.2, 62.1, 2′-*C* is buried in DMSO-d_6 peaks, 21.2. HRMS calcd for $C_{17}H_{19}N_5O_4$, $[MH]^+$358.1515 (calcd), 358.1505 (found).

4.2.11. N^1-*m*-Nitrophenyl-2′-deoxyguanosine (2k). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.34 (m, 1H), 8.32 (d, J=6.5 Hz, 1H), 7.98 (s, 1H), 7.79 (m, 2H), 6.61 (br, 2H), 6.16 (m, 1H), 5.30 (br, 1H), 4.95 (br, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.51 (m, 2H), 2.52 (m, 1H), 2.47 (s, 3H), 2.22 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 157.0, 153.91, 149.2, 137.4, 136.9, 136.0, 131.6, 125.4, 124.5, 116.4, 88.0, 82.8, 71.2, 62.0, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{16}H_{16}N_6O_6$, $[MH]^+$389.1210 (calcd), 389.1216 (found).

4.2.12. N^1-*o*-Tolylphenyl-2′-deoxyguanosine (2l). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.18 (s, 1H), 7.29 (d, J=7.3 Hz, 1H), 7.23 (t, J=7.6 Hz, 1H), 7.15 (t, J=7.3 Hz, 1H), 7.29 (d, J=7.9 Hz, 1H), 6.40 (br, 2H), 6.22 (m, 1H), 5.27 (d, J=3.9 Hz, 1H), 4.95 (t, J=5.5 Hz, 1H), 4.34 (m, 1H), 3.81 (m, 1H), 3.53 (m, 2H), 2.60 (m, 1H), 2.34 (s, 3H), 2.22 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 159.8, 154.8, 151.0, 138.6, 131.2, 130.2, 127.2, 125.5, 122.3, 113.8, 87.7, 82.8, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks, 16.1. HRMS calcd for $C_{17}H_{19}N_5O_4$, $[MH]^+$358.1515 (calcd), 358.1531 (found).

4.2.13. N^1-[2-(6-Methoxynaphthyl)]-2′-deoxyguanosine (2m). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.98 (s, 1H), 7.94 (d, J=8.6 Hz, 1H), 7.88 (dd, J=9.0, 1.8 Hz, 1H), 7.78 (d, J=7.6 Hz, 1H), 7.41 (s, 1H), 7.26 (m, 1H), 7.21 (dd, J= 9.0, 2.2 Hz, 1H), 6.46 (br, 2H), 6.17 (m, 1H), 5.29 (br, 1H), 4.97 (br, 1H), 4.35 (m, 1H), 3.88 (s, 3H), 3.81 (m, 1H), 3.53

(m, 2H), 2.53 (m, 1H), 2.21 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 158.0, 157.0, 154.1, 135.6, 134.4, 131.1, 129.7, 129.0, 128.6, 128.0, 127.0, 119.0, 116.2, 106.0, 87.7, 82.4, 70.9, 61.8, 55.4, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{21}H_{21}N_5O_5$, $[MH]^+$424.1621 (calcd), 424.1606 (found).

4.2.14. N^1-(1-Pyrenyl)-2′-deoxyguanosine (2n). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.35 (d, J=8.3 Hz, 1H), 8.32 (d, J=7.6 Hz, 1H), 7.98 (s, 1H), 8.28 (s, 1H), 8.27 (d, J=5.5 Hz, 1H), 8.19 (m, 2H), 8.15 (d, J=5.7 Hz, 1H), 8.07 (t, J=7.4 Hz, 1H), 8.01 (d, J=9.1 Hz, 1H), 7.97 (d, J=8.3 Hz, 1H), 6.33 (br, 2H), 6.26 (m, 1H), 5.31 (br, 1H), 5.00 (br, 1H), 4.38 (m, 1H), 3.84 (m, 1H), 3.54 (m, 2H), 2.62 (m, 1H), 2.25 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 160.6, 159.8, 146.3, 130.7, 130.5, 128.6, 128.1, 127.2, 126.9, 126.8, 125.7, 125.6, 125.4, 124.9, 123.8, 123.1, 120.7, 120.6, 87.7, 83.0, 70.8, 61.8, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{26}H_{21}N_5O_4$, $[MH]^+$468.1672 (calcd), 468.1686 (found).

4.2.15. N^1-(3-Thienyl)-2′-deoxyguanosine (2o). ^{1}H NMR (400.1 MHz) (DMSO-d_6) δ: 7.95 (s, 1H), 7.68 (m, 1H), 7.64 (m, 1H), 6.99 (m, 1H), 6.48 (br, 2H), 6.12 (m, 1H), 5.29 (br, 1H), 4.95 (br, 1H), 4.33 (m, 1H), 3.80 (m, 1H), 3.49 (m, 2H), 2.50 (m, 2H), 2.19 (m, 2H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 156.9, 154.3, 150.0, 136.0, 133.4, 127.4, 127.2, 125.2, 116.3, 88.0, 82.8, 71.1, 62.1, 2′-*C* is buried in DMSO-d_6 peaks. HRMS calcd for $C_{14}H_{15}N_5O_4S$, $[MH]^+$350.0923 (calcd), 350.0922 (found).

4.2.16. N^3-*p*-Tolyl-2′-deoxyuridine (3b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.97 (d, J=8.2 Hz, 1H), 7.22 (d, J=8.1 Hz, 2H), 7.97 (d, J=8.2 Hz, 2H), 6.14 (t, J=3.6 Hz, 1H), 5.83 (d, J=8.2 Hz, 1H), 5.26 (br, 1H), 5.05 (br, 1H), 4.23 (m, 1H), 3.80 (m, 1H), 3.56 (m, 2H), 2.32 (s, 3H), 2.12 (m, 2H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 162.5, 151.0, 140.0, 137.9, 133.4, 129.7, 128.8, 101.8, 87.9, 85.6, 70.7, 61.6, 2′-*C* is buried in DMSO-d_6 peaks, 21.1. HRMS calcd for $C_{16}H_{18}N_2O_5$, $[MH]^+$319.1294 (calcd), 319.1288 (found).

4.2.17. N^3-*p*-Tolyl-thymidine (4b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 7.84 (s, 1H), 7.22 (d, J=8.1 Hz, 2H), 7.05 (d, J=8.2 Hz, 2H), 6.17 (t, J=6.8 Hz, 1H), 5.25 (d, J=4.0 Hz, 1H), 5.06 (t, J=4.8 Hz, 1H), 4.24 (t, J=3.0 Hz, 1H), 3.75 (m, 1H), 3.58 (m, 2H), 2.32 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 163.3, 150.9, 137.8, 135.7, 133.7, 129.7, 128.8, 109.3, 87.7, 85.1, 70.7, 61.6, 2′-*C* is buried in DMSO-d_6 peaks, 21.1, 13.4. HRMS calcd for $C_{17}H_{20}N_2O_5$, $[MH]^+$333.1450 (calcd), 333.1448 (found).

4.2.18. N^1-*p*-Tolyl-2′-deoxyinosine (5b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.38 (s, 1H), 8.31 (s, 1H), 8.34 (s, 1H), 7.32 (m, 4H), 6.33 (t, J=6.7 Hz, 1H), 5.72 (br, 1H), 5.36 (br, 1H), 4.39 (t, J=2.8 Hz, 1H), 3.86 (m, 1H), 3.55 (m, 2H), 2.64 (m, 1H), 2.36 (s, 3H), 2.32 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 156.0, 148.3, 147.1, 139.3, 138.4, 135.0, 129.6, 127.6, 123.8, 88.0, 83.7, 70.7, 61.6, 2′-*C* is buried in DMSO-d_6 peaks, 20.7. HRMS calcd for $C_{17}H_{18}N_4O_4$, $[MH]^+$343.1406 (calcd), 343.1421 (found).

4.2.19. N^4-*p*-Tolyl-2′-deoxycytidine (6b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 9.63 (br, 1H), 7.91 (d, J=7.5 Hz, 1H), 7.56 (br, 2H), 7.10 (d, J=8.3 Hz, 1H), 6.15 (t, J=6.7 Hz, 1H), 5.95 (d, J=7.4 Hz, 1H), 5.21 (br, 1H), 4.98 (br, 1H), 4.19 (t, J=2.9 Hz, 1H), 3.77 (m, 1H), 3.55 (m, 2H), 2.24 (s, 3H), 2.13 (m, 1H), 1.95 (m, 1H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 155.1, 141.5, 141.2, 137.2, 129.4, 120.9, 87.7, 85.5, 70.7, 61.7, 2′-*C* is buried in DMSO-d_6 peaks, 20.8. HRMS calcd for $C_{16}H_{19}N_3O_4$, $[MH]^+$318.1454 (calcd), 318.1476 (found).

4.2.20. N^6-*p*-Tolyl-2′-deoxyadenosine (7b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 9.81 (s, 1H), 9.48 (s, 1H), 8.34 (s, 1H), 7.78 (d, J=8.4 Hz, 2H), 7.10 (d, J=8.3 Hz, 2H), 6.38 (m, 1H), 5.33 (br, 1H), 5.15 (br, 1H), 4.41 (t, J=2.7 Hz, 1H), 3.87 (m, 1H), 3.57 (m, 2H), 2.73 (m, 1H), 2.26 (m, 1H), 2.24 (s, 3H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 152.5, 152.3, 149.2, 140.6, 137.3, 132.0, 129.2, 121.3, 120.6, 88.4, 84.3, 71.3, 62.2, 2′-*C* is buried in DMSO-d_6 peaks, 20.8. HRMS calcd for $C_{17}H_{19}N_5O_3$, $[MH]^+$342.1566 (calcd), 342.1575 (found).

4.2.21. N^3-*p*-Tolyluridine (8b). ^{1}H NMR (500.1 MHz) (DMSO-d_6) δ: 8.03 (d, J=8.2 Hz, 1H), 8.03 (d, J=8.1 Hz, 2H), 8.03 (d, J=8.2 Hz, 2H), 5.83 (d, J=8.2 Hz, 1H), 5.76 (d, J=4.9 Hz, 1H), 5.45 (br, 1H), 5.15 (br, 2H), 4.06 (t, J=4.9 Hz, 1H), 3.97 (t, J=4.7 Hz, 1H), 3.83 (m, 1H), 3.56 (m, 2H), 2.32 (s, 3H). ^{13}C NMR (125.8 Hz) (DMSO-d_6) δ: 162.5, 151.3, 140.1, 137.9, 133.4, 129.8, 128.8, 101.7, 89.3, 85.1, 74.1, 70.0, 61.0, 21.1. HRMS calcd for $C_{16}H_{18}N_2O_6$, 335.1240 $[MH]^+$ (calcd), 335.1243 (found).

4.2.22. 3′,5′-Diacetoxy-N^1-*p*-tolyl-2′-deoxyguanosine (9b). ^{1}H NMR (500.1 MHz) ($CDCl_3$) δ: 7.76 (br, 1H), 7.33 (d, J=8.0 Hz, 2H), 7.15 (d, J=8.0 Hz, 2H), 6.21 (m, 1H), 5.39 (m, 1H), 4.98 (br, 2H), 4.48 (m, 1H), 4.33 (m, 2H), 2.92 (m, 1H), 2.51 (m, 1H), 2.11 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (125.8 Hz) ($CDCl_3$) δ: 170.8, 170.3, 153.2, 140.1, 132.1, 131.2, 131.1, 129.4, 128.23, 128.21, 123.1, 84.5, 82.3, 74.5, 63.7, 40.6, 36.9, 21.2, 20.8. HRMS calcd for $C_{21}H_{23}N_5O_6$, 442.1727 $[MH]^+$ (calcd), 442.1724 (found).

Acknowledgements

This investigation was supported by a grant (CA 92537) from the National Cancer Institute, DHHS.

We wish to thank one of the reviewers for calling our attention to the recent report by Strouse et al.[14] on synthesis of N^1-aryl inosine and guanosine derivatives by copper(II)-mediated coupling of the ribonucleosides with arylboronic acids.

References and notes

1. For leading references on biological activities of 2-, 6-, 8-, and 9-aryl purine and purine nucleoside derivatives see: (a) Hocek, M. *Eur. J. Org. Chem.* **2003**, 245–254. (b) Bakkestuen, A. K.; Gundersen, L.-L. *Tetrahedron Lett.* **2003**,

44, 3359–3362. (c) Turek, P.; Kotora, M.; Hocek, M.; Cisarova, I. *Tetrahedron Lett.* **2003**, *44*, 785–788.
2. Beland, F. A.; Kadlubar, F. F. In Cooper, C. S., Grover, P. I., Eds.; Handbook of Experimental Pharmacology: Chemical Carcinogenesis and Mutagenesis; Springer: Heidelberg, Germany, 1990; Vol. 94/I, pp 267–325.
3. Harvey, R. G. *Polycyclic Aromatic Hydrocarbons: Chemistry and Carcinogenicity*; Cambridge University Press: Cambridge, UK, 1991.
4. Dipple, A. *DNA Adducts: Identification and Biological Significance*; Hemminki, K., Dipple, A., Segerbäck, D., Kadulbar, F. F., Shuker, D., Bartsch, H., Eds.; 1994, 107–129. IARC Sci. Pub. No. 125.
5. (a) Ran, C.; Dai, Q.; Harvey, R. G. *J. Org. Chem.* **2005**, *70*, 3724–3726. (b) Agrofoglio, L. A.; Gillaizeau, I.; Saito, Y. *Chem. Rev.* **2003**, *103*, 1875–1916. (c) Liu, J.; Robins, M. *Org. Lett.* **2004**, *6*, 3421–3423. (d) Joshi, R. A.; Patil, P. S.; Muthukrishnan, M.; Ramana, C. V.; Gurjar, M. K. *Tetrahedron Lett.* **2004**, *45*, 195–197. (e) Gannett, P. M.; Heavner, S.; Daft, J. R.; Shaughnessy, K. H.; Epperson, J. D.; Greenbaum, N. L. *Chem. Res. Toxicol.* **2003**, *16*, 1385–1394. (f) Western, E. C.; Daft, J. R.; Johnson, E. M., II,; Gannett, P. M.; Shaughnessy, K. H. *J. Org. Chem.* **2003**, *68*, 6767–6774. (g) Gannett, P. M.; Powell, J. H.; Rao, R.; Shi, X.; Lawson, T.; Kolar, C.; Toth, B. *Chem. Res. Toxicol.* **1999**, *12*, 297–304.
6. (a) Gunda, P.; Russon, L. M.; Lakshman, M. K. *Angew. Chem., Int. Ed.* **2004**, *43*, 6372–6377. (b) Lakshman, M. K.; Ngassa, F. N.; Bae, S.; Buchanan, D. C.; Hahn, H.-D.; Mah, H. *J. Org. Chem.* **2003**, *68*, 6020–6030. (c) Johnson, F.; Bonala, R.; Tawde, D.; Torres, M. C.; Iden, C. R. *Chem. Res. Toxicol.* **2002**, *15*, 1489–1494. (d) Lakshman, M. K.; Hilmer, J. H.; Martin, J. Q.; Keeler, J. C.; Dinh, Y. Q. V.; Ngassa, F. N.; Russon, L. M. *J. Am. Chem. Soc.* **2001**, *123*, 7779–7787. (e) Lee, H.; Luna, E.; Hinz, M.; Stezowski, J. J.; Kiselyov, A. S.; Harvey, R. G. *J. Org. Chem.* **1995**, *60*, 5604–5613.
7. Dai, Q.; Ran, C.; Harvey, R. G. *Org. Lett.* **2005**, *5*, 999–1001.
8. Branco, P. S.; Antunes, A. M. M.; Marques, M. M.; Chiarelli, M. P.; Lobo, A. M.; Prabhaker, S. *Chem. Res. Toxicol.* **1999**, *12*, 1223–1233. Deoxygenation of nitro- and nitrosoarylamines with triethyl phosphite in the presence of dG affords low yields of mixtures of arylated-dG products consisting principally of C^8-aryl-dG (2–12%), N^1-aryl-dG (1–6%)..
9. (a) Chan, D. T.; Monaco, K. L.; Wang, R.-U.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933–2936. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, *39*, 2941–2944.
10. (a) Collman, J. P.; Zhong, M.; Zhang, C.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 7892–7897. (b) Collman, J. P.; Zhong, M.; Zeng, L.; Costanzo, S. *J. Org. Chem.* **2001**, *66*, 1528–1531. (c) Mederski, W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757–12770.
11. Joshi, R. A.; Patil, P. S.; Muthukrishnan, M.; Ramana, C. V.; Gurjar, M. K. *Tetrahedron Lett.* **2004**, *45*, 195–197.
12. Streiter, E. R.; Blackmond, D. G.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4120–4121.
13. Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581–584.
14. Strouse, J.; Jeselnik, M.; Tapaha, F.; Jonsson, C. B.; Parker, W. B.; Arterburrn, J. B. *Tetrahedron. Lett.* **2005**, *46*, 5699–5702.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1772–1776
Tetrahedron

Bromination of α-tocopherol methano-dimer and ethano-dimer

Thomas Rosenau,[a,*] Christian Adelwöhrer,[a] Elisabeth Kloser,[a] Kurt Mereiter[b] and Thomas Netscher[c]

[a]*Department of Chemistry, University of Natural Resources and Applied Life Sciences Vienna (BOKU), Muthgasse 18, A-1190 Vienna, Austria*
[b]*Department of Chemistry, Vienna University of Technology, Getreidemarkt 9, A-1060 Vienna, Austria*
[c]*DSM Nutritional Products, Research and Development, PO Box 3255, CH-4002 Basel, Switzerland*

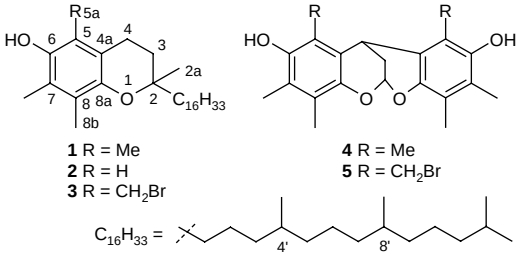
Received 4 November 2005; accepted 21 November 2005

Available online 19 December 2005

Abstract—Bromination of the ethano-dimer of α-tocopherol (**6**) afforded pyrano-spirodimer of α-tocopherol (**7**) quantitatively, while the methano-dimer of α-tocopherol (**10**) produced a mixture of products, including the furano-spirodimer **11**, pyrano-spirodimer **7**, and 5-bromo-γ-tocopherol (**12**), the latter two formed in an unusual dealkylative fragmentation step. The mechanisms were studied by a combination of trapping reactions as well as kinetic and computational studies.

1. Introduction

Bromination of α-tocopherol (**1**), the main component of vitamin E,[1] with elemental bromine affords 5a-bromo-α-tocopherol (**3**) in high yields according to a non-radical oxidation–addition mechanism involving an *ortho*-quinone methide (oQM) intermediate that adds the HBr evolved.[2] Recently we observed that the bromination of the 'twin chromanol' **4**, containing two rigidly linked aromatic units, each with a substitution pattern typical of α-tocopherol **1**,[3] proceeded twice—via oQMs on each side of the twin—to afford bisbromide **5**. Later, a method was found to extend the lifetime of tocopherol-derived oQMs by low-temperature stabilization with amine *N*-oxides[4] to make them accessible to analytical characterization and better usable in subsequent reactions. Continuing our studies on oQMs, we were interested in the bromination behavior of the α-tocopherol ethano-dimer (**6**)[5] and the α-tocopherol methano-dimer (**10**),[5] as these compounds contain two separate tocopheryl moieties being much more flexible conformationally than those in **4**. Both compounds **6** and **10** are well-known as products of homolytic and heterolytic coupling reactions involving α- (**1**), γ-tocopherol (**2**) and their tocopheroxyl radicals. The present studies revealed some novel facets of the reaction behavior of the physiologically important tocopherol system, and provided some interesting mechanistic aspects, which showed that the chemical behavior of tocopherols is still far from being fully understood and still holds surprises.

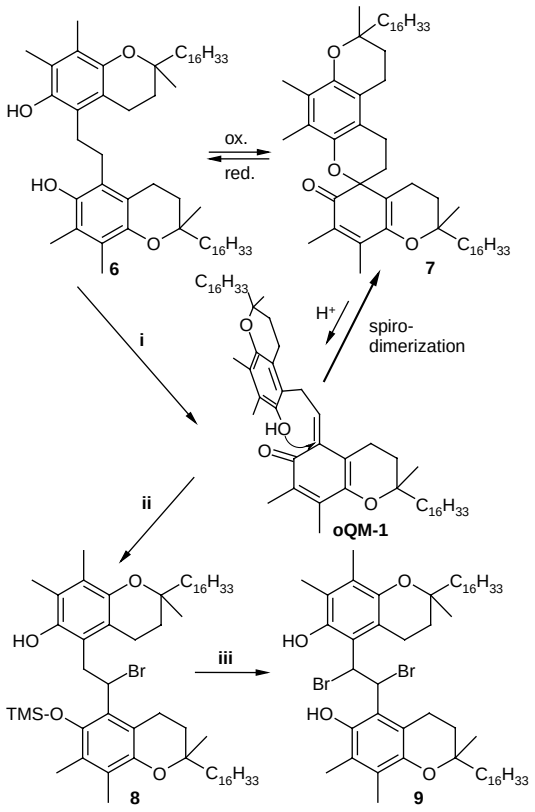


2. Results and discussion

Bromination of ethano-dimer **6** afforded the pyrano-spirodimer of α-tocopherol (**7**)[6] in yields above 95%, independent of the bromine excess used. This is in complete agreement with the use of other oxidants giving the same results.[7] In fact, **6** and **7** seem to constitute a largely reversible redox pair. Bromine oxidizes one α-tocopherol side in **6** to an *ortho*-quinone methide (oQM) intermediate (**oQM-1**, see Scheme 1), which immediately adds the phenolic OH group of the second tocopherol, a process, which is evidently favored over the 1,4-addition of evolving HBr by a pre-organizational effect, as the ethano-bridge keeps the two reacting moieties in close distance. This explains why the intramolecular reaction of the oQM intermediate proceeds so readily.

Keywords: Tocopherol; Vitamin E; Bromination; Tocopherol dimers; Reaction mechanism.
* Corresponding author. Tel.: +43 1 36006 6071; fax: +43 1 36006 6059; e-mail: thomas.rosenau@boku.ac.at

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.050

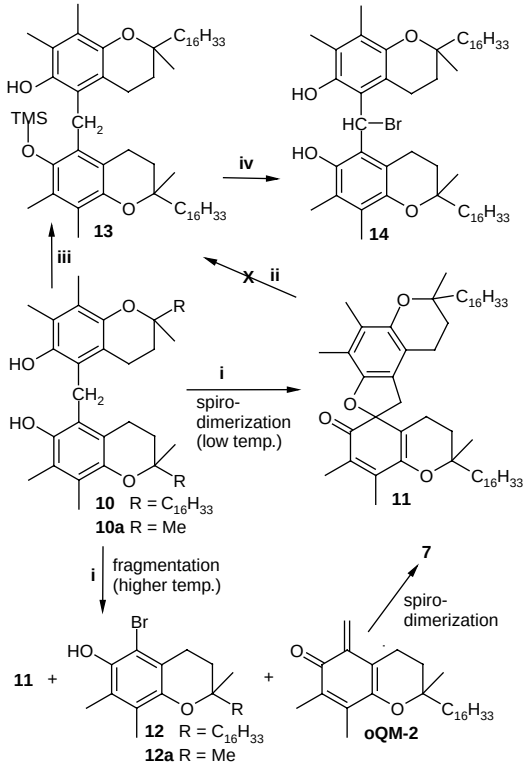


Scheme 1. Bromination of α-tocopherol ethano-dimer and synthesis of the corresponding 1,2-dibromide **9**.

Reaction of **6** in a way analogous to the bromination of α-tocopherol, that is, under formation of 1,2-dibromo-1,2-bis(5-γ-tocopheryl)-ethane (**9**), was thus not possible by simple bromination. The latter product was accessible only indirectly by treatment of spiro-dimer **7** with TMS-Br and catalytic amounts of acid[8] to give **8** (Scheme 1). The acid facilitates the opening of **7** to regenerate **oQM-1**.[9] Even though the concentration of this intermediate is quite low and the reaction back to the pyrano-spirodimer dominates by far, the TMS continuously traps a small percentage of the oQM intermediate present, which now cannot react back to **7** due to the protected OH group. In this way, **7** is eventually completely converted into **8**.[10] Further reaction of **8** with elemental bromine, which now proceeds similar to α-tocopherol at the non-protected 'half' of **8**, followed by desilylation provided the target bisbromide **9**. The bromination of **8** was carried out in the presence of small amounts (5%) of TMS-Br to minimize formation of **7** as byproduct.

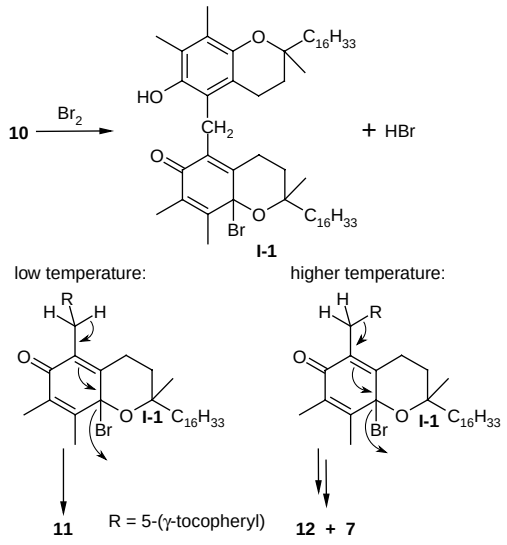
Bromination of methano-dimer **10** at approx. −10 °C proceeded quantitatively to the furano-spirodimer **11**, in analogy to **6** giving pyrano-spirodimer **7**. At rt—and increasingly at higher temperatures (40–100 °C)—byproducts are formed, one of them being the pyrano-spirodimer **7**.

This result seemed unreasonable at a first glance as this product possessed one carbon more than the starting methano-dimer; indeed we initially suspected **7** to arise from impurities. However, by comparison to authentic samples[11] and especially through identification of the second major byproduct as 5-bromo-γ-tocopherol (**12**) it became clear that methano-dimer **10** must have fragmented into an 'α-tocopherol part', forming **oQM-2**, which then 'traditionally' dimerized to **7**, and a 'γ-tocopherol part', which gave rise to **12** (see Scheme 2). The theoretical molar ratio of 2:1 between bromide **12** and spiro-dimer **7**—as dictated by stoichiometry—was nearly perfectly obtained in all cases, which additionally corroborated the mechanistic proposal in Scheme 2.



Scheme 2. Bromination of α-tocopherol methano-dimer and synthesis of the corresponding benzyl bromide **14**.

The dependence of the product distribution—the ratio between **11** and **12** (**11** and **7**, respectively)—on the reaction temperature allowed estimating the difference between the free activation energies of spiro-dimerization and fragmentation, which was 71.4 ± 4.8 kJ mol^{-1},[12] meaning that the rate-determining step of the spiro-dimerization to **11** is about 70 kJ mol^{-1} more favored than the rate-determining step of the fragmentation eventually leading to **7** and **12**, which can reasonably be assumed to be the C–C bond cleavage (Scheme 3). The process with the lower activation energy, the spiro-dimerization to **11**, proceeds preferably at lower temperatures, while the process with the higher activation energy, the 'disproportionation' to **7** and **12**, becomes increasingly favored at higher temperatures. It should be noted that by these kinetic studies, it is only possible to obtain the relative free activation energies. It does unfortunately not allow to derive thermodynamical



Scheme 3. Mechanistic proposal for the two competitive reactions occurring upon bromination of **10**.

parameters, such as product stabilities, or a detailed mechanism.

Analogous results were obtained with model compound **10a**, which contains a methyl group instead of the isoprenoid side chain (Scheme 2). Bromination provided **12a** as a colorless solid, of which the crystal structure was recorded (Fig. 1). The compound contained four chemically equivalent, but crystallographically different molecules per monoclinic unit cell. All OH hydrogens formed intramolecular H-bonds to the bromine, two OH hydrogens exhibited bifurcated H-bonds to neighboring hydroxyls.

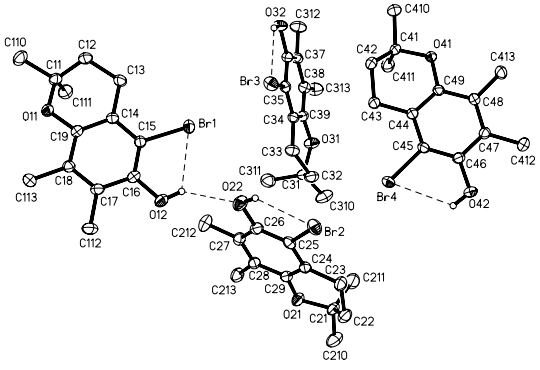


Figure 1. Thermal ellipsoid plot (40% ellipsoids, C-bound hydrogens omitted) and crystallographic atom labeling of 5-bromo-2,2,7,8-tetramethylchroman-6-ol (**12a**, truncated model compound of 5-bromo-α-tocopherol, **12**).

As to the detailed mechanism of the higher-temperature pathway, the fragmentation is unlikely to start from an oQM similar to **oQM-1** in Scheme 1, it seems more likely that a fragmentation produces such an intermediate. As proposed in Scheme 3, the primary bromination intermediate **I-1** undergoes 1,4-elimination of HBr to yield **11** as the favored process. At increasing temperatures, the competing process, 1,4-elimination of RBr, becomes more and more dominant: with R being the 5-(γ-tocopheryl) moiety, **12** (RBr) is eliminated, and **oQM-2** remains, which immediately dimerizes into **7**.[13] Intermediate **I-1** is postulated by analogy to the bromination of α-tocopherol[2] and to the structure of other α-tocopherol derivatives having similar quinone monoketal structure, such as 8a-hydroxy-tocopherone[14] and 8a-alkoxy-tocopherones.[15] This mechanism was corroborated by the following experiments. Performing the low-temperature bromination of **10** with deuterated starting material containing two OD groups instead of OH, afforded compound **11** monodeuterated at C-5a. This supported a 1,4-elimination of H–Br from **I-1** with simultaneous (or immediately following) 1,2-addition of the phenolic OD to the intermediate exocyclic methylene as the detailed formation mechanism of **11**. Furthermore, the use of iodine monochloride, ICl, as the oxidant at higher temperatures[16]—instead of elemental bromine—produced 5a-chloro-γ-tocopherol (besides pyrano-spirodimer **7**), which supported the 1,4-elimination mechanism from **I-1** and the fact that the 'γ-tocopherol part' is eliminated in cationic form, that in turn reacted with the halide anion present. Agreeing with this, replacement of elemental bromine by iodine monobromide, IBr, did not influence the outcome of the reaction, since **7** and the bromide **12** were formed.

Calculation of the activation energies for the two competitive processes in Scheme 3 afforded 224.3 kJ mol^{-1} for the HBr elimination process finally leading to **11**, and 308.7 kJ mol^{-1} for the elimination of RBr leading to **7** and **12**. The activation energy difference of 84.4 kJ mol^{-1} agreed reasonable well with the experimentally determined value of 71.4 ± 4.8 kJ mol^{-1} (see above).

Bromination of methano-dimer **10** in a way analogous to the bromination of α-tocopherol, that is, leading to bromo-bis(γ-tocopheryl)-methane (**14**), was only achieved circuitously. Excess methano-dimer **10** was treated with TMS-Br, the mixture of non-, mono-, and bis-silylated products was separated chromatographically on alumina, and the separated mono-TMS derivative (**13**) was brominated and deprotected by analogy to **8**, see Scheme 2.

3. Experimental

(All-*R*)-derivatives (**6**, **7**, **10**) prepared from (2*R*,4′*R*,8′*R*)-tocopherols were used as the starting materials.[17] All other chemicals were obtained from commercial suppliers (Sigma-Aldrich). Thin-layer chromatography (TLC) was performed on silica gel 60 plates (5×10 cm, 0.25 mm) with fluorescence detection under UV light at 254 nm. Column chromatography was performed on silica gel G_{60} (40–63 μm). Melting points, determined on a Kofler-type micro hot stage with Reichert-Biovar microscope, are uncorrected. ^{1}H NMR spectra were recorded at 300.13 MHz for ^{1}H and at 75.47 MHz for ^{13}C NMR in $CDCl_3$ if not otherwise stated. Chemical shifts, relative to TMS as internal standard, are given in δ values, coupling constants in Hz. ^{13}C peaks were assigned by means of APT, HMQC and HMBC spectra. Resonances of the isoprenoid side chain of tocopherols are not influenced by modifications of the chroman ring, and are therefore not listed.

Computations, as implemented through Spartan Pro 02 by Wavefunction, Inc., Irvine, CA, USA, were carried out on

geometries pre-optimized by the semi-empirical PM3 method. For full geometry optimization the widely employed B3LYP hybrid method, which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang, and Parr[18,19] parameterized by Becke[20,21] was used, along with the double-zeta split valence basis sets 6-31+G*,[22,23] which includes diffuse functions.

3.1. Preparation of bisbromide 9

Under inert atmosphere, trimethylsilyl bromide (TMS-Br, 153.1 g mol^{-1}, 15 mmol, 2.30 g) dissolved in chloroform (5 mL) was quickly added to an *n*-hexane solution (20 mL) of α-tocopherol spiro-dimer (**7**, 857.41 g mol^{-1}, 10 mmol, 8.57 g) at rt. After stirring the mixture for 48 h at rt, a solution of bromine (159.81 g mol^{-1}, 10.5 mmol, 1.68 g) in *n*-hexane (10 mL) was added at once, and the mixture was stirred for 2 h at rt. Solvent and excess reagents were removed in vacuo, and the resulting mixture, consisting of non-TMS (minor), mono-TMS (main product) and bis-TMS (minor) derivatives of **9**, was directly subjected to desilylation by dissolution in a 1 M solution of tetrabutylammonium fluoride in ethanol (5 mL). After stirring for 1 h at rt, *n*-hexane (50 mL) and water (20 mL) were added. The organic phase was washed with 2 M aqueous HBr, water, and was dried over Na_2SO_4. The solvent was evaporated in vacuo at rt, and the crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane, v/v=1:10) to give bisbromide **9** in 71% overall yield (7.22 g) as a yellow oil solidifying to a wax at about 4 °C.

Instead of reacting ethano-dimer **6** with bromine to **7**, then with TMS-Br to **8**, and then again with bromine to **9**, dimer **6** can be directly treated with a mixture of TMS-Br and bromine (2 equiv), followed by desilylation, to provide **9** in a one-pot procedure, albeit at the expense of yield (59% overall).

3.1.1. 1,2-Dibromo-1,2-bis(5-γ-tocopheryl)ethane (9). ^{1}H NMR: δ 1.80 (4H, m, H-3), 2.08 (6H, s, H-7a), 2.12 (6H, s, H-8b), 2.63 (4H, 't', H-4), 4.00–4.12 (2H, s, br, OH), 5.32 (2H, s, br, CH–Br). ^{13}C NMR: δ 11.9 (C-8b), 12.2 (C-7a), 20.4 (C-4), 23.5 (C-2a), 31.2 (C-3), 46.8 (C-5a), 74.5 (C-2), 115.7 (C-4a), 122.5 (C-7), 123.1 (C-8), 124.8 (C-5), 144.1 (C-6), 146.2 (C-8a). Elemental analysis calcd for $C_{58}H_{96}Br_2O_4$ (1017.22 g mol^{-1}): C 68.49, H 9.51, Br 15.71; found C 68.23, H 9.63, Br 15.42. Resonances of the isoprenoid side chain are not listed as they are only negligibly affected (<0.1 ppm for ^{13}C) by modifications of the chroman skeleton.

3.2. Preparation of 5-bromo-γ-tocopherol (12)

In a vessel covered with aluminium foil to conduct the reaction in the dark, a solution of the tocopherol methano-dimer **10** (845.40 g mol^{-1}, 1 mmol, 0.845 g) in toluene (50 mL) was heated to reflux in an inert atmosphere. A solution of bromine (159.81 g mol^{-1}, 1.05 mmol, 0.17 g) in *n*-hexane was added at once into the solution close to the magnetic stirrer. The color of the bromine disappeared immediately, and the solution was quickly cooled to about 5 °C in an ice bath. The solution was concentrated to a volume of 2 mL, and chromatographed on silica gel (toluene/*n*-hexane, v/v=1:5) to give 5-bromo-γ-tocopherol (**12**) as a faint yellow oil in 29% overall yield (0.143 g), besides spiro-dimer **7**.

3.2.1. 5-Bromo-2,7,8-trimethyl-2-(4,8,12-trimethyltridecyl)-chroman-6-ol (12). ^{1}H NMR: δ 1.22 (s, 3H, H-2a), 1.68–1.87 (2H, m, H-3), 2.07 (6H, s, H-7a, H-8b), 2.65 (2H, 't', H-4, ^3J=7.2 Hz), 5.17 (1H, s, br, OH). ^{13}C NMR: δ 11.8 (C-7a), 12.9 (C-8b), 24.1 (C-4), 23.7 (C-2a), 31.5 (C-3), 75.4 (C-2), 109.3 (C-5), 117.3 (C-4a), 122.4 (C-7), 125.4 (C-8), 143.4 (C-6), 145.9 (C-8a). Elemental analysis calcd for $C_{28}H_{47}BrO_2$ (495.59 g mol^{-1}): C 67.86, H 9.56, Br 16.12; found C 67.99, H 9.82. The identity of **12** was additionally confirmed by comparison with an authentic sample obtained by direct bromination of γ-tocopherol (**2**).

Analogous results were obtained according to the above procedure using model compound **10a** containing a methyl group instead of the isoprenoid side chain, providing **12a** (27%) as a colorless solid, which was recrystallized from EtOH–H_2O (v/v=1/1), see Figure 1 and crystal structure section below.

3.3. X-ray crystallographic study

X-ray data collection was performed with a Bruker AXS Smart APEX CCD diffractometer and graphite monochromatized Mo K_α radiation, λ=0.71073 Å; corrections for absorption with the program SADABS, structure solution with direct methods, structure refinement on F^2 (Bruker AXS, 2001: programs SMART, version 5.626; SAINT, version 6.36A; SADABS version 2.05; XPREP, version 6.12; SHELXTL, version 6.10. Bruker AXS Inc., Madison, WI, USA).

CCDC 270830 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (internet) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk].

3.3.1. 5-Bromo-2,2,7,8-tetramethyl-chroman-6-ol (12a). Small crystals from EtOH/H_2O=1:1. The crystal structure was preliminarily determined at rt, then measured and refined at −100 °C. $C_{13}H_{17}BrO_2$, M=285.18, monoclinic, space group $P2_1/c$, a=10.9451(4) Å, b=24.3852(10) Å, c=19.1413(8) Å, β=90.550(1)°, V=5108.5 (4) Å^3, Z=16, D_c=1.483 g/cm^3, T=173 K, μ=3.203 mm^{-1}, $F(000)$=2336; total reflections=61706, unique reflections=11127, R_{int}=0.0376, final refinement: data/restraints/parameters=11127/444/597, goodness-of-fit on F^2=1.006, R_1=0.0284 ($I>2\sigma(I)$), wR_2=0.0736 (all data).

^{1}H NMR: δ 1.29 (s, 6H, H-2a and H-2b), 1.78 (2H, t, H-3, ^3J=7.2 Hz), 2.08 (3H, s, H-7a), 2.21 (3H, s, H-8b), 2.68 (2H, 't', H-4, ^3J=7.2 Hz), 5.19 (1H, s, OH). ^{13}C NMR: δ 11.8 (C-7a), 12.9 (C-8b), 24.3 (C-4), 26.5 (C-2a and C-2b), 33.0 (C-3), 73.3 (C-2), 109.3 (C-5), 117.1 (C-4a), 122.4 (C-7), 125.4 (C-8), 143.4 (C-6), 146.0 (C-8a). The identity of **12a** was additionally confirmed by comparison with an authentic sample obtained by direct bromination of

the γ-tocopherol model compound 2,2,7,8-tetramethylchroman-6-ol.

3.4. Preparation of monobromide 14

A solution of trimethylsilyl bromide (TMS-Br, 153.1 g mol^{-1}, 0.8 mmol, 0.12 g) in chloroform (5 mL) was added to a solution of tocopherol methano-dimer **10** (845.40 g mol^{-1}, 1 mmol, 0.845 g) in a mixture of pyridine (2 mL) and chloroform (10 mL), and the mixture was stirred overnight at rt. The solvents were evaporated in vacuo, the remainder suspended in *n*-hexane (2 mL) and chromatographed on neutral alumina (*n*-hexane). Elution provided the bis-TMS derivative of **10** (5%), mono-TMS-derivative of **10** (**13**, 70%), and unprotected **10** (25%). The ratio TMS-Br:methano-dimer of 0.8 appeared to be an optimum with regard to mono-TMS derivative **13**. Both lowering (52% at 0.7) and increasing this ratio (62% at 0.9, 45% at 1.25) appeared to be counterproductive. A solution of bromine (159.81 g mol^{-1}, 0.75 mmol, 0.12 g) in *n*-hexane (1 mL) was added at once to a solution of **13** in *n*-hexane (5 mL), and the mixture was stirred for 2 h at rt. Solvent and excess bromine were removed in vacuo, and the residue was dissolved in a 1 M solution of tetrabutylammonium fluoride in ethanol (2 mL) under vortexing. After standing for 1 h at rt, *n*-hexane (5 mL) and water (5 mL) were added. The organic phase was washed with water, and was dried over Na_2SO_4. The solvent was evaporated in vacuo at rt, and the crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane, v/v=1:10) to give monobromide **14** in 22% overall yield (0.203 g, relative to starting **10**) as a greenish semi-solid wax.

3.4.1. Bromo-bis(5-γ-tocopheryl)methane (14). ^{1}H NMR: δ 1.81 (4H, m, H-3), 2.12 (6H, s, H-7a), 2.13 (6H, s, H-8b), 2.64 (4H, 't', H-4), 4.56–4.89 (1H, s, br, OH), 5.18 (1H, s, CH-Br), 8.68 (1H, s, OH). ^{13}C NMR: δ 11.8 (C-8b), 12.5 (C-7a), 18.4 (C-5a), 20.3 (C-4), 23.5 (C-2a), 31.1 (C-3), 75.4 (C-2), 117.2 (C-4a), 119.1 (C-5), 122.1 (C-7), 122.8 (C-8), 146.3 (C-6), 147.4 (C-8a). Elemental analysis calcd for $C_{57}H_{95}BrO_4$ (924.29): C 74.07, H 10.36, Br 8.64; found C 73.78, H 10.19, Br 8.93.

Acknowledgements

The financial support by the Austrian Fonds zur Förderung der wissenschaftlichen Forschung, project P-14687 is gratefully acknowledged. The authors would like to thank Dr. Andreas Hofinger, Department of Chemistry at the University of Natural Resources and Applied Life Sciences (BOKU), Vienna, for recording the NMR spectra.

References and notes

1. (a) Packer, L.; Fuchs, J. *Vitamin E in Health and Disease*; Marcel Dekker: New York, 1993. (b) Isler, O.; Brubacher, G. *Vitamins I*; Thieme: Stuttgart, 1982; p 126. For a general review on chromans and tocopherols see: Parkhurst, R. M.; Skinner, W. A. In Ellis, G. P., Lockhardt, I. M., Eds.; Chromans and Tocopherols in Chemistry of Heterocyclic Compounds; Wiley: New York, 1981; Vol. 36.
2. Rosenau, T.; Habicher, W. D. *Tetrahedron* **1995**, *51*, 7919–7926.
3. Rosenau, T.; Potthast, A.; Hofinger, A.; Kosma, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 1171–1173.
4. Rosenau, T.; Potthast, A.; Elder, T.; Kosma, P. *Org. Lett.* **2002**, *4*, 4285.
5. (a) Nelan, D. R.; Robeson, C. D. *J. Am. Chem. Soc.* **1962**, *84*, 2963. (b) Schudel, P.; Mayer, H.; Metzger, J.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 636.(c) See also Ref. 9.
6. The preparation is given in Ref. 5b.
7. T. N., Unpublished results.
8. The small amount of HBr generated from TMS-Br and water in solvents (not specially dried) is sufficient. All syntheses used *RRR*-tocopherols as starting materials. It was not tested whether the integrity of stereochemistry was maintained over the reaction steps.
9. The issue of the two diastereomers formed by attack of the phenolic OH at either side of **oQM-1** and their interconversion has been discussed, and also a full NMR assignment is given: Schröder, H.; Netscher, T. *Magn. Reson. Chem.* **2001**, *39*, 701–708. An earlier work proposed a fluxational structure with the two diastereomers contributing: Fales, H. M.; Lloyd, H. A.; Ferretti, J. A.; Silverton, J. V.; Davis, D. G.; Kon, H. J. *J. Chem. Soc., Perkin Trans. 2* **1990**, 1005–1010.
10. A similar reaction between *para*-tocopherylquinone and TMS halides has been used to obtain the *O*-TMS-protected 5a-bromo-α-tocopherol: Rosenau, T.; Habicher, W. D. *Tetrahedron Lett.* **1997**, *38*, 5959–5960.
11. Authentic material was available from earlier work: see the first publication in Ref. 9.
12. The ratio *R* between **11** and **12** was determined at −20, 0, 20, 60, 80, 90, and 100 °C (toluene, quick dropwise addition of bromine in the dark). $R=\exp(-(\Delta E^{\#}_{\text{fragment}}-\Delta E^{\#}_{\text{spiro}})/RT)$, so that a plot 'ln *R* versus 1/*T*' gives the slope $-\Delta(\Delta E^{\#})/R$, and thus the difference of activation energies.
13. It should be noted that this mechanism is still a proposal only. Clarifying computations are underway.
14. (a) Dürckheimer, W.; Cohen, L. A. *Biochem. Biophys. Res. Commun.* **1962**, *9*, 262. (b) Kohar, I.; Southwell-Keely, P. T. *Redox Rep.* **2002**, *7*, 251.
15. Omura, K. *J. Org. Chem.* **1989**, *54*, 1987.
16. The use of ICl or IBr had no effect on the outcome of the low-temperature route leading to **11**.
17. Possible erosion of the stereochemistry, especially at C-2, as a consequence of the chemical manipulations was not further studied. However, comparison of the spiro-dimeric products with stereochemically pure (all-*R*)-compounds gave no indication of such a process.
18. Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev.* **1988**, *B37*, 785–789.
19. Miehlich, B.; Savin, A.; Stoll, H.; Preuss, H. *Chem. Phys. Lett.* **1989**, *157*, 200–206.
20. Becke, A. *Phys. Rev.* **1988**, *A38*, 3098–3100.
21. Becke, A. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
22. Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213–222.
23. Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654–3665.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1777–1786

Facile synthesis of substituted 2,3,4,7-tetrahydro-1*H*-azepines via ring-closing metathesis

Sascha Brass, Hans-Dieter Gerber, Stefanie Dörr and Wibke E. Diederich*

Institut für Pharmazeutische Chemie, Fachbereich Pharmazie, Philipps-Universität Marburg, Marbacher Weg 6, D-35037 Marburg, Germany

Received 10 October 2005; revised 17 November 2005; accepted 21 November 2005

Available online 19 December 2005

Abstract—A highly efficient synthesis based on inexpensive and readily available starting material towards the pharmacologically interesting class of substituted 2,3,4,7-tetrahydro-1*H*-azepines via a ring-closing metathesis (RCM) approach employing Grubbs catalysts 1 and 2 is described. The influence of the substituents R^1 and R^2 on the outcome of the RCM reaction is discussed. The seemingly first example of an RCM approach towards seven-membered azacycles bearing a substituent at the alkene moiety utilizing Grubbs catalyst 1 is presented.

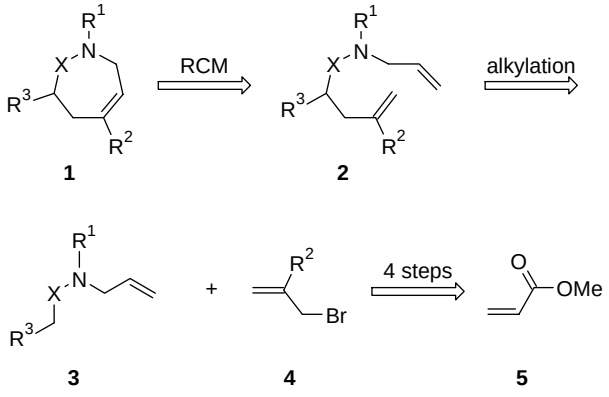
1. Introduction

During the last decade, ring-closing metathesis (RCM) has emerged as a powerful tool for the efficient synthesis of a plethora of carbo- and heterocycles of different size and substitution pattern.[1] In the case of nitrogen-containing heterocyles, the synthesis of five-, six-membered, and fused ringsystems bearing various substituents via RCM is well documented.[2,3]

However, the synthesis of medium-sized azacycles such as azepines and unsaturated seven-membered lactames has not been investigated in detail yet.[4] Moreover, medium-sized unsaturated azacycles bearing a substituent at the alkene moiety are hardly known in literature.[5]

Rising interest in these classes of azacycles as putative pharmaceuticals prompted us to develop a synthetic sequence leading to 3-substituted as well as 3,5-disubstituted azepines and 3,5-disubstituted azepine-2-ones, respectively, via an RCM approach.[6]

As outlined in Scheme 1, our straightforward convergent synthetic strategy towards these azacycles is mainly based on inexpensive and readily available starting material such as methyl acrylate, allylamine, allylbromide, and enables us to introduce a variety of different substituents at a later stage of the synthesis to optimize our preliminary synthesized lead structure.



for X: CH_2, C=O, R^1: Boc, Bn, R^2: H, CH_2OH, CH_2OTBS, R^3: CO_2Me

Scheme 1. Retrosynthetic analysis of the target structure.

For the key step of the synthetic approach only the commercially available Grubbs catalysts 1 and 2 were employed (Fig. 1).

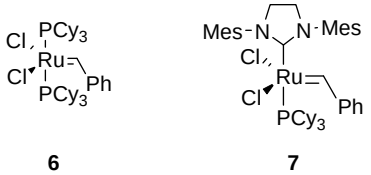


Figure 1. Grubbs catalysts 1 (**6**) and 2 (**7**).

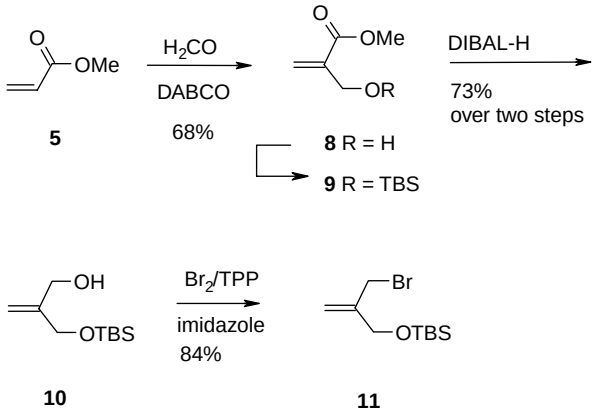
Keywords: Azacycles; Lactames; β-Amino ester.
* Corresponding author. Tel.: +49 6421 2825810; fax: +49 6421 2828994; e-mail: diederic@staff.uni-marburg.de

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.049

2. Results and discussion

2.1. Synthesis of the RCM precursors

As depicted in Scheme 1, we sought to synthesize our RCM precursors of type **2** via an alkylation of an appropriately functionalized allylamine derivative of type **3** with bromoallyl derivative **4**, each of them readily accessible from methyl acrylate. Starting with a Baylis–Hillmann reaction of methyl acrylate with formaldehyde, the α-hydroxymethylated ester **8** could easily be obtained in large quantities.[7,8] Conversion of **8** into its TBS–ether **9**, followed by subsequent reduction with DIBAL-H gave rise to the TBS-protected allylic alcohol **10** (Scheme 2).[9]

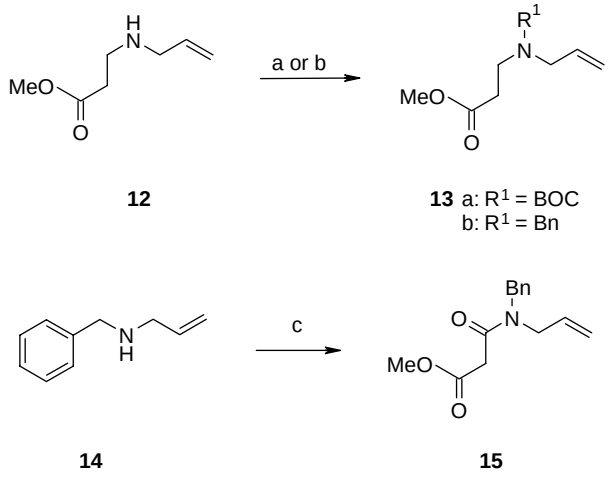


Scheme 2. Synthesis of the substituted allylic fragment **11**.

Following standard procedures for the required activation of the unprotected allylic alcohol functionality in the next step of our synthetic sequence, the corresponding mesylate as well as the trifluoroacetate were obtained in good yields. As we encountered difficulties in the following substitution reaction with these activated precursors, we switched to an alternative activation method such as the commonly used transformation of the alcohol into its halogenated derivative by means of a variety of reagents. For allylic alcohols, triphenylphosphine (TPP) and CCl_4 or TPP/CBr_4 are usually employed as they convert them into the corresponding halides in general without allylic rearrangement.[10]

However, in our case the usage of TPP/CBr_4 employing various reaction conditions surprisingly gave rise to a mixture of isomers and di-brominated derivatives as indicated by ^{1}H NMR. Moreover, the reaction proceeded only in moderate and varying yields and we were not able to isolate the desired product in appropriate purity. Nevertheless, conversion of the allylic alcohol to the corresponding bromide was successfully accomplished employing TPP/Br_2 as alternative brominating agent, even though it is known that trialkylsilyl ethers can directly be converted to alkyl bromides under these reaction conditions.[11,12] In order to prevent the cleavage of our protecting group we therefore added a slight excess of imidazole as a mild proton scavenger and were thus able to obtain our first building block, the desired bromide **11**, not only with excellent yield but also in high purity.[13]

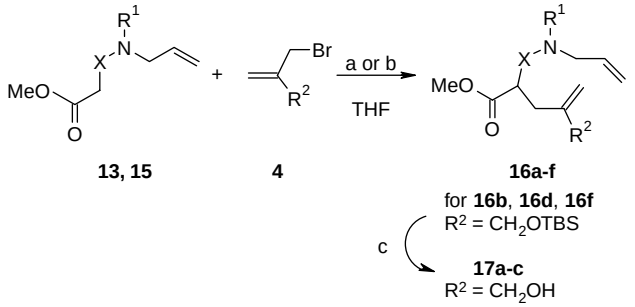
The syntheses of allylamines **13** and amide **15** being our second building blocks were carried out according to slightly modified literature procedures (Scheme 3). Addition of allylamine to methyl acrylate led to the corresponding β-amino ester **12**.[14] Subsequent reaction of ester **12** with benzyl chloride and di-*tert*-butyl-dicarbonate, respectively, furnished the *N*-protected-*N*-allyl-3-amino methyl propanoates **13** in excellent overall yield. Analogously, the corresponding 3-oxo-derivative of **13b**, methyl 3-[allyl(benzyl)amino]-3-oxopropanoate **15**, was prepared starting from allylbenzylamine and methyl malonyl chloride, which proceeded in high overall yield.[15]



Scheme 3. Synthesis of the allylamines **13** and **15**. Reagents and conditions: (a) $(Boc)_2O$, TEA, cat. DMAP, DCM, rt, 14 h, 93%; (b) BnCl, K_2CO_3, CH_3CN, reflux, 3 h, 89%; (c) $ClCOCH_2CO_2Me$, TEA, cat. DMAP, DCM, −30 °C to rt, 16 h, 86%.

The next step of our synthetic approach (Table 1) was the formation of the α-substituted β-amino esters **16** and **17** as precursors for the subsequent RCM. The required substitution

Table 1. Synthesis of the RCM precursors **16** and **17**[a]



Entry	Substrate	R^1	R^2	X	Product (yield, %)
1	**13b**	Bn	H	CH_2	**16a** (96)
2	**13b**	Bn	CH_2OTBS	CH_2	**16b** (70)
3	**15**	Bn	H	C=O	**16c** (70)
4	**15**	Bn	CH_2OTBS	C=O	**16d** (65)
5	**13a**	Boc	H	CH_2	**16e** (62)
6	**13a**	Boc	CH_2OTBS	CH_2	**16f** (82)
7	**16b**	Bn	CH_2OH	CH_2	**17a** (65)
8	**16d**	Bn	CH_2OH	C=O	**17b** (79)
9	**16f**	Boc	CH_2OH	CH_2	**17c** (79)

[a] Reagents and conditions: (a) for **13**: LDA, HMPT, THF, −40 °C, 5 h; (b) for **15**: LiHMDS, THF, −50 °C to rt, 14 h; (c) HCl in THF, rt, 25 min.

at the α-carbon of esters **13** and **15** with bromoallyl precursor **4** turned out to be a crucial step in our reaction sequence. Deprotonation of **15** employing LiHMDS, followed by the addition of the appropriate electrophile **4** easily rendered the corresponding substitution products **16c** and **16d** in good yields. In case of **13**, however, generation of the intermediate carbanion utilizing a variety of commercially available bases such as LiHMDS or KHMDS, NaH, and LDA followed by the subsequent addition of allylbromide did not give rise to any of the desired product. Nevertheless, the use of HMPA as carbanion-stabilizing additive and freshly prepared LDA easily rendered the substituted β-amino esters **16** in high yields.[16,17]

Selective cleavage of the TBS group in **16b**, **d**, and **16f** proceeded smoothly and resulted in formation of the hydroxymethylated compounds **17a–c**.

2.2. Synthesis of the azepine core structure via RCM

With the acyclic diolefins **16** and **17** in hand, we then studied the outcome of the RCM reaction employing Grubbs catalysts 1 (**6**) and 2 (**7**) as outlined in Table 2. All RCM reactions were run with 1 mmol of the appropriate diolefinic precursor and 5 mol% of the corresponding catalyst in DCM at 40 °C for 8 h. Due to the rather sluggish reaction employing Grubbs catalyst 1, the reaction mixtures were stirred for an additional 12 h at room temperature.

In general, substrates bearing basic amine moieties are believed to be incompatible with ruthenium catalysts.[1] In contrast to that, the six-membered alkaloid coniine has recently been obtained in high yield via an RCM reaction employing a tertiary amine as precursor and Grubbs catalyst **6**.[18] Hence, we subjected diene **16a** to our standardized reaction conditions. However, the corresponding azepine **18a** was only formed in low yield applying **6** (Table 2, entry 1), whereas we observed decomposition of the second generation catalyst during this reaction.

In case of substrates **16c** and **16e**, in which the electronic environment of the nitrogen had been changed through implementation of neighboring electron withdrawing groups (amide vs carbamate), both catalysts rendered the desired azepines **18b** and **18e** in comparably high yields, indicating that the precursors bearing either an amide functionality (**16c**) or a Boc-protecting group at the nitrogen (**16e**) were suitable as starting material for the RCM reaction.

To investigate the dependency of the outcome of the RCM reaction on the presence of a substituent attached to one of the terminal alkene moieties, we exposed *gem*-disubstituted olefins (**16d**, **16f**, **17b**, and **17c**) to ruthenium catalysts **6** and **7**. It is remarkable that in all cases using catalyst **6**, the substituted azepines **18c**, **d**, **f**, and **18g** could be obtained in moderate yields. To the best of our knowledge, seven-membered azacycles bearing a substituent at the alkene moiety have not yet been successfully synthesized utilizing **6**. Moreover, yields even improved surprisingly applying **6** with increasing steric demand of the substituent at the alkene moiety (OH vs OTBS, Table 2, entries 3, 4, 6, and 7).

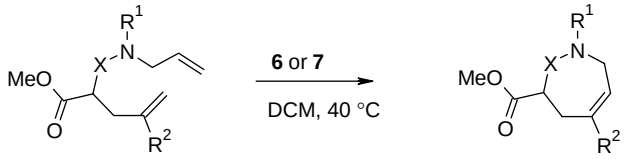
As expected, **7** overall performed significantly better giving rise to the desired azepines **18c**, **d**, **f**, and **18g** with yields ranging from 74–95%. However, yields dropped slightly for substrates bearing the bulkier TBS protecting group. Furthermore, we noticed that the *N*-Boc-protected substrates **16f** and **17c** in general gave higher yields in comparison to the analogous amide derivatives **16d** and **17b** employing either catalyst **6** or **7**.

These results clearly show that the outcome of the RCM reaction in case of these seven-membered azacycles is not only dependent on the substitution pattern of the alkene moieties, but also strongly depends upon the nature of the electron withdrawing group implemented in the RCM precursors (**16** and **17**) and thus on the concomitantly resulting geometry of the nitrogen atom (amide vs carbamate).

3. Conclusion

In summary we have developed a short and highly efficient synthetic strategy towards the hitherto hardly known

Table 2. Synthesis of substituted 2,3,4,7-tetrahydro-1*H*-azepines **18**



Entry	Substrate	R^1	R^2	X	Compound	Catalyst **6** yield (%)[a]	Catalyst **7** yield (%)[a]
1	**16a**	Bn	H	CH_2	**18a**	8[b]	0[c]
2	**16c**	Bn	H	C=O	**18b**	88	90
3	**17b**	Bn	CH_2OH	C=O	**18c**	16[b]	81
4	**16d**	Bn	CH_2OTBS	C=O	**18d**	23[b]	74
5	**16e**	Boc	H	CH_2	**18e**	87	86
6	**17c**	Boc	CH_2OH	CH_2	**18f**	37[b]	95
7	**16f**	Boc	CH_2OTBS	CH_2	**18g**	44[b]	87

[a] Reported yields refer to the analytically pure product obtained after column chromatography.
[b] Remaining starting material could be re-isolated.
[c] Decomposition of Grubbs 2 catalyst observed; starting material nearly quantitatively re-isolated.

substituted azepines of type **18** based on inexpensive and commercially available starting material. Derivative **18g** for example is accessible via a six-step sequence in 30% overall yield. This core structure can easily be modified by means of standard synthetic chemistry giving rise to a variety of putative pharmacologically active derivatives and thus enables us to probe structure–activity relationships in detail. To our knowledge, utilizing **6** in our reaction pathway represents the first synthesis of seven-membered azacycles bearing a substituent at the alkene moiety. Furthermore, we have presented a reliable large scale synthetic sequence towards bromide **11**, which serves as an interesting building block.

4. Experimental

4.1. General

Reported yields refer to the analytically pure product obtained by distillation or column chromatography. All proton and carbon nuclear magnetic resonance spectra were recorded on a 500 MHz spectrometer (^{1}H NMR: 500 MHz, ^{13}C NMR: 125 MHz). Chemical shifts are stated in parts per million (ppm) and were referenced to TMS at 0.00 ppm (^{1}H) except for compounds containing a silyl protecting group, which were referenced to the residual $CHCl_3$ in $CDCl_3$ at 7.24 ppm and to $CDCl_3$ at 77.0 ppm (^{13}C), respectively. NMR spectra were recorded in $CDCl_3$ unless otherwise indicated. Abbreviations: br dd=broad doublet of doublets, br m=broad multiplet, br s=broad singlet, d=doublet, m=multiplet, sm=symmetric multiplet, q=quartet, s=singlet, t=triplet, ps=pseudo, APT=attached proton test, COM=single pulse complete decoupling experiment. Mass spectra were obtained from a double-focussing sectorfield spectrometer. Combustion analyses were determined on a CH analyzer or a CHN autoanalyzer (only nitrogen). Flash column chromatography was performed using silica gel 60 (50–100 ASTM mesh) or silica gel 60 (40–63 ASTM mesh). TLC was carried out using 0.2 mm aluminium plates coated with silica gel 60 F_{254} and the products were visualized by UV detection, iodine or by utilization of phosphormolybdic acid ('blue stain'). Solvents and reagents that are commercially available were used without further purification unless otherwise noted. Tetrahydrofuran was dried by distillation from sodium/benzophenone. All moisture-sensitive reactions were carried out using oven-dried glassware under a positive pressure of argon. If necessary, solvents were deoxygenated by standard procedures. Grubbs catalysts 1 and 2 were purchased from Sigma-Aldrich.

4.1.1. 2-Hydroxymethyl-acrylic acid methyl ester (8). The title compound was prepared according to literature procedures.[8] Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.58; H, 6.86. Other spectral data were identical to those reported previously.

4.1.2. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-acrylic acid methyl ester (9). To a stirred solution of **8** (19.14 g, 165.0 mmol, 1.0 equiv) in DCM (420 mL) were added TEA (27.83 mL, 198.0 mmol, 1.2 equiv) and DMAP (2.02 g, 16.5 mmol, 0.1 equiv) followed by the dropwise addition of a solution of TBSCl (27.36 g, 181.5 mmol, 1.1 equiv) in DCM at 0 °C. The reaction mixture was allowed to reach room temperature and was stirred for 15 h at ambient temperature. After addition of *t*-BuOMe, the reaction mixture was filtered and the solvent removed under reduced pressure. The resulting slurry was re-dissolved in *t*-BuOMe and washed with a saturated NH_4Cl-solution. The aqueous layer was extracted twice with *t*-BuOMe. The combined organic layers were washed with saturated $NaHCO_3$-solution, brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (100°C/1.5 mbar) afforded 34.71 g (91%) of **9** as a colorless liquid: ^{1}H NMR δ 6.24 (dt, 1H, J=2.0, 2.0 Hz), 5.89 (dt, 1H, J=2.0, 2.0 Hz), 4.35 (t, 2H, J=2.0 Hz), 3.72 (s, 3H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR δ 166.2, 139.6, 123.7, 61.4, 51.5, 25.8, 18.2, −5.5; MS (ES+) *m/z* 231 (21 $[M+H]^+$), 253 (100, $[M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{11}H_{22}O_3SiNa$ $(M+Na)^+$: 253.123593 found 253.124812. Anal. Calcd for $C_{11}H_{22}O_3Si$: C, 57.35; H, 9.63. Found: C, 57.15; H, 9.28.

4.1.3. 2-(*tert*-Butyl-dimethyl-silanyloxymethyl)-prop-2-en-1-ol (10).[9] DIBAL-H (115 mL of a 1.5 M solution in toluene, 172.5 mmol, 2.16 equiv) was added dropwise over a period of 45 min to a stirred solution of **9** (18.43 g, 80.0 mmol, 1.0 equiv) in THF (200 mL) at −78 °C. After 90 min the reaction mixture was slowly warmed to 0 °C, stirred for 30 min and then carefully quenched by addition of 4.5 mL H_2O in 10 mL of THF. Subsequent addition of 300 mL Et_2O and 200 mL of saturated Rochelle's solution produced a gelatin-like solid, which, after addition of 100 mL of a saturated NH_4Cl-solution, was stirred at room temperature until the slurry re-dissolved and a separation of the layers was observed (30 min). The aqueous layer was extracted three times with Et_2O and the combined organic layers were washed twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (100 °C/0.3 mbar) yielded 12.99 g (80%) of **10** as a colorless liquid: ^{1}H NMR δ 5.08 (s, 1H), 5.06 (s, 1H), 4.22 (s, 2H), 4.15 (d, 2H, J=5.7 Hz), 2.00 (t, 1H, J=5.9 Hz), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR δ 147.5, 110.8, 64.9, 64.3, 25.8, 18.2, −5.5; MS (ES+) *m/z* 203 (18, $[M+H]^+$), 225 (100, $[M+Na]^+$). Anal. Calcd for $C_{10}H_{22}O_2Si$: C, 59.35; H, 10.96. Found: C, 59.48; H, 10.72.

4.1.4. (2-Bromomethyl-allyloxy)-*tert*-butyl-dimethyl-silane (11).[13] To a solution of triphenylphosphine (TPP, 7.68 g, 29.3 mmol, 1.1 equiv) in DCM (70 mL), a solution of bromine (4.68 g, 29.3 mmol, 1.1 equiv) in 10 mL of DCM was added dropwise at 0 °C. The reaction mixture was stirred until a colorless precipitate indicated the formation of the desired phosphonium salt, which was then added slowly to a solution of imidazole (2.18 g, 31.9 mmol, 1.2 equiv) and **10** (5.39 g, 26.6 mmol, 1.0 equiv) in 140 mL DCM at 0 °C. After stirring for 30 min maintaining the temperature at 0 °C, the reaction mixture was poured into an ice–water mixture and extracted twice with *t*-BuOMe. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residual slurry was re-dissolved in a small amount of DCM and added dropwise into hexane giving rise to a suspension, which was filtered and the remaining residue was washed several times with hexane. After concentration under vacuum, hexane was added to the residual suspension,

which was filtered again and concentrated under reduced pressure. Column chromatography (hexane/*t*-BuOMe: 22:1) afforded 5.90 g (84%) of **11** as a colorless liquid: ^{1}H NMR δ 5.218 (d, 1H, J=1.4 Hz), 5.215 (d, 1H, J=1.4 Hz), 4.25 (s, 2H), 3.99 (s, 2H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR δ 144.8, 114.7, 63.5, 32.7, 25.9, 18.3, −5.4; MS (ES+) *m/z* 265 (100, $[M(^{79}Br)+H]^+$), 267 (85, $[M(^{81}Br)+H]^+$), 289 (22, $[M(^{81}Br)+Na]^+$). Anal. Calcd for $C_{10}H_{21}BrOSi$: C, 45.28; H, 7.98; Br, 30.12. Found: C, 45.50; H, 7.80; Br, 30.38.

4.1.5. 3-(Allylamino)-propionic acid methyl ester (12). The title compound was prepared according to a modified literature procedure.[14] A solution of methyl acrylate (17.2 g, 200 mmol, 1.0 equiv) and allylamine (11.7 g, 205 mmol, 1.03 equiv) in 250 mL of MeOH was stirred at 40 °C for 4 h. Removal of the solvent under reduced pressure followed by bulb to bulb distillation (105 °C/5 mbar) of the resulting residue gave rise to 21.40 g (75%) of **12** as a colorless oil: ^{1}H NMR δ 5.86 (ddt, 1H, J=17.2, 10.0, 6.0 Hz), 5.18 (ddt, 1H, J=17.2, 1.6, 1.6 Hz), 5.10 (ddt, 1H, J=10.2, 1.4, 1.4 Hz), 3.69 (s, 3H), 3.26 (dt, 2H, J=6.0, 1.4 Hz), 2.87 (t, 2H, J=6.5 Hz), 2.51 (t, 2H, J=6.5 Hz), 1.4 (br s, 1H); ^{13}C NMR δ 172.7, 136.4, 115.5, 51.8, 51.1, 44.2, 34.3; MS (EI) *m/z* 143 (13, M^+), 102 (11), 84 (14), 70 (100), 68 (18), 55 (43); HRMS (EI) *m/z* calcd for $C_7H_{13}NO_2$ 143.094629 found 143.096734. Anal. Calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.55; H, 8.64; N, 9.99.

4.1.6. 3-(Allyl-*tert*-butoxycarbonyl-amino)-propionic acid methyl ester (13a). To a solution of **12** (4.29 g, 30.0 mmol), TEA (5.06 mL, 36.0 mmol, 1.2 equiv) and a catalytic amount of DMAP in DCM at 0 °C, a solution of $(Boc)_2O$ (7.86 g, 36.0 mmol, 1.2 equiv) in DCM was added dropwise over a period of 30 min. The reaction mixture was allowed to reach room temperature and stirred for an additional 14 h. After addition of *t*-BuOMe, the organic layer was washed consecutively with 1% aqueous HCl, a saturated $NaHCO_3$-solution, brine, and finally dried over $MgSO_4$. Removal of the solvents under reduced pressure followed by column chromatography (hexane/ethyl acetate:9:1) gave rise to 6.75 g (93%) of **13a** as a colorless oil. For a large scale preparation, distillation (105 °C/0.6 mbar) of the resulting residue after extractive work up is preferable: ^{1}H NMR (CD_3OD, rotamers, ratio: ~1:1) δ 5.77 (br s, 1H), 5.14 (br s, 1H), 5.12 (br s, 1H), 3.84 (d, 2H, J=5.5 Hz), 3.65 (s, 3H), 3.46 (t, 2H, J=7.0 Hz), 2.56 (t, 2H, J=7.0 Hz), 1.45 (s, 9H); ^{13}C NMR (CD_3OD, rotamers) δ 173.9, 157.1, 135.6, 135.4, 117.4, 116.9, 81.4, 52.3, 51.7, 50.9, 44.4, 34.7, 34.3, 29.0; MS (EI) *m/z* 243 (2, M^+), 187 (100), 170 (90), 156 (96), 142 (96). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 59.30; H, 8.52; N, 5.48.

4.1.7. 3-(Allyl-benzyl-amino)-propionic acid methyl ester (13b).[19] A suspension of **12** (7.16 g, 50.0 mmol, 1.0 equiv), benzyl chloride (6.65 g, 52.5 mmol, 1.05 equiv), and K_2CO_3 (8.295 g, 60.0 mmol, 1.2 equiv) in CH_3CN was refluxed for 3 h, diluted with *n*-hexane (200 mL), and washed with water and brine. The aqueous layer was extracted twice with hexane, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Bulb to bulb distillation (150 °C/0.4 mbar) of the remaining oily residue afforded 10.38 g (89%) of **13b** as a colorless oil: ^{1}H NMR δ 7.32–7.21 (m, 5H), 5.85 (ddt, 1H, J=17.2, 10.3, 6.5 Hz), 5.18 (psdd, 1H, J=17.2, 1.6 Hz), 5.14 (psd, 1H, J=10.1 Hz), 3.65 (s, 3H), 3.60 (s, 2H), 3.08 (d, 2H, J=6.5 Hz), 2.81 (t, 2H, J=7.0 Hz), 2.49 (t, 2H, J=7.0 Hz); ^{13}C NMR δ 172.6, 139.1, 135.4, 128.5, 127.9, 126.7, 117.1, 57.8, 56.4, 51.1, 48.8, 32.4; MS (EI) *m/z* 233 (5, M^+), 192 (10), 160 (70), 142 (58), 91 (100). Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 72.08; H, 7.99; N, 6.25.

4.1.8. Allylbenzylamine (14). The title compound was prepared according to a literature procedure.[15] ^{1}H NMR δ 7.35–7.23 (m, 5H), 5.94 (ddt, 1H, J=17.2, 10.3, 6.0 Hz), 5.20 (ddt, 1H, J=17.2, 1.6, 1.6 Hz), 5.12 (ddt, 1H, J=10.1, 1.7, 1.4 Hz), 3.80 (s, 2H), 3.28 (psdt, 2H, J=6.0, 1.4 Hz); ^{13}C NMR δ 140.2, 136.7, 128.2, 128.0, 126.8, 115.8, 53.1, 51.6; MS (EI) *m/z* 147 (38, M^+), 146 (61), 106 (28), 91 (100), 56 (12); HRMS (EI) calcd for $C_{10}H_{13}N$ 147.1048 found 147.1043.

4.1.9. *N*-Allyl-*N*-benzyl-malonamic acid methyl ester (15). To a solution of **14** (2.95 g, 20.0 mmol, 1.0 equiv), TEA (3.37 mL, 24.0 mmol, 1.2 equiv), and a catalytic amount of DMAP in DCM at −30 °C, a solution of methyl malonyl chloride (2.57 mL, 24.0 mmol, 1.2 equiv) in 70 mL of DCM was added dropwise maintaining the temperature. After additional stirring for 16 h at room temperature, the reaction mixture was diluted with Et_2O and consecutively washed once with 1% HCl, a saturated $NaHCO_3$-solution, three times with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Column chromatography (hexane/ethyl acetate: 2.5:1) of the oily residue gave rise to 4.25 g (86%) of **15** as a colorless oil: ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.39–7.17 (m, 5H), 5.83–5.69 (sm, 1H), 5.27–5.14 (m, 2H), 4.63 (s, 1.29H), 4.52 (s, 0.78H), 4.03 (psd, 0.79H, J=6.0 Hz), 3.82 (psd, 1.31H, J=5.5 Hz), 3.77 (s, 1.88H), 3.73 (s, 1.15H), 3.52 (s, 1.22H), 3.49 (s, 0.76H); ^{13}C NMR (rotamers) δ 167.9, 167.8, 166.3, 166.1, 136.7, 135.9, 132.1, 132.0, 128.8, 128.4, 128.14, 128.07, 127.9, 127.6, 127.3, 126.2, 117.6, 117.1, 52.2, 50.6, 49.5, 48.2, 48.0, 41.0, 40.7; MS (EI) *m/z* 248 (20, M^++H), 247 (85, M^+), 216 (37), 207 (59), 206 (100), 174 (28), 156 (37), 146 (53), 91 (49); HRMS (EI) *m/z* calcd for $C_{14}H_{17}NO_3$ 247.1208 found 247.1211.

4.2. General procedure for the synthesis of the RCM precursors 16a, 16b, 16e, and 16f

To a solution of *n*-BuLi (1.6 mol in hexane, 1.5 equiv) in THF, neat diisopropyl amine (1.5 equiv) was added at −78 °C. The reaction mixture was allowed to reach 0 °C, stirred for additional 15 min, and cooled again to −78 °C. A solution of the respective ester (**13a**, **b**, 1.5 equiv) dissolved in THF was added slowly. After stirring for 30 min, a solution of the respective allylbromide derivative (1.0 equiv) in HMPT (1.0 equiv) was then added slowly. The reaction mixture was warmed to −40 °C and kept at this temperature until TLC indicated the completion of the reaction (approx. 5 h). After subsequent addition of Et_2O and a saturated NH_4Cl-solution, the organic layer was separated and the aqueous layer was extracted twice with ether. The combined organic layers were washed with brine,

dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by flash chromatography.

4.2.1. 2-[(Allyl-benzyl-amino)-methyl]-pent-4-enoic acid methyl ester (16a).[19] The title compound was prepared according to the general procedure utilizing **13b** (2.80 g, 12.0 mmol, 1.5 equiv), and 0.968 g of allylbromide (8 mmol, 1.0 equiv). Column chromatography (hexane/ethyl acetate: 14:1) gave rise to 2.10 g (96%) of **16a** as colorless oil: ^{1}H NMR δ 7.31–7.20 (m, 5H), 5.81 (ddt, 1H, J=17.0, 10.6, 6.2 Hz), 5.70 (ddt, 1H, J=17.2, 10.3, 6.9 Hz), 5.17–5.11 (m, 2H), 5.03 (psdd, 1H, J=17.0, 1.6 Hz), 4.99 (psd, 1H, J=10.1 Hz), 3.67 (d, 1H, J=13.8 Hz), 3.66 (s, 3H), 3.47 (d, 1H, J=13.8 Hz), 3.10 (dd, 1H, J=14.2, 6.0 Hz), 2.98 (dd, 1H, J=14.2, 6.9 Hz), 2.80–2.71 (m, 2H), 2.55–2.46 (m, 1H), 2.32–2.21 (m, 2H); ^{13}C NMR δ 174.9, 139.2, 135.4, 135.1, 128.7, 128.0, 126.7, 117.2, 116.5, 58.3, 56.7, 55.4, 51.1, 44.5, 34.4; MS (EI) m/z 273 (25, M^+), 272 (33, M^+-H), 258 (44), 232 (32), 182 (68), 160 (100), 91 (66); HRMS (EI) m/z calcd for $C_{17}H_{23}NO_2$ 273.1729 found 273.1741. Anal. Calcd for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.77; H, 8.38; N, 4.95.

4.2.2. 2-[(Allyl-benzyl-amino)-methyl]-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16b). The title compound was prepared according to the general procedure utilizing **13b** (2.1 g, 9.0 mmol, 1.5 equiv) and 1.59 g (6.0 mmol, 1.0 equiv) of bromide **11**. Column chromatography (hexane/ethyl acetate: 10:1) gave rise to 1.75 g (70%) of **16b** as colorless oil: ^{1}H NMR δ 7.27–7.24 (m, 5H), 5.83–5.75 (sm, 1H), 5.15–5.10 (m, 2H), 5.01 (d, 1H, J=1.3 Hz), 4.80 (s, 1H), 4.03 (d, 1H, J=15.5 Hz), 4.00 (d, 1H, J=14.9 Hz), 3.69 (d, 1H, J=13.8 Hz), 3.62 (s, 3H), 3.43 (d, 1H, J=13.8 Hz), 3.09 (dd, 1H, J=14.0, 5.8 Hz), 2.95 (dd, 1H, J=14.2, 7.1 Hz), 2.88 (br dd, 1H, J=15.4, 7.1 Hz), 2.77 (dd, 1H, J=12.6, 9.7 Hz), 2.46 (dd, 1H, J=12.6, 5.7 Hz), 2.20 (d, 2H, J=7.6 Hz), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR δ 175.2, 145.7, 139.2, 135.5, 128.7, 128.0, 126.8, 117.3, 110.4, 65.6, 58.4, 56.7, 56.1, 51.2, 43.5, 33.5, 25.8, 18.3, −5.4; MS (EI) m/z 417 (17, M^+), 402 (12), 376 (17), 326 (40), 284 (41), 160 (100), 91 (37); HRMS (EI) m/z calcd for $C_{24}H_{39}NO_3Si$ 417.2699 found 417.2703. Anal. Calcd for $C_{24}H_{39}NO_3Si$: C, 69.02; H, 9.41; N, 3.35. Found: C, 69.07; H, 9.38; N, 3.25.

4.2.3. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-pent-4-enoic acid methyl ester (16e). The title compound was prepared according to the general procedure utilizing **13a** (2.55 g, 10.5 mmol, 1.5 equiv), and 0.85 g (7.0 mmol, 1.0 equiv) allylbromide. Column chromatography (hexane/ethyl acetate: 14:1) yielded 1.20 g (62%) of **16e** as colorless oil: ^{1}H NMR (CD_3OD, rotamers, ratio: 1:1) δ 5.75 (sm, 2H), 5.17–4.98 (m, 4H), 3.94–3.80 (br t, 1H), 3.79–3.69 (br s, 1H), 3.65 (s, 3H), 3.36 (d, 1H, J=6.2 Hz), 3.35 (d, 1H, J=8.5 Hz), 2.34–2.27 (m, 1H), 2.23–2.15 (m, 2H), 1.46 (s, 4.5H), 1.44 (s, 4.5H); ^{13}C NMR (rotamers) δ 174.3, 155.1, 155.0, 134.4, 133.7, 116.8, 116.2, 115.7, 79.5, 79.4, 51.3, 50.5, 49.7, 48.5, 48.0, 44.5, 44.1, 34.1, 28.0; MS (ES+) m/z 306 (100, $[M+Na]^+$), 589 (18, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{15}H_{25}NO_4Na$ 306.168128 found 306.166972. Anal. Calcd for $C_{15}H_{25}NO_4$: C, 63.58; H, 8.89; N, 4.94. Found: C, 63.10; H, 8.54; N, 4.84.

4.2.4. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16f). The title compound was prepared according to the general procedure employing **13a** (1.82 g, 7.5 mmol, 1.5 equiv), and 1.33 g of bromide **11** (5.0 mmol, 1.0 equiv). Column chromatography (hexane/ethyl acetate: 14:1) afforded 1.76 g (82%) of **16f** as colorless oil: ^{1}H NMR (DMSO-d_6) δ 5.72 (br s, 1H), 5.09 (dd, 1H, J=10.0, 1.5 Hz), 5.05 (d, 1H, J=17.0 Hz), 4.99 (s, 1H), 4.78 (s, 1H), 4.03 (s, 2H), 3.84–3.73 (br s, 1H), 3.64 (dd, 1H, J=16.0, 5.0 Hz), 3.55 (s, 3H), 3.30–3.24 (br m, 2H), 2.88 (sm, 1H), 2.20 (dd, 1H, J=14.3, 9.0 Hz), 2.09 (dd, 1H, J=14.3, 6.0 Hz), 1.37 (s, 9H), 0.89 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (DMSO-d_6, rotamers) δ 174.8, 155.3, 145.3, 133.9, 133.7, 116.5, 116.0, 110.8, 110.7, 79.9, 79.5, 65.5, 51.6, 50.7, 49.9, 49.1, 48.9, 43.6, 43.2, 33.2, 28.3, 25.8, 18.3, −5.5; MS (ES+) m/z 428 (43, $[M+H]^+$), 450 (100, $[M+Na]^+$), 877 (70, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{22}H_{41}NO_5NaSi$ 450.265172 found 450.265767. Anal. Calcd for $C_{22}H_{41}NO_5Si$: C, 61.79; H, 9.66; N, 3.28. Found: C, 61.71; H, 9.51; N, 3.13.

4.3. General procedure for the synthesis of the RCM precursors 16c and 16d

To a solution of LiHMDS (1.0 mol in THF, 1.1 equiv) in THF, *N*-allyl-*N*-benzyl-malonamic acid methyl ester **15** in THF (1.0 equiv) was added at −50 °C, and gently warmed to −10 °C. After stirring for additional 30 min, the reaction mixture was cooled again to −50 °C and a solution of the respective allylbromide derivative (1.0 equiv) in THF was added slowly. The reaction mixture was warmed to room temperature and stirred for an additional 14 h at ambient temperature, diluted with Et_2O and washed with NH_4Cl-solution. The aqueous layer was extracted twice with Et_2O and the combined organic layers were washed with water, twice with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The remaining product was purified by flash chromatography.

4.3.1. 2-(Allyl-benzyl-carbamoyl)-pent-4-enoic acid methyl ester (16c). The title compound was prepared according to the general procedure employing **15** (1.38 g, 5.6 mmol), and 0.71 g of allylbromide (5.9 mmol, 1.06 equiv). Column chromatography (hexane/ethyl acetate: 3:1) furnished 1.11 g (70%) of **16c** as colorless oil: ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.38–7.18 (m, 5H), 5.83–5.67 (m, 4ddt overlapping, 2H), 5.26–5.05 (m, 4ddt overlapping, 4H), 4.79 (d, 0.66H, J=14.7 Hz), 4.68 (d, 0.40H, J=17.2 Hz), 4.51 (d, 0.41H, J=17.2 Hz), 4.47 (d, 0.64H, J=14.7 Hz), 4.13 (psdd, 0.41H, J=15.4, 5.5 Hz), 3.99 (psdd, 0.68H, J=17.9, 4.1 Hz), 3.91 (psdd, 0.44H, J=15.4, 5.8 Hz), 3.81 (psdd, 0.77H, J=17.7, 4.6 Hz), 3.73 (s, 1.9H), 3.69 (s, 1.2H), 3.67 (t, 1H, J=7.2 Hz), 2.79–2.63 (sm, 2H); ^{13}C NMR (rotamers) δ 169.6, 169.5, 168.4, 168.2, 136.9, 136.1, 134.5, 134.4, 132.3, 132.2, 128.6, 128.3, 127.8, 127.4, 127.1, 126.2, 117.3, 117.21, 117.19, 116.97, 52.1, 50.1, 49.0, 48.5, 48.4, 48.3, 48.1, 33.3; MS (EI) m/z 288 (75, M^++H), 287 (100, M^+), 256 (62), 246 (74), 228 (70), 196 (48), 174 (37), 146 (55),

91 (42); HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3$ 287.1521 found 287.1525. Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.06; H, 7.37; N, 4.87. Found: C, 70.86; H, 7.37; N, 4.73.

4.3.2. 2-(Allyl-benzyl-carbamoyl)-4-(*tert*-butyl-dimethyl-silanyloxymethyl)-pent-4-enoic acid methyl ester (16d). The title compound was prepared according to the general procedure utilizing 1.484 g (6.0 mmol, 1.0 equiv) of **15** and 1.687 g (6.36 mmol, 1.06 equiv) of bromide **11** to furnish 1.69 g (65%) of **16d** as colorless oil after column chromatography (hexane/ethyl acetate: 4:1): ^{1}H NMR (rotamers, ratio: 1.6:1) δ 7.35–7.15 (m, 5H), 5.72 (sm, 1H), 5.23–5.08 (m, 2H, 4ddt, overlapping), 5.06 (br d, 0.66H, J=1.2 Hz), 5.03 (br d, 0.42H, J=1.4 Hz), 4.85 (br d, 0.64H, J=1.2 Hz), 4.78 (br d, 0.39H, J=1.0 Hz), 4.67 (d, 0.63H, J=14.9 Hz), 4.62 (d, 0.41H, J=17.0 Hz), 4.54 (d, 0.40H, J=17.2 Hz), 4.50 (d, 0.66H, J=14.9 Hz), 4.10–3.91 (m, 3.4H), 3.91–3.80 (m, 1.7H), 3.69 (s, 1.9H), 3.65 (s, 1.2H), 2.76–2.57 (sm, 2H), 0.87 (s, 5.68H), 0.84 (s, 3.77H), 0.03 (s, 3.64H), −0.02 (s, 2.44H); ^{13}C NMR (rotamers) δ 169.7, 169.6, 168.5, 168.4, 145.0, 144.8, 137.0, 136.1, 132.5, 132.3, 128.6, 128.3, 127.8, 127.4, 127.1, 126.3, 117.2, 117.1, 111.2, 111.0, 65.9, 65.7, 52.0, 50.1, 49.0, 48.3, 48.1, 47.8, 47.6, 32.0, 25.6, 18.04, 18.01, −5.69, −5.72; MS (EI) *m/z* 431 (10, M^+), 375 (60), 374 (100), 91 (17); HRMS (EI) *m/z* calcd for $C_{24}H_{37}NO_4Si$ 431.2492 found 431.2503. Anal. Calcd for $C_{24}H_{37}NO_4Si$: C, 66.78; H, 8.64; N, 3.24. Found: C, 66.64; H, 8.84; N, 3.17.

4.4. General procedure for the synthesis of hydroxymethylated compounds 17a–c

The respective TBS-protected derivative (**16b**, **16d**, or **16f**) was dissolved in a 30:1 mixture of THF and aqueous HCl 32% and stirred at room temperature for 25 min. After addition of a saturated $NaHCO_3$-solution, the reaction mixture was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated under vacuum. Column chromatography of the oily residue afforded the corresponding hydroxymethyl derivative **17a–c**.

4.4.1. 2-[(Allyl-benzyl-amino)-methyl]4-hydroxymethyl-pent-4-enoic acid methyl ester (17a). According to the general procedure utilizing 1.286 g (3.1 mmol) of **16b**, 0.610 g (65%) of 2-[(allyl-benzyl-amino)-methyl]-4-hydroxymethyl-pent-4-enoic acid methyl ester (**17a**) was obtained after column chromatography (hexane/ethyl acetate: 3:1) as colorless oil: ^{1}H NMR δ 7.32–7.22 (m, 5H), 5.87–5.78 (sm, 1H), 5.16 (d, 1H, J=17.4 Hz), 5.15 (d, 1H, J=9.6 Hz), 5.02 (s, 1H), 4.86 (s, 1H), 4.04 (s, 2H), 3.69–3.62 (sm, 1H), 3.66 (s, 3H), 3.51 (br d, 1H, J=13.5 Hz), 3.10 (dd, 1H, J=14.2, 6.0 Hz), 3.02 (dd, 1H, J=14.0, 6.4 Hz), 2.97–2.89 (sm, 1H), 2.77 (dd, 1H, J=12.6, 12.4 Hz), 2.53 (dd, 1H, J=12.4, 6.0 Hz), 2.36–2.25 (m, 2H), 2.07 (br s, 1H); ^{13}C NMR δ 175.3, 146.0, 138.8, 135.1, 128.8, 128.0, 126.8, 117.5, 111.5, 65.4, 58.2, 56.6, 55.8, 51.3, 43.4, 33.7; MS (EI) *m/z* 303 (3, M^+), 230 (64), 212 (13), 180 (95), 161 (61), 160 (100), 91 (61); HRMS (EI) *m/z* calcd for $C_{18}H_{25}NO_3$ 303.1834 found 303.1800. Anal. Calcd for $C_{18}H_{25}NO_3$: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.05; H, 8.78; N, 4.57.

4.4.2. 2-(Allyl-benzyl-carbamoyl)-4-hydroxymethyl-pent-4-enoic acid methyl ester (17b). According to the general procedure employing 1.530 g (3.5 mmol) of **16d**, 0.871 g (79%) of 2-(allyl-benzyl-carbamoyl)-4-hydroxymethyl-pent-4-enoic acid methyl ester (**17b**) was obtained as colorless oil after column chromatography (hexane/ethyl acetate: 1:1): ^{1}H NMR (rotamers, ratio: ~1.6:1) δ 7.38–7.17 (m, 5H), 5.80–5.70 (m, 1H), 5.24 (dd, 0.66H, J=10.3, 1.2 Hz), 5.20 (psdd, 0.53H, J=5.4, 0.9 Hz), 5.17 (pst, 0.47H, J=1.4 Hz), 5.12 (psdd, 0.45H, J=17.2, 1.4 Hz), 5.08 (d, 0.60H, J=0.9 Hz), 5.03 (d, 0.40H, J=0.9 Hz), 4.91 (s, 0.63H), 4.81 (s, 0.36H), 4.80 (d, 0.64H, J=14.7 Hz), 4.69 (d, 0.38H, J=17.2 Hz), 4.53 (d, 0.39H, J=17.0 Hz), 4.44 (d, 0.64H, J=14.9 Hz), 4.19 (dd, 0.42H, J=15.4, 4.8 Hz), 4.07 (s, 1.2H), 4.01 (sm, 0.76H), 3.96 (s, 0.70H), 3.93–3.80 (sm, 2.20H), 3.73 (s, 1.89H), 3.68 (s, 1.16H), 2.83–2.68 (m, 2H), 2.20 (br s, 1H); ^{13}C NMR (rotamers) δ 170.0, 169.8, 168.8, 168.7, 145.6, 145.4, 136.8, 136.1, 132.2, 132.1, 128.7, 128.4, 127.9, 127.6, 127.3, 126.4, 117.5, 117.3, 112.5, 112.3, 65.8, 65.7, 52.3, 50.2, 49.2, 48.6, 48.5, 48.2, 48.0, 31.9; MS (EI) *m/z* 317 (15, M^+), 286 (19), 285 (55), 245 (33), 244 (100), 194 (60), 147 (36), 146 (75), 106 (54), 91 (44); HRMS (EI) *m/z* calcd for $C_{18}H_{23}NO_4$ 317.1627 found 317.1589. Anal. Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 67.88; H, 7.63; N, 4.43.

4.4.3. 2-[(Allyl-*tert*-butoxycarbonyl-amino)-methyl]-4-hydroxymethyl-pent-4-enoic acid methyl ester (17c). The title compound was prepared according to the general procedure employing 4.786 g (11.19 mmol) of **16f**. After column chromatography (hexane/ethyl acetate: 2:1) 2.77 g (79%) of **17c** were obtained as colorless oil: ^{1}H NMR (rotamers, ratio: ~1:1) δ 5.80–5.67 (br s, 1H), 5.09 (psddd, 2H, J=17.7, 10.3, 1.6 Hz), 4.97 (d, 1H, J=1.6 Hz), 4.82 (t, 1H, J=5.5 Hz), 4.75 (s, 1H), 3.84 (d, 2H, J=5.5 Hz), 3.83–3.75 (br s, 1H), 3.69–3.61 (br s, 1H), 3.57 (s, 3H), 3.31–3.21 (sm, 2H), 2.90 (br s, 1H), 2.21 (dd, 1H, J=14.7, 9.3 Hz), 2.08 (dd, 1H, J=14.7, 5.7 Hz), 1.38 (s, 9H); ^{13}C NMR (rotamers) δ 175.0, 174.9, 155.5, 155.2, 145.6, 133.7, 116.5, 116.0, 112.2, 111.7, 79.9, 65.4, 51.7, 50.9, 49.9, 48.9, 43.7, 43.3, 33.6, 28.2; MS (ES+) *m/z* 336 (100, $[M+Na]^+$), 649 (28, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{16}H_{27}NO_5Na$ 336.178693 found 336.178391. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.38; H, 8.44; N, 4.98. Anal. Calcd for $C_{16}H_{27}NO_5$: C, 61.32; H, 8.68; N, 4.47. Found: C, 61.01; H, 8.68; N, 4.48.

4.5. General procedure for the synthesis of 18a–g

Method A. A solution of the corresponding precursor (**16a**, **16c–f**, and **17b**, **c**) in 90 mL of thoroughly degassed DCM was heated to 40 °C and bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride **6** (Grubbs 1 catalyst, 5 mol%), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature and stirred for an additional 12 h. After quenching the reaction through addition of 20 mL of DMSO and subsequent stirring for 12 h, the reaction mixture was extracted three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, and filtered.[20] Removal of the solvent under reduced pressure followed by column

chromatography of the oily residue gave rise to the corresponding azepines **18**.

Method B. A solution of the corresponding precursor (**16a**, **16c–f**, and **17b**, **c**) in 90 mL of thoroughly degassed DCM was heated to 40 °C and benzyliden-[1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro-(tricyclohexylphosphine)-ruthenium **7** (Grubbs 2 catalyst, 5 mol%), dissolved in 5 mL of degassed DCM, was added to the reaction mixture. After stirring for 8 h at 40 °C, the reaction mixture was allowed to reach room temperature. After quenching the reaction through addition of 20 mL of DMSO and subsequent stirring for 12 h, the reaction mixture was washed three times with diluted NaCl-solution, twice with brine, dried over $MgSO_4$, and filtered.[20] Removal of the solvent under reduced pressure followed by column chromatography of the oily residue gave rise to the corresponding azepines **18**.

4.5.1. 1-Benzyl-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18a). The title compound was prepared according to the general procedure (Method A) employing 0.311 g (1.14 mmol) of **16a** and 47 mg (0.057 mmol, 5 mol%) of **6**. Column chromatography (hexane/ethyl acetate: 14:1) gave rise to 0.235 g (76%) of the recovered starting material and to 0.023 g (8%) of **18a** as colorless oil: ^{1}H NMR δ 7.35–7.21 (m, 5H), 5.86 (psquint, 1H, J=11.0, 5.5 Hz), 5.66 (sm, 1H), 3.68 (s, 2H), 3.63 (s, 3H), 3.28–3.20 (m, 3H), 3.07 (dd, 1H, J=13.1, 9.1 Hz), 2.88–2.81 (sm, 1H), 2.62–2.53 (m, 1H), 2.53–2.46 (m, 1H); ^{13}C NMR δ 174.8, 138.7, 130.0, 129.7, 128.9, 128.3, 127.1, 60.2, 58.9, 53.6, 51.7, 41.8, 29.5; MS (EI) *m/z* 246 (15, M^++H), 245 (71, M^+), 244 (18), 214 (30), 186 (30), 158 (25), 155 (31), 154 (100), 121 (31), 120 (27), 119 (35), 94 (27), 91 (54), 88 (57), 84 (88); HRMS (EI) *m/z* calcd for $C_{15}H_{19}NO_2$ 245.1416 found 245.1413.

4.5.2. 1-Benzyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18b). According to the general procedure (Method A) utilizing 0.339 g (1.18 mmol) of **16c** and 49 mg (0.059 mmol, 5 mol%) of **6**, 0.268 g (88%) of **18b** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil: ^{1}H NMR δ 7.34–7.21 (m, 5H), 5.77–5.72 (sm, 1H), 5.63–5.58 (sm, 1H), 4.75 (d, 1H, J=14.9 Hz), 4.54 (d, 1H, J=14.9 Hz), 4.18 (sm, 1H), 4.14 (dd, 1H, J=12.2, 3.7 Hz), 3.80 (s, 3H), 3.42 (dd, 1H, J=17.7, 7.1 Hz), 2.83–2.72 (sm, 1H), 2.62–2.53 (sm, 1H); ^{13}C NMR δ 170.7, 169.8, 136.7, 129.4, 128.3, 127.6, 127.2, 124.1, 51.9, 51.1, 48.4, 44.9, 27.2; MS (EI) *m/z* 260 (36, M^++H), 259 (100, M^+), 228 (42), 200 (14), 168 (66), 146 (63), 136 (31), 108 (28), 101 (32), 91 (41); HRMS (EI) *m/z* calcd for $C_{15}H_{17}NO_3$ 259.1208 found 259.1213. Following the general procedure (Method B) employing 0.287 g (1.00 mmol) of **16c** and 42 mg (0.05 mmol, 5 mol%) of **7**, 0.233 g (90%) of **18b** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method A.

4.5.3. 1-Benzyl-5-hydroxymethyl-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18c). According to the general procedure (Method B) utilizing 0.331 g (1.04 mmol) of **17b** and 44 mg (0.052 mmol, 5 mol%) of **7**, 0.243 g (81%) of **18c** was obtained after column chromatography (hexane/ethyl acetate: 3:1) as colorless oil: ^{1}H NMR δ 7.35–7.21 (m, 5H), 5.69–5.65 (sm, 1H), 4.62 (s, 2H), 4.16 (br d, 1H, J=17.9 Hz), 4.12 (dd, 1H, J=12.1, 3.7 Hz), 3.98 (s, 2H), 3.81 (s, 3H), 3.48 (dd, 1H, J=17.9, 7.3 Hz), 2.77–2.69 (sm, 1H), 2.58 (d, 1H, J=18.3 Hz), 1.70 (s, 1H); ^{13}C NMR δ 170.8, 170.0, 140.6, 136.6, 128.4, 127.7, 127.3, 118.8, 66.5, 52.2, 51.1, 48.0, 44.7, 27.5; MS (ES+) *m/z* 290 (11, $[M+H]^+$), 312 (100, $[M+Na]^+$), 601 (85, $[2M+Na]^+$), 890 (17, $[3M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{16}H_{19}NO_4Na$ 312.121178 found 312.120229. According to the general procedure (Method A) employing 0.331 g (1.04 mmol) of **17b** and 43 mg (0.052 mmol, 5 mol%) of **6**, 0.048 g (16%) of **18c** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method B.

4.5.4. 1-Benzyl-5-(*tert*-butyl-dimethyl-silanyloxymethyl)-2-oxo-2,3,4,7-tetrahydro-1*H*-azepine-3-carboxylic acid methyl ester (18d). The title compound was prepared according to the general procedure (Method B) employing 0.432 g (1.00 mmol) of **16d** and 42 mg (0.05 mmol, 5 mol%) of **7**. Column chromatography (hexane/ethyl acetate: 3:1) gave rise to 0.29 g (74%) of **18d** as colorless oil: ^{1}H NMR δ 7.31–7.19 (m, 5H), 5.66–5.62 (sm, 1H), 4.61 (s, 2H), 4.18–4.11 (sm, 1H), 4.08 (dd, 1H, J=12.4, 3.7 Hz), 3.94 (s, 2H), 3.78 (s, 3H), 3.46 (dd, 1H, J=17.7, 7.6 Hz), 2.68–2.59 (br m, 1H), 2.47 (br d, 1H, J=18.3 Hz), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR δ 170.8, 170.0, 140.3, 136.8, 128.5, 127.8, 127.4, 117.8, 66.8, 52.3, 51.3, 48.2, 44.8, 27.5, 25.8, 18.2, −5.5; MS (EI) *m/z* 403 (23, M^+), 388 (19), 346 (100), 271 (69), 258 (23), 213 (51), 91 (33); HRMS (EI) *m/z* calcd for $C_{22}H_{33}NO_4Si$ 403.2179 found 403.2181. Following the general procedure (Method A) employing 0.432 g (1.00 mmol) of **16d** and 41 mg (0.05 mmol, 5 mol%) of **6**, 0.093 g (23%) of **18d** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method B.

4.5.5. 2,3,4,7-Tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18e). According to the general procedure (Method A) utilizing 0.340 g (1.20 mmol) of **16e** and 49 mg (0.06 mmol, 5 mol%) of **6**, 0.265 g (87%) of **18e** was obtained after column chromatography (hexane/ethyl acetate: 14:1) as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.2:1) δ 5.76–5.61 (m, 2H), 4.20 (br d, 0.56H, J=17.4 Hz), 4.10 (br d, 0.47H, J=15.8 Hz), 4.00 (br dd, 0.43H, J=14.0, 6.2 Hz), 3.84 (br dd, 1.12H, J=14.4, 6.7 Hz), 3.75 (br d, 0.56H, J=17.4 Hz), 3.70 (s, 1.63H), 3.69 (s, 1.36H), 3.58–3.49 (m, 1H), 2.99–2.91 (m, 1H), 2.50–2.40 (m, 2H) 1.46 (s, 5H), 1.45 (s, 4H); ^{13}C NMR (rotamers) δ 173.9, 155.1, 155.0, 129.2, 128.8, 128.1, 126.9, 51.6, 48.0, 47.8, 47.3, 47.1, 43.5, 42.9, 28.2, 28.1, 27.2, 26.5; MS (ES+) *m/z* 278 (100, $[M+Na]^+$), 533 (13, $[2M+Na]^+$); HRMS (ES+) *m/z* calcd for $C_{13}H_{21}NO_4Na$ 278.136828 found 278.135883. According to the general procedure (Method B) employing 0.340 g (1.20 mmol) of **16e** and 51 mg (0.06 mmol, 5 mol%) of **7**, 0.263 g (86%) of **18e** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method A.

4.5.6. 5-Hydroxymethyl-2,3,4,7-tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18f). The title compound was prepared according to the general procedure (Method B) employing 0.313 g (1.00 mmol) of **17c** and 42 mg (0.05 mmol, 5 mol%) of **7**. Column chromatography (hexane/ethyl acetate: 3:2) gave rise to 0.271 g (95%) of **18f** as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.5:1) δ 5.67 (s, 0.4H), 5.64 (s, 0.6H), 4.28 (d, 0.6H, J=17.6 Hz), 4.17 (d, 0.4H, J=17.2 Hz), 4.06–3.95 (m, 2.46H), 3.88–3.74 (m, 1.59H), 3.70 (s, 1.79H), 3.69 (s, 1.31H), 3.52 (sm, 1H), 3.09–2.98 (m, 1H), 2.52–2.41 (sm, 2H), 2.13 (br s, 1H), 1.47 (s, 5.40H), 1.45 (s, 4.18H); ^{13}C NMR (rotamers) δ 174.4, 174.3, 155.0, 139.5, 138.3, 123.0, 122.8, 79.9, 79.7, 67.8, 67.6, 51.8, 47.9, 47.6, 46.9, 46.7, 42.8, 42.1, 28.2, 27.9, 27.4; MS (ES+) m/z 286 (56, $[M+H]^+$), 308 (67, $[M+Na]^+$), 593 (100, $[2M+Na]^+$); HRMS (ES+) m/z calcd for $C_{14}H_{23}NO_5Na$ 308.147393 found 308.150227. Anal. Calcd for $C_{14}H_{23}NO_5$: C, 58.93; H, 8.12; N, 4.91. Found: C, 58.60; H, 7.90; N, 5.16. Following the general procedure (Method A) employing 0.313 g (1.00 mmol) of **17c** and 41 mg (0.05 mmol, 5 mol%) of **6**, 0.105 g (37%) of **18f** was obtained after column chromatography (hexane/ethyl acetate: 2:1) as colorless oil. The isolated product exhibited identical spectroscopic data to those obtained using Method B.

4.5.7. 5-(*tert*-Butyl-dimethyl-silanyloxymethyl)-2,3,4,7-tetrahydro-1*H*-azepine-1,3-dicarboxylic acid-1-*tert*-butyl ester 3-methyl ester (18g). According to the general procedure (Method A) utilizing 0.658 g (1.54 mmol) of **16f** and 63 mg (0.077 mmol, 5 mol%) of **6**, 0.267 g (44%) of **18g** was obtained after column chromatography (hexane/ethyl acetate: 10:1) as colorless oil: ^{1}H NMR (rotamers, ratio: ~1.1:1) δ 5.68 (s, 0.5H), 5.61 (s, 0.5H), 4.16 (d, 0.5H, J=17.9 Hz), 4.10 (d, 0.5H, J=16.7 Hz), 4.04–3.93 (m, 2.6H), 3.86 (d, 0.5H, J=17.1 Hz), 3.79 (dd, 0.5H, J=14.5, 6.8 Hz), 3.71 (br d, 0.5H, J=19.5 Hz), 3.67 (s, 1.50H), 3.65 (s, 1.50H), 3.52 (dd, 0.50H, J=14.3, 8.3 Hz), 3.44 (dd, 0.5H, J=14.0, 8.8 Hz), 2.91–2.83 (m, 1H), 2.32 (s, 1H), 2.31 (s, 1H), 1.43 (s, 4.6H), 1.42 (s, 4.4H), 0.88 (s, 4.9H), 0.87 (s, 4.5H), 0.04 (s, 6H); ^{13}C NMR (rotamers) δ 174.0, 155.2, 155.0, 139.6, 138.0, 121.7, 121.3, 79.8, 79.6, 67.3, 67.1, 51.7, 48.4, 47.8, 46.7, 46.6, 42.7, 42.3, 28.3, 28.2, 27.4, 25.8, 18.2, −5.4, −5.5; MS (ES+) m/z 422 (100, $[M+Na]^+$); HRMS (ES+) m/z calcd for $C_{20}H_{37}NO_5SiNa$ 422.233872 found 4222.229903. According to the general procedure (Method B) employing 0.460 g (1.08 mmol) of **16f** and 46 mg (0.054 mmol, 5 mol%) of **7**, 0.375 g (87%) of **18g** was obtained as a colorless oil, which exhibited identical spectroscopic data to those obtained using Method A.

Acknowledgements

We gratefully acknowledge the financial support of our research by the Deutsche Pharmazeutische Gesellschaft (DPhG) within the fellowship 'DPhG Stiftung zur Förderung des wissenschaftlichen Nachwuchses' for W.E.D. We also thank Wacker-Chemie GmbH for supplying the TBSCl. The authors in particular would like to thank Prof. Dr. G. Klebe, Philipps Universität Marburg, for his generous support of their research.

References and notes

1. For recent reviews on ring-closing metathesis see: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed.* **1997**, *36*, 2036–2056. (b) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413–4450. (c) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 37–72. (d) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012–3043. (e) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18–29.
2. For reviews see: (a) Phillips, A. J.; Abell, A. D. *Aldrichim. Acta* **1999**, *32*, 75–89. (b) Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3493–3513. (c) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2553–2581. (d) Mitchinson, A.; Nadin, A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2862–2892. (e) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693–3712. (f) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
3. (a) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251–7264. (b) Campagne, J.-M.; Ghosez, L. *Tetrahedron Lett.* **1998**, *39*, 6175–6178. (c) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517–1519. (d) Gille, S.; Ferry, A.; Billard, T.; Langlois, B. R. *J. Org. Chem.* **2003**, *68*, 8932–8935. (e) González-Pérez, P.; Pérez-Serrano, L.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *Tetrahedron Lett.* **2002**, *43*, 4765–4767. (f) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372–8381.
4. (a) Fürstner, A.; Thiel, O. R. *J. Org. Chem.* **2000**, *65*, 1738–1742. (b) Vo-Thanh, G.; Boucard, V.; Sauriat-Dorizon, H.; Guibé, F. *Synlett* **2001**, 37–40. (c) Li, H.; Blériot, Y.; Chantereau, C.; Mallet, J.-M.; Sollogoub, M.; Zhang, Y.; Rodríguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinaÿ, P. *Org. Biomol. Chem.* **2004**, *2*, 1492–1499. (d) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838–3844. (e) Tarling, C. A.; Holmes, A. B.; Markwell, R. E.; Pearson, N. D. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1695–1701.
5. (a) Hoffmann, T.; Waibel, R.; Gmeiner, P. *J. Org. Chem.* **2003**, *68*, 62–69. (b) Chen, Y.; Zhang, H.; Nan, F. *J. Comb. Chem.* **2004**, *6*, 684–687.
6. (a) Friebe, W.-G.; Masjost, B.; Schumacher, R. U.S. 2003/0181716 A1, Hoffmann-La Roche Inc., 2003. (b) Wos, J. A.; Wang, Y.; Oppong, K. A.; O'Neill, S. V.; Laufer-Sweiler, M. C.; Soper, D. L.; De, B. WO 03/103677 A1, The Procter and Gamble Company, 2003. (c) Bair, K. W.; Kinder, F. R., Jr.; Versace, R. W. WO 2005/014574 A1, Novartis AG, 2005.
7. For a recent discussion on the mechanism see: (a) Price, K. E.; Broadwater, S. J.; Jung, H. M.; McQuade, D. T. *Org. Lett.* **2005**, *7*, 147–150. (b) Price, K. E.; Broadwater, S. J.; Walker, B. J.; McQuade, D. T. *J. Org. Chem.* **2005**, *70*, 3980–3987.
8. (a) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413–5418. (b) Coelho, F.; Almeida, W. P.; Veronese, D.; Mateus, C. R.; Lopez, E. C. S.; Rossi, R. C.; Silveira, G. P. C.; Pavam, C. H. *Tetrahedron* **2002**, *58*, 7437–7447. (c) Vloon, W. J.; van den

Bos, J. C.; Koomen, G.-J.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 8317–8328. (d) Drewes, S. E.; Loizou, G.; Roos, G. H. P. *Synth. Commun.* **1987**, *17*, 291–298.

9. Compound **10** has already been synthesized via a different sequence: (a) Navé, J.-F.; Casara, P. J.; Taylor, D. L.; Tyms, A. S.; Kenny, M.; Halazy, S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 179–184. (b) Lee, H.-Y.; Tae, H. S.; Kim, B. G.; Choi, H.-M. *Tetrahedron Lett.* **2003**, *44*, 5803–5806. (c) Via a similar sequence: Danishefsky, S. J.; Mantlo, N. *J. Am. Chem. Soc.* **1988**, *110*, 8129–8133.
10. (a) Appel, R. *Angew. Chem., Int. Ed.* **1975**, *14*, 801–811. (b) Baughman, T. W.; Sworen, J. C.; Wagener, K. B. *Tetrahedron* **2004**, *60*, 10943–10948. (c) Bartra, M.; Vilarrasa, J. *J. Org. Chem.* **1991**, *56*, 5132–5138. (d) Magid, R. M. *Tetrahedron* **1980**, *36*, 1901–1930.
11. Kałuża, Z.; Kazimierski, A.; Lewandowski, K.; Suwińska, K.; Szczęsna, B.; Chmielewski, M. *Tetrahedron* **2003**, *59*, 5893–5903.
12. (a) Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1987**, *28*, 1697–1698. (b) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941–4943.
13. Compound **11** has already been prepared via two different procedures: (a) Ref. 6b; reported yield (39%) was significantly lower. (b) Kurosu, M.; Marcin, L. R.; Grinsteiner, T. J.; Kishi, Y. *J. Am. Chem. Soc.* **1998**, *120*, 6627–6628 the described method seems to be less convenient.
14. Sundberg, R. J.; Pearce, B. C.; Laurino, J. P. *J. Heterocycl. Chem.* **1986**, *23*, 537–539.
15. Makino, T.; Itoh, K. *J. Org. Chem.* **2004**, *69*, 395–405.
16. (a) Yu, L.-C.; Helquist, P. *J. Org. Chem.* **1981**, *46*, 4536–4541. (b) Gutiérrez-García, V. M.; López-Ruiz, H.; Reyes-Rangel, G.; Juaristi, E. *Tetrahedron* **2001**, *57*, 6487–6496.
17. Due to the high toxicity of HMPT, we reduced the employed amount to 1 equiv. Employing these modified reaction conditions, we did not notice any significant decrease in yield.
18. (a) Pachamuthu, K.; Vankar, Y. D. *J. Organomet. Chem.* **2001**, *624*, 359–363. (b) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, *7*, 1146–1148.
19. Compounds **13b** and **16a** have already been described, however, no spectral data were given. Denes, F.; Chemla, F.; Noemant, J. F. *Synlett* **2002**, *6*, 919–922.
20. Ahn, Y. M.; Yang, K.-L.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1411–1413.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1787–1798

First stereoselective synthesis of potassium aeschynomate and its no-natural stereomers

Stéphanie Claudel,[a] Tomasz Krzysztof Olszewski,[b] Pierre Mutzenardt,[c] Christie Aroulanda,[c] Philippe Coutrot[a] and Claude Grison[b,*]

[a]*Laboratoire de Chimie Organique Biomoléculaire, UMR 7565, Université Henri Poincaré, Nancy 1, BP 239, 54506 Vandoeuvre-lès-Nancy cédex, France*
[b]*Laboratoire de Chimie Biomoléculaire, UMR 5032, ERT 5, 8 rue de l'Ecole Normale, 34296 Montpellier, France*
[c]*Laboratoire de Méthodologie RMN, UMR 7565, Université Henri Poincaré, Nancy 1, BP 239, 54506 Vandoeuvre-lès-Nancy cédex, France*

Received 19 October 2005; revised 17 November 2005; accepted 21 November 2005

Available online 20 December 2005

Abstract—The synthesis of potassium aeshynomate and its non-natural stereomers was achieved using the Sharpless catalytic asymmetric dihydroxylation of (*Z*) or (*E*) vinylogous glycine as the key step. The resulting γ-amino α,β-dihydroxyester stereomer was deprotected and coupled with the caffeic acid to afford stereoselectively potassium aeshynomate or its stereomers. A detailed study of the NMR data of the different stereomers is reported that corrects the literature data.

1. Introduction

Recently, potassium aeshynomate **1** was identified as a leaf-opening substance in a nyctinastic plant, *Aeshynomene indica* L. Among the different bioactive molecules that control the leaf-movement of Leguminosae plants, **1** was found to be a new type of leaf-opening substances. Efforts have been realized by Yamamura and co-workers to isolate potassium aeshynomate **1** in small quantities from *Aeshynomene indica* L. and to determinate the corresponding structure (Fig. 1).

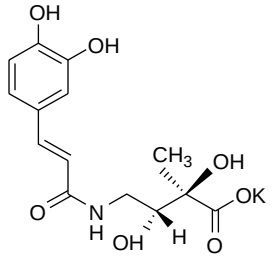


Figure 1. Potassium aeshynomate **1**.

These authors have established that the diol entity of **1** possessed the *anti*-relation on the basis of a variety of NMR techniques.[1] Nonetheless, the absolute stereochemistry of the natural molecule was not assigned.

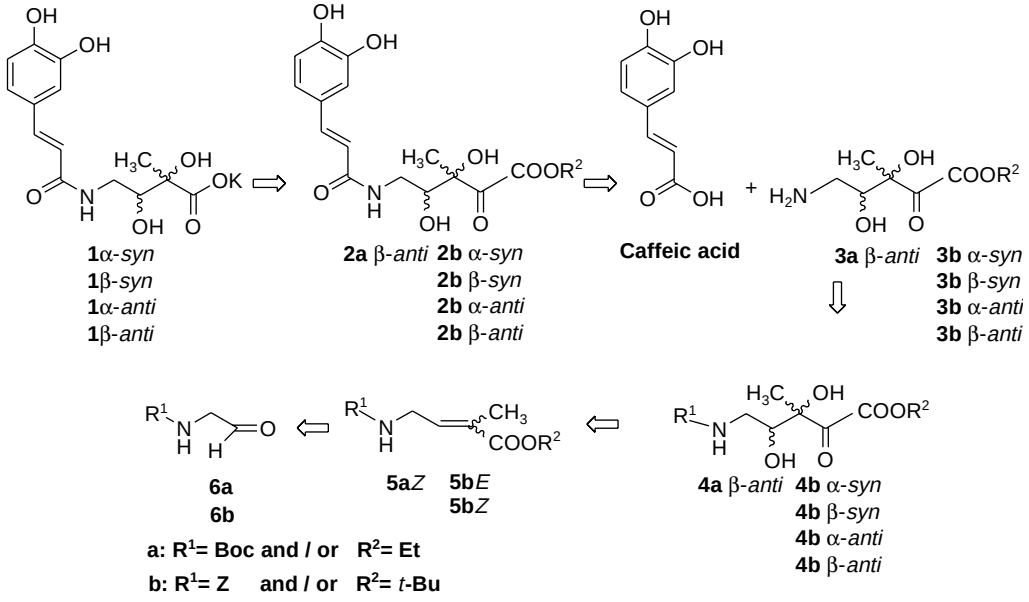
In the present work, we report the first stereoselective syntheses of **1** and its three stereomers in the order to obtain practically and conveniently these potent 'clean' herbicide compounds and to confirm the structure of the isolated natural compound.

2. Results and discussion

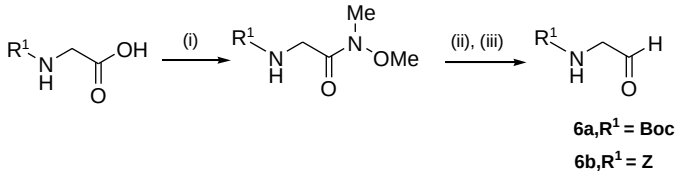
Retrosynthetically, potassium aeshynomate can be devised into the two components caffeic acid and an appropriate α,β-dihydroxy-γ-aminoester **3** (Scheme 1). The synthetic design of the chiral part was based on an initial stereoselective Horner reaction for the elaboration of the α,β-unsaturated-γ-aminoester precursor **5** followed by the Sharpless asymmetric dihydroxylation (SAD) of the ethylenic double bond using the AD-mix system.[2] The stereoselective olefination–SAD sequence allows theoretically an enantioselective *syn* or *anti* diastereocontrol. In this paper, we use the designation *syn*/*anti* to differentiate the pairs of diastereomers, but a difficulty arises for a simple appellation of the different enantiomers, since the absolute configuration of the natural product is unknown and cannot serve of reference. Thus, for facilitating the discussion, we

Keywords: Potassium aeshynomate; Vinylogous peptides; Aminoaldehydes; Horner reaction; Asymmetric dihydroxylation; Natural product.
* Corresponding author. Tel./fax: +33 467 144342;
e-mail: cgrison@univ-montp2.fr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.051



Scheme 1. Retrosynthetic analysis.



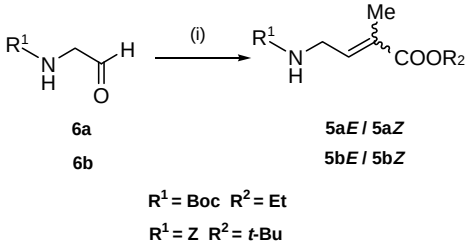
Scheme 2. Synthesis of Boc or *Z*-glycinal **6a**,**b**: (i) (MeO)NHMe·HCl, BOP, Et_3N, CH_2Cl_2, rt, 2 h, 85%; (ii) $LiAlH_4$ 1 M/Et_2O, O °C, 20 min; (iii) $KHSO_4/H_2O$.

assign α or β to the enantiomeric diols **4** which are prepared respectively from AD-mix-α or AD-mix-β.[2]

Two approaches were studied. The first strategy used ethyl γ-*N*-Boc-amino-α,β-dihydroxy ester **4a**β-*anti* as the chiral intermediate precursor but was unsuccessful as a result of a surprising fragility of the carboxamide bond, especially during the basic hydrolysis of the ester **2a**β-*anti* in the last step of the reaction sequence. Although this approach brought useful information concerning the stability of the potassium aeschynomate and its precursors in basic or acidic medium, this excluded the use of a ethyl ester protecting group that needed a basic deprotection step. Thus, a synthetic plan using protecting groups cleavable by acidolysis (*t*-butyl ester) and hydrogenolysis (Z-NH group) was adopted in the second successfully approach using *t*-butyl γ-*N*-*Z*-amino-α,β-dihydroxy esters **4b** as the chiral intermediate precursors.

The starting compounds *N*-protected glycinal **6a** and **6b** were prepared according to the method of Castro et al. in which a Weinreb amide derived from a *N*-Boc aminoacid is reduced with lithium aluminium hydride.[3] The *N*-*t*-butyloxycarbonyl glycine *N*′-methoxy *N*′-methylamide and *N*-benzyloxycarbonyl glycine *N*′-methoxy *N*′-methylamide were prepared by reaction between the Boc or *Z*-glycine and *O*,*N*-dimethylhydroxylamine hydrochloride, respectively, in the presence of triethylamine and benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluoro phosphate (BOP) as coupling reagent. The reduction of the *N*′-methoxy-*N*′-methylamide led to a lithium salt intermediate which was stabilized by intramolecular complexation. The desired aldehyde **6a**,**b** was obtained upon hydrolysis of the reaction mixture in excellent yield (82, 85% overall yields, respectively) (Scheme 2).

On the basis of our previous works concerning the syntheses of vinylogous peptides,[4] the lithium anion derived from ethyl 2-diethylphosphonopropanoate reacted with the *N*-Boc-glycinal **6a** to afford stereoselectively the unsaturated ethyl ester **5a**. Similarly, the lithium anion derived from *t*-butyl 2-diethylphosphonopropanoate reacted with the *N*-*Z*-glycinal **6b** to provide stereoselectively the unsaturated *t*-butyl ester **5b** (Scheme 3).



Scheme 3. Preparation of the vinylogous ethyl glycinate **5a** and *t*-Butyl glycinate **5b**: (i) $(EtO)_2P(O)CHLiCOOEt$, THF or $(EtO)_2P(O)CHLiCOOt$-Bu, THF, respectively.

Pure *Z* or *E* vinylogous glycine derivatives **5a** or **5b** necessary for the different syntheses of the stereomers of potassium aeschynomate were easily obtained after a chromatographic separation.

It was noted that the nature of the *N*-protecting group combined with the steric hindrance of the phosphonate have a marked effect on the stereoselectivity of the olefination. *Z* selectivity could be obtained with the *N*-Boc-glycinal **6a** and ethyl 2-diethylphosphonoacetate,[4] whereas a *E* preference was observed with *N*-*Z*-glycinal **6b** and the lithiated *t*-butyl 2-diethylphosphonopropanoate (Table 1).

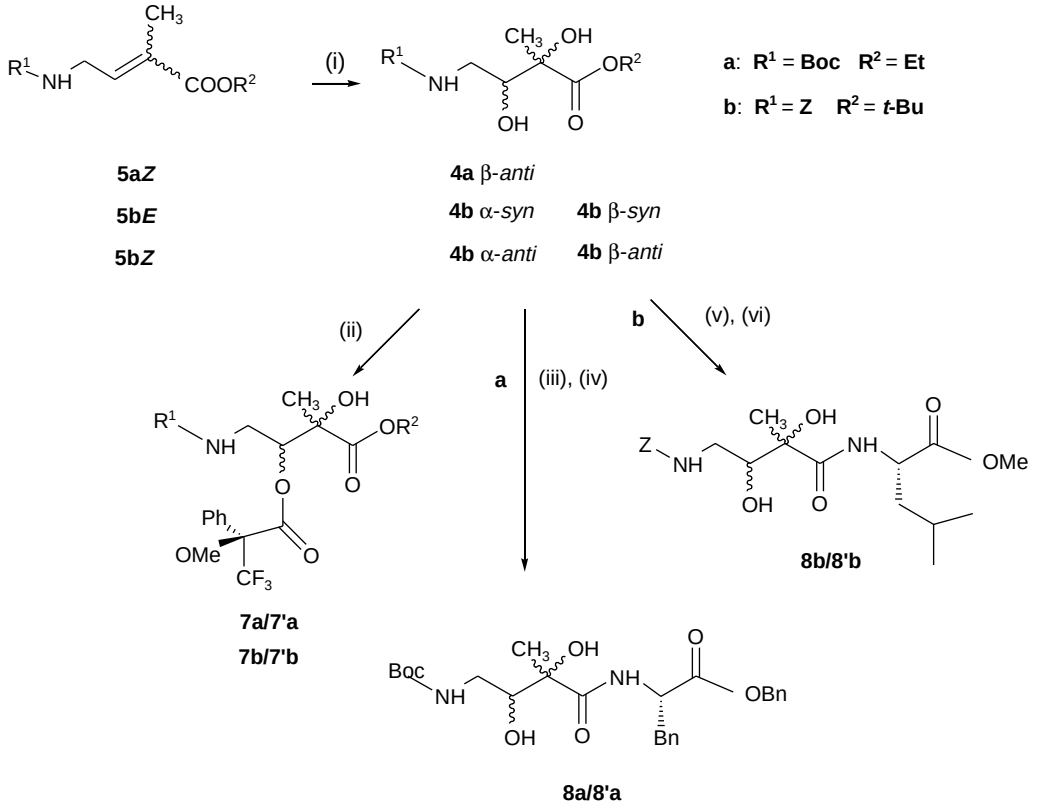
The following step of the strategy was the construction of the diol entity via the Sharpless catalytic asymmetric dihydroxylation[2] of pure *Z* or *E* vinylogous glycine derivative **5**. Recent works relate the asymmetric dihydroxylation of *trans*-1,2-disubstituted γ-amino-α,β-unsaturated ester derivatives,[5] but, to our knowledge, no reports concern the asymmetric dihydroxylation of *E*- and *Z*-trisubstituted substrates. Thus, we studied successively the osmium-catalyzed asymmetric dihydroxylation of the trisubstituted vinylogous glycine derivative **5a*Z***, using the commercially available 'AD-mix β' that afforded **4a**β-*anti*. Similarly, **5b*E*** should lead to **4b**α-*syn* or its enantiomer **4b**β-*syn*, using the commercially available 'AD-mix α' or 'AD-mix β' respectively, whereas **5b*Z*** should provide **4b**α-*anti* or its enantiomer **4b**β-*anti*, using the same reagents. The enantiomeric excesses of the different stereomers **4a**,**b** were evaluated by NMR analysis of the corresponding Mosher ester derivatives **7a**,**b**/**7′a**,**b**. They were confirmed by NMR analysis of the diasteromers **8a/8′a** and **8b/8′b** produced by coupling the carboxylic acid issued from **4a** with H-Phe-OBn and by coupling the carboxylic acid issued from **4b** with H-Leu-OMe, respectively (Scheme 4, Table 2).

Dihydroxylation was very slow. However, the **5b*Z*** derivative underwent dihydroxylation faster (48 h) than the **5b*E*** stereomer (192 h).

Table 1. Preparation of the vinylogous alkyl *Z*- or *E*-glycinate **5b** and **5a** from aminoaldehyde **6**

6	Horner reagent	Reaction conditions	**5** (Yield %)	*Z*/*E*[a]
6a	$(EtO)_2P(O)CHLiCOOEt$	3 h at −78 °C/hydrolysis at −78 °C	**5a** (63%)	86/14
6b	$(EtO)_2P(O)CHLiCOO$*t*-Bu	3 h at −78 °C/hydrolysis at −78 °C	**5b** (60%)	55/45
		1.5 h at −78 °C/hydrolysis at −78 °C	**5b** (40%)	40/60
		0.75 h at −78 °C/hydrolysis at −78 °C	**5b** (40%)	48/62
		1 h at −78 °C/0.75 h at 20 °C/hydrolysis at −78 °C	**5b** (60%)	20/80

[a] *Z*/*E* ratio was determined by ^{1}H NMR on the crude product.



Scheme 4. Asymmetric dihydroxylation of vinylogous glycine derivatives **5a*Z***, **5b*E*** or **5b*Z***: (i) AD-mix α or AD-mix β, $MeSO_2NH_2$, *t*-BuOH/H_2O; (ii) (*S*)-MTPA-Cl/pyridine/CH_2Cl_2, 25 °C, 2 days; (iii) NaOH/EtOH/H_2O; (iv) H-Phe-OBn·HCl, Et_3N, BOP, CH_2Cl_2, 25 °C, 2 h; (v) TFA, 25 °C, 30 mn; (vi) H-Leu-OMe·HCl, Et_3N, BOP, CH_2Cl_2, 25 °C, 2 h.

Table 2. Asymmetric dihydroxylation of vinylogous glycine derivatives **5a*Z***, **5b*E*** or **5b*Z***

5	Reaction conditions	4[a]	ee[b] (Yield%)[c]	7	de (yield %)[c]	8	de (Yield %)[c]
5a*Z*	AD-mix-β *t*-BuOH/H_2O, 0 °C, $MeSO_2NH_2$/72 h	**4a** β-*anti*	61 (83)	**7a/7′a** β-*anti*	60 (72)	**8a/8′a** β-*anti*	62 (85)
5b*E*	AD-mix-α *t*-BuOH/H_2O, 0 °C, $MeSO_2NH_2$/192 h	**4b** α-*syn*	22 (85)	**7b/7′b** α-*syn*	24 (69)	**8b/8′b** α-*syn*	20 (80)
5b*E*	AD-mix-β *t*-BuOH /H_2O, 0 °C, $MeSO_2NH_2$/192 h	**4b** β-*syn*	9 (82)	**7b/7′b** β-*syn*	8 (70)	**8b/8′b** β-*syn*	10 (82)
5b*Z*	AD-mix-α *t*-BuOH /H_2O, 0 °C, $MeSO_2NH_2$/48 h	**4b** α-*anti*	29 (90)	**7b/7′b** α-*anti*	28 (72)	**8b/8′b** α-*anti*	30 (85)
5b*Z*	AD-mix-β *t*-BuOH /H_2O, 0 °C, $MeSO_2NH_2$/48 h	**4b** β-*anti*	61 (85)	**7b/7′b** β-*anti*	60 (68)	**8b/8′b** β-*anti*	62 (82)

[a] Major product.
[b] ee is deduced from the average between the two values of de.
[c] Yields after chromatographic purification.

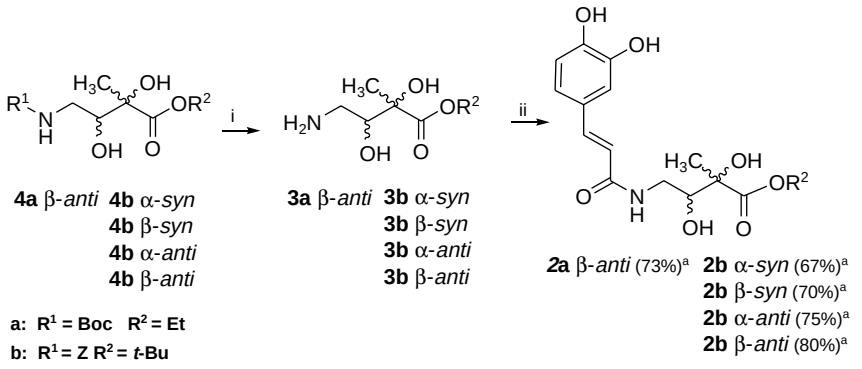
In the case of **5b*E*** the reaction rate can be compared favourably with the SAD of *trans*-1,2-disubstituted γ-amino-α,β-unsaturated ester (168 h), being done the trisubstitution of the double bond in **5b*E***.[5] Surprisingly, the yields were even better. The transformation of the diols **4a**,**b** into the Mosher esters **7a**,**b**/**7′a**,**b** was also slow and was stopped after 48 h, leading to **7a**,**b**/**7′a**,**b** accompanied with approximately 30% of the starting compound **4a**,**b**. In these conditions the estimation of the enantiomeric excesses was questionable, as kinetic resolution could arise with one of the two enantiomers of **4a**,**b**. Therefore a second method based on the transformation of **4a**,**b** into dipeptides **8a**,**b**/**8′a**,**b** was tested. After hydrolysis of the ethyl ester **4a** with NaOH or cleavage of the *t*-butyl ester of **4b** with pure TFA, the resulting acid was coupled with respectively H-Phe-OBn hydrochloride or H-Leu-OMe hydrochloride in the presence of BOP as coupling reagent. After 2 h, the reaction was complete and led to the desired dipeptide diastereomers **8a**,**b**/**8′a**,**b** in high yield after a chromatographic purification.

Beforehand, the ratio of the so-obtained diastereomers **8a**/**8′a** and **8b**/**8′b** was determined by ^{1}H NMR on the crude product and compared to the Mosher esters ratio. The results accorded and shown that kinetic resolution did not probably arise. However, the enantiomeric excesses were modest. AD-mix-β and **5a*Z***, **5b*Z*** gave the best result (in the 60% ee range), while **5b*E*** olefin revealed the much poorest substrate.

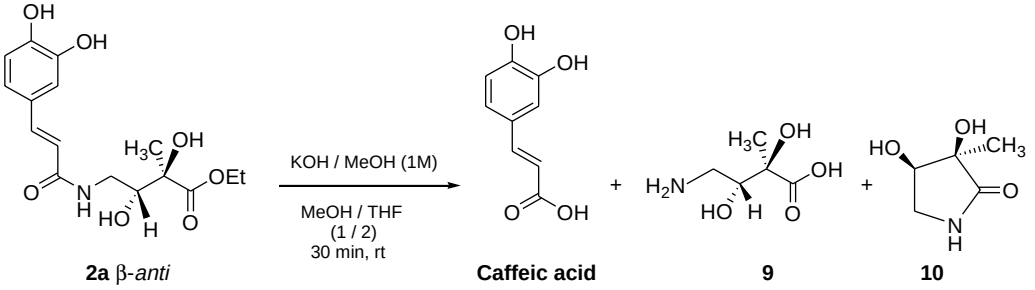
After removal of Boc in **4a**β-*anti* by bubble of gaseous HCl in anhydrous ether or removal of Z by hydrogenolysis into **4b**, the resulting crude ethyl amino-α,β-dihydroxy ester **3a**β-*anti* hydrochloride or *t*-butyl amino-α,β-dihydroxy ester **3b**α-*syn*, **3b**β-*syn*, **3b**α-*anti*, or **3b**β-*anti*, was coupled with caffeic acid using BOP as coupling reagent to provide the corresponding product **2a** or **b** in good yields (Scheme 5).

In the first approach,[6] the hydrolysis of the ethyl ester moiety of **2a**β-*anti* to obtain the desired product **1a**β-*anti* was the last troublesome step. The monitoring by TLC of a stirred mixture of KOH/MeOH, 1 M (1 equiv) and **2a**β-*anti* dissolved in MeOH/THF (1/2) indicated a complete disappearance of the starting compound after 30 min. After a classical acidic treatment of the aqueous phase at pH = 4 and successive extractions with ether and dichloromethane, the ^{1}H and ^{13}C NMR analyses of the crude product allowed to identify caffeic acid and the γ-aminoacid **9**. Similar NMR analyses of the product issued from the organic phase revealed the presence of the lactame **10** which formally resulted from a cyclization of the γ-aminoester **3a**β-*anti* (Scheme 6).

Thus, the amide bond presented an unusual fragility, being hydrolysed concurrently to the ethyl ester group in a basic medium. A hydrogen bond between the C=O of the amide and one of the neighbouring OH (or a aromatic OH via an intermolecular H-bond) can favour this hydrolysis by electrophilic assistance (Fig. 2a). Another possible explanation is a mechanism where the nitrogen of the amide at the γ-C relatively to the ethyl ester involves a easy intramolecular cyclisation into lactame **10** and makes



Scheme 5. Deprotection of **4** and coupling with caffeic acid: (i) **4a**β-*anti*: bubble of gaseous HCl in anhydrous ether provided **3a**β-*anti*,HCl; **4b**: H_2 (30 bars), Pd/C 10%, MeOH, 20 °C, 12 h; (ii) caffeic acid, Et_3N, BOP, DMF, 25 °C, 2 h; [a]Yield of purified products from **4**.



Scheme 6. Break of the amide bond in basic medium.

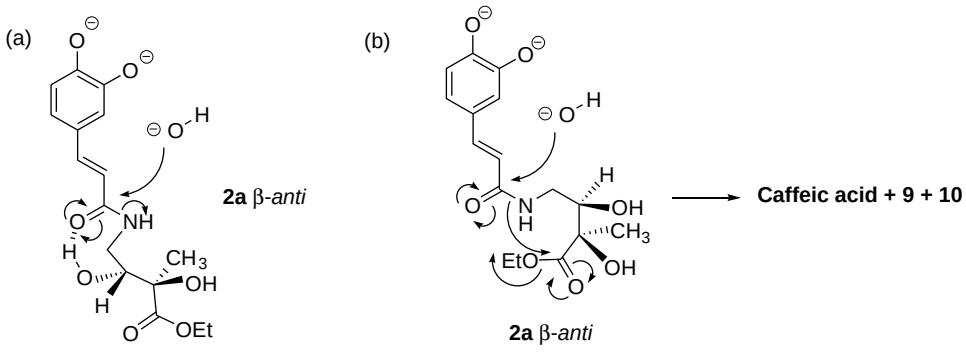


Figure 2. The hydrogen bonding between C═O of the amide bond and the neighbouring OH favours the hydrolysis of the amide link (a). Concerted mechanism (b).

simultaneous hydrolysis easier for the amide bond in a fully concerted mechanism (Fig. 2b).

With the aim to remove the possible H-bond assistance to the amide hydrolysis, a novel synthesis similar to that described above to obtain **2a**β-*anti* was then carried out to obtain **12** with a complete protection of OH. Starting from the commercially available 3,4-dimethoxycinnamic acid, the compound **12** was obtained as described in Scheme 7.

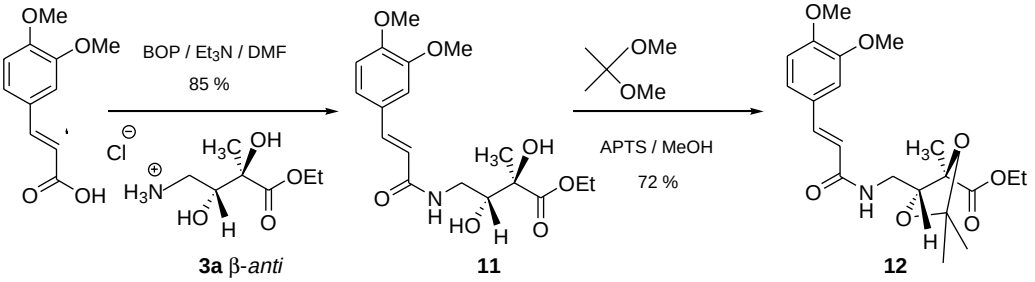
The saponification of ethyl ester **12** was attempted in the same precedent conditions that for **2a**β-*anti*. A transesterification into the methyl ester **13** was only observed after 30 min at rt. A prolonged reaction time shown a slow hydrolysis of the methyl ester intermediate **13** into 3,4-dimethoxycinnamic acid and aminoacid **14** until 72 h when the amide bond was entirely hydrolysed (Scheme 8).

Consequently, the absence of a free OH or the steric hindrance of the ketal moiety involves a cleanly reduced rate of the amide bond hydrolysis and can explain this relative decrease of the amide reactivity. However, this decreased reactivity was not sufficient to insure the complete stability of the amide link in the basic medium.

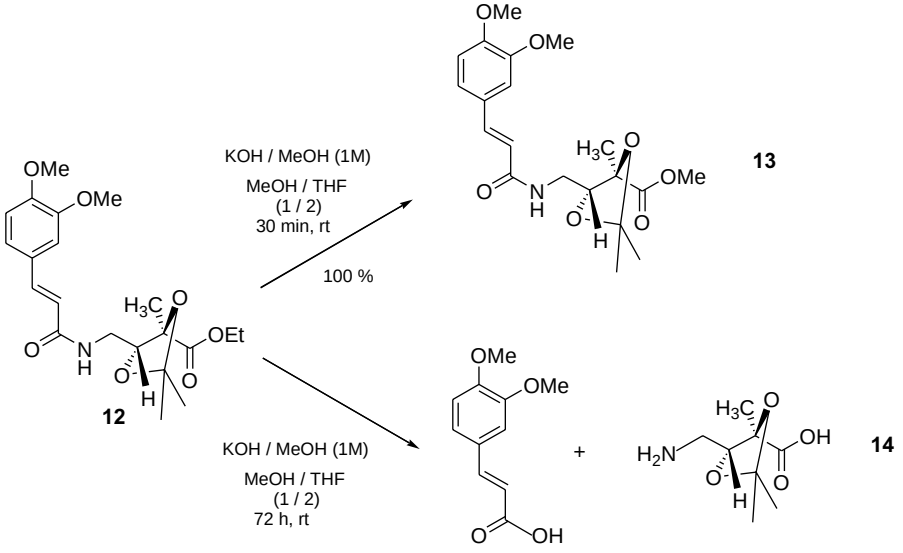
Indeed, the steric hindrance was also responsible of the difficult hydrolysis of the methyl ester moiety of **13**, so that both slow hydrolyses of the methyl ester and the amide occurred competitively.

Thus, it seems particularly difficult to carry out a chimioselective basic hydrolysis of ethyl or methyl ester without a competitive hydrolysis of the amide bond in the case of the structures **2a**β-*anti* and **12**.

As a result, the chemoselective acidic hydrolysis of the ethyl ester moiety of **2a**β-*anti* was studied. In a previous work we describe the use of trimethylbromosilane in methanol to hydrolyse a isopropyl ester linked to a tri-substituted hindered carbon bearing notably a tertiary alcohol.[7] However, whatever the different attempts using various amounts of Me_3SiBr onto **2a**β-*anti*, only a partial transesterification into the corresponding methyl ester was observed. No trace of the expected acid was detected,



Scheme 7. Preparation of the ethyl ester **12** with protected OH.



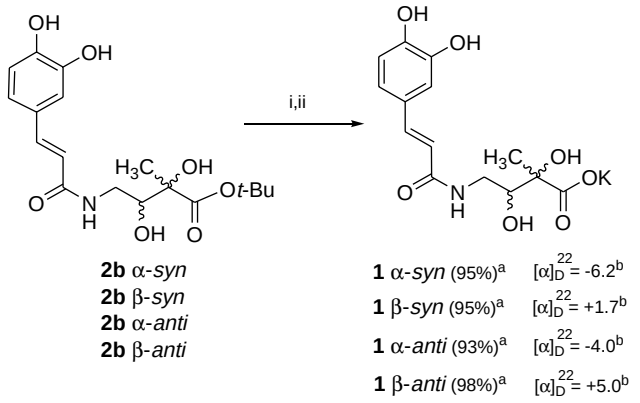
Scheme 8. Basic hydrolysis of ethyl ester **12**.

neither hydrolysis of the amide bond. As the molecule **2a**β-*anti* was difficult to dissolve in another solvent than methanol or THF, a classical hydrolysis with a 1 N aqueous solution of sulphuric acid (2 equiv) in THF (3 mL) was also realized, but unsuccessfully, the starting compound being recovered.

Consequently, the study of the second strategy using precursors with a *t*-Bu ester protection such as stereomers **2b** was justified by the possible releasing of the carboxylic acid in acidic medium which could preserve the amide bond. Nevertheless, the removal of the *t*-Bu ester into **2b** revealed also troublesome.

This *t*-Bu ester **2b** presented, as the potassium aeschynomate **1**, a low solubility in most of the used solvents and was practically only soluble in MeOH or THF, that complicated the different attempts. A degradation occurred when **2b** was treated with formic acid.[8] The treatment of **2b** with Me_3SiBr in MeOH only yielded the corresponding methyl ester (100% yield). Other attempts using a bubble of gaseous HCl in ether/THF or in ether in the same conditions that those used for the removal of Boc did not succeed. It has to be noted that similar difficulties in the hydrolysis of *t*-Bu ester have been mentioned.[9] Finally, the reaction of **2** with neat trifluoroacetic acid for 30 min at 25 °C succeeded and led to the expected carboxylic acid (100% yield). A subsequent treatment of the acid with a titrated solution of MeOK in MeOH (0.13 M, 1 equiv) yielded the potassium salt **1**. It was noted that this last step required a careful control to avoid the cleavage of the carboxamide bond (Scheme 9).

NMR studies of **1** and **2** were carried out at 400 MHz. The solvents (MeOH-d_4/D_2O: 1/1 or MeOH-d_4) and the concentration (*c* 0.24) were chosen for a sake of comparison with the results reported in Ref. 1 However, the potassium salts **1** revealed weakly soluble in MeOH-d_4/D_2O: 1/1 or D_2O, even at 35 °C, contrary to the data of Yamamura et al.[1] This observed little solubility has constituted a real difficulty in this study, particularly with the diastereomers syn. Sometimes, the small differences observed in the



Scheme 9. Removal of the *t*-butyl ester of **2b** and preparation of the stereomers of potassium aeschynomate **1**: (i) TFA, 25 °C, 30 min; (ii) MeOK/MeOH (0.13 M, 1 equiv), 25 °C, 5 mn; [a]yield of purified product from **2**; [b]$[\alpha]_D^{22}$ (*c* 0.24, 50% MeOH aq.).

chemical shifts of stereomers are the consequence of the necessity of a change of solvent for the NMR analysis.

The reader is referred to the Figure 3 for the structure and numeration of the hydrogens and carbons into **1** and **2**. The hydrogens are labeled the same the carbon they are linked to, in particular the two diastereotopic hydrogens bounded to the carbon 4′ are noted $H_{4'a}$ and $H_{4'b}$ hereafter.

The structures of the four stereomers **1** were assigned from their NMR data and from their comparison with the NMR data of the natural potassium aeshynomate. Assignments have been made on all the stereomers synthesized using ^1H, and ^{13}C 1D experiments, ^1H–^1H 2D COSY, ^1H–^{13}C gradient enhanced inverse HSQC and HMBC experiments. Due to the fragility of the carboxamide group, HMBC experiments are a valuable tool for establishing the connectivity between the caffeyl and the α,β-dihydroxy-γ-aminoacid moieties in the carboxylate compounds **1**.

A small *J*-correlation between the ^{13}C carbonyl and the ^1H methylene group 4′ through the NH group allows to demonstrate the existence of this amide link.

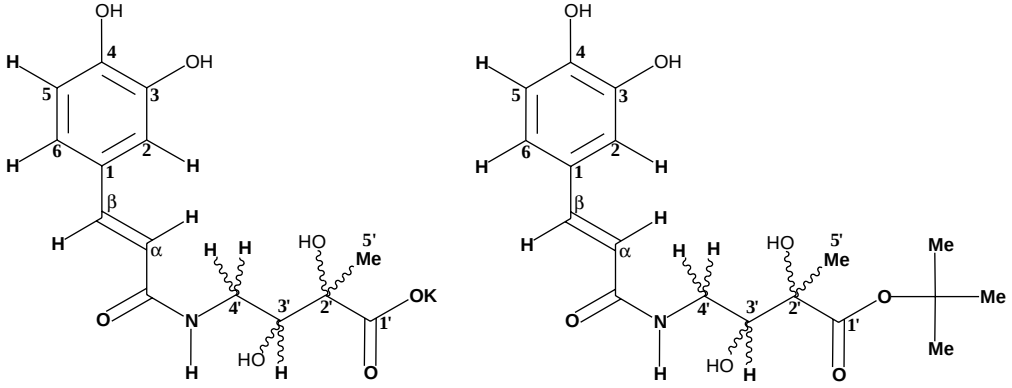


Figure 3. Schemes and generic cartbon and hydrogen labels of diols **1** and **2**.

Table 3. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) of **1**

	$H_{3'}$	$H_{4'}$	$H_{5'}$	H_{α}	H_{β}	H_2	H_5	H_6
1α-*syn*[a]	3.73	3.34	1.48	6.41	7.38	7.01	6.76	6.90
1β-*syn*[b]	3.74	3.23	1.47	6.45	7.38	7.09	6.85	7.02
1α-*anti*[a]	3.80	3.43	1.37	6.40	7.36	7.02	6.75	6.88
1β-*anti*[b]	3.82	3.37	1.36	6.44	7.37	7.08	6.84	7.00
Natural aeschynomate[b]	4.03	4.25	1.40	6.35	7.60	6.95	6.85	7.02

	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	C(O)NH	C_{α}	C_{β}	C_1	C_2	C_3	C_4	C_5	C_6
1α-*syn*[a]	181.8	76.0		42.7	23.4	169.8	118.2	142.3	128.1	115.5	148.9	148.9	117.2	122.3
1β-*syn*[b]	181.8	78.0	75.5	42.5	23.4	169.3	118.6	142.7	128.1	115.5	145.3	147.9	117.1	123.2
1α-*anti*[a]	181.9	77.7	76.1	42.9	23.3	170.0	118.6	142.3	128.2	115.1	147.0	149.9	116.6	122.3
1β-*anti*[b]	181.5	78.0	75.5	42.5	23.5	170.0	118.5	142.0	128.5	115.5	145.7	147.9	117.0	123.0
Natural aeschynomate[c]	181.3	77.6	74.3	66.5	23.3	170.3	115.3	147.0	127.9	115.9	145.4	148.3	117.1	123.5

[a] Solvent: MeOH-d_4.
[b] Solvent: MeOH-d_4/D_2O:1/1.
[c] D_2O (See Ref. 1).

As it can be observed in Table 3, the NMR chemical shifts of the different stereomers **1** are very close, and it is difficult to differentiate the diastereomers **1**-*syn* and **1**-*anti* in ^{1}H and ^{13}C NMR. All chemical shifts are in a good agreement with those of the natural potassium aeshynomate described by Yamamura except for the chemical shifts of $C_{4'}$ and $H_{4'}$ which are practically identical in the case of the four products **1** prepared by us from four different syntheses, and cleanly different from the values reported by Yamamura. The corresponding assignments have been safely determined using HSQC and HMBC correlations with both $H_{4'}$, and with $H_{3'}$ respectively.

The detailed study of the NMR data has been hence made more likely on the *t*-butyl ester precursors **2b** (Table 4). These compounds are indeed slightly more soluble than the salts **1** and their spectra present a best resolution. HSQC and HMBC experiments show also clearly the link between the two moieties caffeic acid and α,β-dihydroxy-γ-amino ester. In these cases, it is noteworthy that the identification of the diastereomers **2**-*syn* and **2**-*anti* can be easily established by NMR from the resonance signals of $H_{4'a}$ which are cleanly different in MeOH-d_4 or MeOH-d_4/D_2O: 1/1 (3.72 ppm for **2**-*syn*, 3.54 for **2**-*anti*).

Table 4. ^{1}H and ^{13}C NMR chemical shifts (δ, ppm) of **2**

2	$H_{3'}$	$H_{4a'}$	$H_{4b'}$	$H_{5'}$	$C(CH_3)_3$	H_{α}	H_{β}	H_2	H_5	H_6
2α-*syn*[a]	3.88	3.72	3.21	1.34	1.48	6.40	7.39	7.00	6.75	6.90
2β-*syn*[a]	3.88	3.72	3.21	1.34	1.48	6.40	7.39	7.00	6.75	6.90
2α-*anti*[a]	3.82	3.54	3.23	1.39	1.50	6.38	7.38	6.99	6.75	6.89
2β-*anti*[b]	3.82	3.54	3.25	1.34	1.45	6.38	7.40	7.00	6.75	6.90

	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C(Me)_3$	$C(CH_3)_3$	C(O)NH	C_{α}	C_{β}	C_1	C_2	C_3	C_4	C_5	C_6
2α-*syn*[a]	175.9	78.3	75.6	42.2	22.6	83.2	28.3	169.9	118.5	142.5	128.4	115.2	146.8	148.9	117.2	122.3
2β-*syn*[a]	175.9	78.3	75.6	42.2	22.6	83.2	28.3	169.9	118.5	142.5	128.4	115.2	146.8	148.9	116.6	122.3
2α-*anti*[a]	175.7	77.8	75.6	42.8	23.2	83.5	28.3	169.8	118.6	142.4	128.5	115.2	146.8	148.9	116.6	122.2
2β-*anti*[b]	174.7	76.7	74.4	41.6	22.1	82.6	27.2	168.8	117.3	141.5	127.3	114.1	147.5	147.8	115.5	121.2

[a] Solvent: MeOH-d_4.
[b] Solvent: MeOH-d_4/D_2O: 1/1.

In conclusion, the synthetic way leading to the natural isomer can be deduced from the known stereochemical relationship *anti* of both $C_{2'}$–OH and $C_{3'}$–OH into the natural compound and from the comparison between the specific rotations measured for the products **1**α-*syn*, **1**β-*syn*, **1**α-*anti*, or **1**β-*anti* and that of the natural compound ($[\alpha]_D^{22}$ −3.39 *c* 0.24, 50% MeOH aq.).[1] Data of Table 3 cleanly indicate the compound **1**α-*anti* ($[\alpha]_D^{22}$ −4.0 *c* 0.24, 50% MeOH aq.), which presents the nearest specific rotation, as being the stereomer corresponding to the natural potassium aeschynomate. Consequently, the asymmetric dihydroxylation of the 'cis'-vinylogous glycine derivative precursor **5b*Z*** with the system AD-mix-α appears as the correct combination to obtain the natural potassium aeshynomate.

Thus, the structure of the potassium aeschynomate which has been established by Yamamura et al. from NMR and SM spectroscopic data is confirmed by the syntheses of the natural compound and its three no-natural stereomers. However, the absolute chemistry of these different stereomers remains a problem to be studied, since the stereomers or their precursors described here have not crystallised and therefore X-ray analysis has not been possible.

3. Experimental

3.1. General

NMR experiments were recorded on Bruker spectrometers (AC 250, AM 400, DRX 400) and internal references used were TMS when available (^{1}H NMR, ^{13}C NMR), CCl_3F (^{19}F NMR) or H_3PO_4 (^{31}P NMR). The NMR signals of the solvent, methanol-d_4, have been used as internal reference for the calibration of the spectra for the compounds generically labeled **1** and **2** (3.30 ppm for the remaining –CD_2H resonance in proton, and 49.15 ppm in C-13 for the seven-lines CD_3 for the methanol-d_4 whenever used). Inverse experiments have been recovered on a Bruker DRX 400 equipped with a 5 mm TBI-Z probe. Chemical shifts are reported in δ ppm values and J values in Hertz (Hz). Isomer ratios were determined by ^{1}H NMR and ^{19}F NMR on the crude products. IR spectra were recorded on a Nicolet 210 FT-IR spectrometer, ν_{max} are given in cm^{-1}. Mass spectra (EI) were obtained with a Waters 2615 Micromass/zq spectrometer. Merck silica gel 60 (230–400 mesh) was used as stationary phase for column chromatography. TLC (Merck Kieselgel 60, F_{254}) were viewed on UV light or with the Cifonelli and Smith reagent for the diol structures: (a) 0.1% aq. solution of sodium metaperiodate; (b) solution of benzidine (1.8 g of benzidine, 50 mL H_20, 50 mL EtOH, 20 mL of acetone and 10 mL 0.2 M aq. HCl; diols gave a white spot.[10] Melting points were measured in a capillary tube on Electrothermal IA 9000. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. All reactions were carried out under nitrogen atmosphere. All solvents were purified prior to use using the standard techniques.

3.1.1. *N*-Benzyloxycarbonyl glycine *N′*-methoxy-*N′*-methylamide. To a solution of *Z*-glycine (8.0 g, 38.2 mmol) in dry CH_2Cl_2 (25 mL) at room temp. were added Et_3N (3.86 g, 38.2 mmol), benzotriazol-1-yloxytris (dimethylamino)phosphonium hexafluorophosphate (BOP) (16.9 g, 38.2 mmol) and *N*,*O*-dimethylhydroxylamine hydrochloride (4.1 g, 42.02 mmol). The mixture was stirred for 5 min and an extra portion of Et_3N (~1 equiv) was added to obtain pH 9–10. The reaction was stirred for 2 h and then diluted with 50 mL of CH_2Cl_2 before phase separation. The organic phase was washed with 3 M HCl aq. (3×15 mL) and aq. NaCl sat. (1×20 mL) then with aq. $NaHCO_3$ sat. (3×15 mL) and aq. NaCl sat. (3×20 mL). The organic layer was dried over $MgSO_4$. After evaporation the resulting oil was purified by chromatography (Hexane/EtOAc 2:1) to give the pure product as a white solid, 8.20 g, 85%, mp 75–78 °C, R_f (0.33 Hexane/EtOAc 1:1). ^{1}H NMR (250 MHz, $CDCl_3$) 7.36 (s, 5H, Ph), 5.56 (m, 1H, NH), 5.14 (s, 2H, CH_2Ph), 4.15 (d, 2H, J=4.3 Hz, NH–CH_2), 3.72 (s, 3H, N–OCH_3), 3.21 (s, 3H, N–CH_3). ^{13}C/{^{1}H} NMR (62.9 MHz, $CDCl_3$) 170.0 (*C*O–N–OMe), 155.7 (*C*O–NH), 136.2 (Ph), 128.6 (Ph), 128.4 (Ph), 128.3 (Ph), 67.1 (Ph–CH_2–O), 61.2 (N–OCH_3), 41.4 (NH–CH_2), 31.9 (N–CH_3). IR (cm^{-1}) 3310, 1715, 1660.

3.1.2. *N*-Benzyloxycarbonyl-glycinal 6b. To a solution of *N*-benzyloxycarbonyl glycine *N′*-methoxy-*N′*-methylamide (3.5 g, 14.0 mmol) in dry THF (65 mL) at 0 °C was added drop wise a 1 M ethereal solution of lithiumaluminium hydride (14.0 mL, 14.0 mmol) during 25 min. The reaction was stirred for additional 20 min at 0 °C and quenched by aq. $KHSO_4$ (3.74 g in 15 mL H_2O) followed by extraction with CH_2Cl_2 (3×30 mL). The organic layer was then washed with 3 N HCl (3×15 mL), aq. NaCl sat. (1×10 mL), aq. $NaHCO_3$ (3×15 mL) and aq. NaCl sat. (3×15 mL). The organic layer was dried over $MgSO_4$. After evaporation a resulting colourless oil was obtained, 2.27 g, 85%, R_f (0.42 AcOEt/Hexane 1:1). The crude product was used in further transformations. ^{1}H NMR (250 MHz $CDCl_3$): 9.67 (s, 1H, CHO), 7.37 (s, 5H, Ph), 5.45 (m, 1H, NH), 5.15 (s, 2H, CH_2–Ph), 4.17 (d, 2H, J=4.8 Hz, NH–CH_2). ^{13}C (62.9 MHz, $CDCl_3$) 196.5 (*C*HO), 158.1 (NH–*C*O), 136.3 (Ph), 128.7 (Ph), 128.5 (Ph), 128.3 (Ph), 67.4 (*C*H_2–Ph), 51.8 (NH–*C*H_2). IR (cm^{-1}) 3320, 1725, 1690.

3.1.3. *t*-Butyl-4-[(benzyloxycarbonyl)amino]-2-methyl-2-butanoate 5b*Z*, 5b*E*. To a solution of *t*-butyl 2-diethylphosphonopropanoate (2.93 g, 11.0 mmol) in dry THF (50 mL) at −78 °C was added drop wise *n*-BuLi 1.4 M sol. in hexane (8.0 mL). The reaction was stirred at this temperature for 30 min and *N*-benzyloxycarbonyl-glycinal **6** in 10 mL THF was added (2.08 g, 11.0 mmol). The reaction mixture was stirred for 3 h at −78 °C and then hydrolysed with 25 ml aq. NH_4Cl sat. The phases were separated and the aqueous phase was extracted with Et_2O (3×20 mL). The organic phases were combined, dried over $MgSO_4$ and evaporated to give a yellow syrup which was purified by flash chromatography (Hexane/EtOAc 7:1), 1.97 g, 60%, **5b*Z***: R_f (0.48 EtOAc/Hexane 2:1), ^{1}H NMR (250 MHz, $CDCl_3$) 7.36 (s, 5H, Ph), 5.94 (t, 1H, J=6.3 Hz, CH=C(CH_3)), 5.12 (s, 2H, PhCH_2), 4.10 (t, 2H, J=6.4 Hz, NH–CH_2), 1.87 (s, 3H, CH=C(CH_3)), 1.50 (s, 9H, C(CH_3)$_3$), ^{13}C/{^{1}H} NMR (62.9 MHz, $CDCl_3$) cis 168.4 (*C*O*O*t-Bu), 158.1 (NH–*C*O), 137.6 (*C*H=), 135.3 (=*C*(CH_3)), 128.6 (Ph), 128.4 (Ph), 128.2 (Ph), 80.9 (*C*(CH_3)$_3$), 67.4 (Ph–*C*H_2), 39.0

(NH–CH_2), 28.3 (C(CH_3)$_3$), 20.4 (C(CH_3)). **5b*E***: R_f (0.39 EtOAc/Hexane 2:1), ^{1}H NMR (250 MHz, $CDCl_3$): 7.36 (s, 5H, Ph), 6.55 (t, 1H, J=6.5 Hz, CH=C(CH_3)), 5.12 (s, 2H, PhCH_2), 4.85 (m, 1H,NH–CH_2), 3.95 (m, 2H, NH–CH_2), 1.82 (s, 3H, CH=C(CH_3)), 1.48 (s, 9H, C(CH_3)$_3$), ^{13}C/{^{1}H} NMR (62.9 MHz, $CDCl_3$) trans 166.8 (*C*OO*t*-Bu), 156.4 (NH–*C*O), 136.4 (*C*H=), 131.1 (=*C*(CH_3)), 128.5 (Ph), 128.1 (Ph), 126.9 (Ph), 80.5 (*C*(CH_3)$_3$), 66.8 (Ph–*C*H_2), 39.3 (NH–*C*H_2), 28.0 (C(*C*H_3)$_3$), 12.5 (C(*C*H_3)). IR (cm^{-1}) 3345, 1800–1705, 1650. HR MS (FAB): *m/z* Calcd for $C_{17}H_{23}NO_4$ [M]$^+$ 305.37, found 306.30 ([M+1]$^+$, 45%), 250.20 ([M+1–*t*-Bu]$^+$, 100%).

3.2. Asymmetric dihydroxylation of vinylogous glycine derivative 5

General procedure. To 50 mL of a solution of H_2O/*t*-BuOH (1/1) was added AD-mix (6.41 g) followed by methane sulfonamide (440 mg, 4.58 mmol) and this was stirred until total homogenising. The reaction mixture was then cooled to 0 °C and stirred for 15 min until orange solid precipitated. Olefin **5** (1.4 g, 4.58 mmol) was added to this mixture and the reaction mixture was left stirring for an additional 1 h at 0 °C, then allowed to warm to room temperature. Stirring was continued for 48 h in the case of olefin **5b*Z***, and for 192 h in the case of **5b*E***. Then, the reaction was quenched with solid $Na_2S_2O_5$ (6.9 g) and stirred for 1 h. The phases were separated and the aqueous layer was extracted with EtOAc (3×20 mL) The organic phases were combined, washed with aq. KOH 2 M (3×5 mL), dried over $MgSO_4$, and evaporated to give an oil which was purified by chromatography (Hexane/EtOAc 1:1, then EtOAc).

3.2.1. *t*-Butyl-4-[*N*-(benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methyl butanoate 4b. *α-syn*. White solid, 1.31 g 85%, mp 87–90 °C, R_f 0.28 (EtOAc/Hexane 1:1), $[\alpha]_D^{22}$ −4.4 (*c* 0.4 CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) 7.36 (s, 5H, Ph), 5.20–5.37 (m, 1H, NH), 5.12 (s, 2H, Ph–CH_2), 3.82 (dd, 1H, J=8.5, 3.2 Hz, CH_2C*H*), 3.59 (s, 1H, OH), 3.57 (m, 1H, NH–CH_2), 3.15 (ddd, 1H, J=14.3, 8.1, 3.2 Hz, NH–CH_2), 2.46 (m, 1H, OH), 1.51 (s, 9H, C(CH_3)$_3$), 1.35 (s, 3H, C(CH_3)), IR (cm^{-1}) 3600–3140, 1760–1645, 1150, 1080. HR MS (FAB): *m/z* Calcd for $C_{17}H_{25}NO_6$ [M]$^+$ 339.39, found 340.30 [M+1]$^+$, 42%), 284.20 ([M+1–*t*Bu]$^+$, 100%), ([M+1–*t*-BuOC(O)]$^+$, 50%).

3.2.2. *t*-Butyl-4-[*N*-(benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methylbutanoate 4b. *β-syn*. White solid, 1.27 g, 82%, mp 90–92 °C, R_f 0.28 (EtOAc/Hexane 1:1), $[\alpha]_D^{22}$ +2.33 (*c* 0.4 CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) 7.36 (s, 5H, Ph), 5.20–5.37 (m, 1H, NH), 5.12 (s, 2H, Ph–CH_2), 3.82 (dd, 1H, J=8.5, 3.2 Hz, CH_2C*H*), 3.59 (s, 1H, OH), 3.57 (m, 1H, NH–CH_2), 3.15 (ddd, 1H, J=14.3, 8.1 Hz, J=3.2 Hz, NH–CH_2), 2.46 (m, 1H, OH), 1.51 (s, 9H, C(CH_3)$_3$), 1.35 (s, 3H, C(CH_3)). ^{13}C/{^{1}H} NMR (62.9 MHz, $CDCl_3$) 174.8 (*C*OO*t*-Bu), 157.1 (NH–*C*O), 136.1 (Ph), 128.6 (Ph), 128.3 (Ph), 128.2 (Ph), 83.6 (*C*(CH_3)$_3$), 75.3 (*C*H–OH), 67.0 (*C*(CH_3), *C*H_2–Ph), 43.0 (NH–CH_2), 28.2 (C(*C*H_3)$_3$), 22.8 (C(*C*H_3).

3.2.3. *t*-Butyl-4-[*N*-(benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methyl butanoate 4b. *α-anti*. White solid, 1.39 g, 90%, mp 78–80 °C, R_f 0.21 (EtOAc/Hexane 1:2), $[\alpha]_D^{22}$ −4.0 (*c* 0.4 CH_2Cl_2). ^{1}H NMR (250 MHz, $CDCl_3$) 7.36 (s, 5H, Ph), 5.08–5.22 (m, 1H, NH), 5.11 (s, 2H, Ph–CH_2), 3.65–3.77 (m, 1H, CH_2C*H*), 3.49 (s, 1H, OH), 3.42–3.56 (m, 1H, NH–CH_2), 3.12 (ddd, 1H, J=13.9, 9.1, 4.0 Hz, NH–CH_2), 2.42 (m, 1H, OH), 1.52 (s, 9H, C(CH_3)$_3$), 1.43 (s, 3H, C(CH_3)).

3.2.4. *t*-Butyl-4-[*N*-(benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methyl butanoate 4b. *β-anti*. White solid, 1.31 g, 85%, R_f 0.21 (EtOAc/Hexane 1:2), $[\alpha]_D^{22}$ +9.5 (*c* 0.4 CH_2Cl_2). ^{1}H NMR (250 MHz $CDCl_3$) 7.36 (s, 5H, Ph), 5.08–5.22 (m, 1H, NH), 5.11 (s, 2H, Ph–CH_2), 3.65–3.77 (m, 1H, CH_2C*H*), 3.49 (s, 1H, OH), 3.42–3.56 (m, 1H, NH–CH_2), 3.12 (ddd, 1H, J=13.9, 9.1, 4.0 Hz, NH–CH_2), 2.42 (m, 1H, OH), 1.52 (s, 9H, C(CH_3)$_3$), 1.43 (s, 3H, C(CH_3)). ^{13}C/{^{1}H} NMR (62.9 MHz, $CDCl_3$) 174.5 (*C*OO*t*Bu), 157.7 (NH–*C*O), 135.8 (Ph), 127.8 (Ph), 128.7 (Ph), 128.3 (Ph), 83.6 (*C*(CH_3)$_3$), 74.2 (*C*H–OH), 67.0 (*C*(CH_3), *C*H_2–Ph), 42.3 (NH–*C*H2), 28.0 (C(*C*H_3)$_3$), 22.8 (C(*C*H_3)), IR (cm^{-1}) 3610–3130, 1755–1645, 1140, 1080. HR MS (FAB): *m/z* Calcd for $C_{17}H_{25}NO_6$ [M]$^+$ 339.39, found 340.30 [M+1]$^+$, 50%), 284.20 ([M+1–*t*Bu]$^+$, 100%), ([M+1–*t*-BuOC(O)]$^+$, 50%).

3.3. General procedure for the hydrogenolysis of the ZNH group of 4

Deprotection of the *N*-benzyloxycarbonyl function was carried out in standard conditions using Pd/C 10% and H_2 (30 bars). The protected molecule (1.03 g, 3.03 mmol) was dissolved in dry MeOH (15 mL). Pd/C was added (40 mg) and after 12 h under H_2 (30 bars) the mixture was filtered through celite and evaporated to give crude **3** which was used directly in further reactions without any purification.

3.3.1. Coupling reaction of 3 with caffeic acid. The caffeic acid (621.0 mg, 3.45 mmol) was dissolved in dry DMF (15 mL) and Et_3N (0.48 mL, 3.45 mmol) was added followed by the addition of BOP (1.52 g, 3.45 mmol) and the appropriate diol **3** (710.0 mg, 3.45 mmol). The mixture was stirred for 5 min and an extra portion of Et_3N (~1 equiv) was added to obtain pH 9–10. The reaction mixture was stirred for 2 h, then evaporated to dryness and the crude product was purified by column chromatography (Hexane/EtOAc 1:2, then EtOAc) to obtain pure product **2**.

3.3.2. *t*-Butyl-4-[[(2*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methylbutanoate 2b. *α-syn*. White solid, 0.85 g, 67%, mp 92–95 °C, R_f 0.32 (EtOAc/Hexane 5:1), $[\alpha]_D^{22}$ −4.17 (*c* 0.21 CH_3OH). ^{1}H NMR (400 MHz, MeOH-d_4): 7.39 (d, 1H, J=15.7 Hz, H_β), 7.00 (d, 1H, J=1.9 Hz, H_2), 6.90 (dd, 1H, ^3J=8.2, ^4J=1.9 Hz, H_6), 6.75 (d, 1H, J=8.2 Hz, H_5), 6.40 (d, 1H, J=15.7 Hz, H_α), 3.88 (dd, 1H, J=9.0, 2.9 Hz, $H_{3'}$), 3.72 (dd, 1H, J=13.9, 2.9 Hz, $H_{4'a}$), 3.21 (dd, 1H, J=13.9, 9.0 Hz, $H_{4'b}$), 1.48 (s, 9H, *t*-Bu), 1.34 (s, 3H, $H_{5'}$), ^{13}C/{^{1}H} NMR (100 MHz, MeOH-d_4) 175.9 ($C_{1'}$), 169.9 (CONH), 148.9 (C_4), 146.8 (C_3), 142.5 (C_β), 128.4 (C_1), 122.3 (C_6), 118.5 (C_α), 116.6 (C_5), 115.2 (C_2), 83.2 (*C*(Me)$_3$), 78.3 ($C_{2'}$), 75.6 ($C_{3'}$), 42.2 ($C_{4'}$), 28.3 (C(*C*H_3)$_3$), 22.6 ($C_{5'}$), IR (cm^{-1}) 3670–3615, 1730, 1640, 1110, 1075, HR MS (FAB): *m/z* Calcd for $C_{18}H_{25}NO_7$ [M]$^+$ 367.39, found 368.30

$[M+1]^+$, 78%), 312.20 ($[M+1-t\text{-Bu}]^+$, 53%), ($[M+1-NH-CH_2-CH(OH)-C(CH3)(OH)-C(O)Ot\text{-Bu}]^+$, 100%).

3.3.3. *t*-Butyl-4-[[(2*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methylbutanoate 2b. *β-syn*. White solid, 0.89 g, 70%, mp 94–96 °C, R_f 0.33 (EtOAc/Hexane 5:1), $[\alpha]_D^{22}$ +2.78 (*c* 0.21 CH_3OH). ^1H NMR (400 MHz, MeOH-d_4) 7.39 (d, 1H, $J=15.7$ Hz, H_β), 7.00 (d, 1H, $J=1.9$ Hz, H_2), 6.90 (dd, 1H, $J=8.2$, 1.9 Hz, H_6), 6.75 (d, 1H, $J=8.2$ Hz, H_5), 6.40 (d, 1H, $J=15.7$ Hz, H_α), 3.88 (dd, 1H, $J=9.0$, 2.9 Hz, $H_{3'}$), 3.72 (dd, 1H, $J=13.9$, 2.9 Hz, $H_{4'a}$), 3.21 (dd, 1H, $J=13.9$, 9.0 Hz, $H_{4'b}$), 1.48 (s, 9H, *t*-Bu), 1.34 (s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4): 175.9 ($C_{1'}$), 169.9 (CONH), 148.9 (C_4), 146.8 (C_3), 142.5 (C_β), 128.4 (C_1), 122.3 (C_6), 118.5 (C_α), 116.6 (C_5), 115.2 (C_2), 83.2 ($C(Me)_3$), 78.3 ($C_{2'}$), 75.6 ($C_{3'}$), 42.2 ($C_{4'}$), 28.3 ($C(CH_3)_3$), 22.6 ($C_{5'}$).

3.3.4. *t*-Butyl-4-[[(2*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methylbutanoate 2b. *α-anti*. White solid, 0.95 g, 75%, mp 86–89 °C, R_f 0.30 (EtOAc/Hexane 5:1), $[\alpha]_D^{22}$ −3.95 (*c* 0.21 CH_3OH). ^1H NMR (400 MHz, MeOH-d_4) 7.38 (d, 1H, $J=15.7$ Hz, H_β), 6.99 (d, 1H, $J=1.9$ Hz, H_2), 6.89 (dd, 1H, $^3J=8.2$, $^4J=1.9$ Hz, H_6), 6.75 (d, 1H, $J=8.2$ Hz, H_5), 6.38 (d, 1H, $J=15.7$ Hz, H_α), 3.82 (dd, 1H, $J=9.1$, 3.2 Hz, $H_{3'}$), 3.54 (dd, 1H, $J=13.7$, 3.2 Hz, $H_{4'a}$), 3.23 (dd, 1H, $J=13.7$, 9.1 Hz, $H_{4'b}$), 1.50 (s, 9H, *t*-Bu), 1.39 (s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4): 175.7 ($C_{1'}$), 169.8 (CONH), 148.9 (C_4), 146.8 (C_3), 142.4 (C_β), 128.5 (C_1), 122.2 (C_6), 118.6 (C_α), 116.6 (C_5), 115.2 (C_2), 83.5 ($C(Me)_3$), 77.8 ($C_{2'}$), 75.6 ($C_{3'}$), 42.8 ($C_{4'}$), 28.3 ($C(CH_3)_3$), 23.2 ($C_{5'}$), IR (cm^{-1}) 3675–3610, 1720, 1650, 1120, 1080, HR MS (FAB): *m/z* Calcd for $C_{18}H_{25}NO_7$ $[M]^+$ 367.39, found 368.30 $[M+1]^+$, 78%), 312.20 ($[M+1-t\text{-Bu}]^+$, 53%), ($[M+1-NH-CH_2-CH(OH)-C(CH3)(OH)-C(O)Ot\text{-Bu}]^+$, 100%).

3.3.5. *t*-Butyl-4-[[(2*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methylbutanoate 2b. *β-anti*. White solid, 1.01 g, 80%, mp 99–100 °C, R_f 0.91 (Acetone/MeOH 8:2), $[\alpha]_D^{22}$ +5.2 (*c* 0.21 CH_3OH). ^1H NMR (400 MHz, MeOH-d_4/D_2O: 1/1) 7.40 (d, 1H, $J=15.5$ Hz, Ph–CH=, noted H_β), 7.00 (d, 1H, $J=2.0$ Hz, Ph, noted H_2), 6.90 (dd, 1H, $J=8.8$, 2 Hz, Ph, noted H_6), 6.75 (d, 1H, $J=8.8$ Hz, Ph, noted H_5), 6.38 (d, 1H, $J=15.5$ Hz, =CH–Ph, noted H_α), 3.82 (dd, 1H, $J=9$, 3.5 Hz, noted $H_{3'}$), 3.54 (dd, 1H, $J=13.9$, 3.5 Hz, noted $H_{4'a}$), 3.25 (dd, 1H, $J=13.9$, 9.0 Hz, noted $H_{4'b}$), 1.45 (s, 9H, *t*-Bu), 1.34 (s, 3H, $H_{5'}$), $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4/D_2O: 1/1) 174.7 ($C_{1'}$), 168.8 (CONH), 147.8 (C_4), 145.7 (C_3), 141.5 (C_β), 127.3 (C_1), 121.2 (C_6), 117.3 (C_α), 115.5 (C_5), 114.1 (C_2), 82.6 ($C(Me)_3$),76.7 ($C_{2'}$), 74.4 ($C_{3'}$), 41.6 ($C_{4'}$), 27.2 ($C(CH_3)_3$), 22.1 ($C_{5'}$).

3.4. Typical procedure for the deprotection of the *t*-butyl-ester 2

The *t*-butyl ester **2** (200 mg, 0.545 mmol) was dissolved in 4 mL of pure TFA and the mixture was stirred for 30 min at rt. The evaporation of TFA followed by co-evaporation with toluene gave the free acid as a solid, which was used directly in the further reaction without any purification.

3.4.1. Preparation of the potassium salt 1 from 4-[[(2*E*)-3-(3,4-dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methyl butanoic acid. The free acid (85 mg, 0.27 mmol) was dissolved in dry MeOH (5 mL) and a 0.15 M solution of potassium methanolate in methanol was added drop wise (1.8 mL, 0.27 mmol). The reaction was stirred for 5 min and evaporated to dryness to give the desired product **1** as a solid.

3.4.2. 4-[[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methyl butanoate potassium salt 1. *α-syn*. White-yellow solid, 90.0 mg, 95%, mp 140–143 °C, $[\alpha]_D^{22}$ −6.25 (*c* 0.24 50% MeOH aq.). ^1H NMR (400 MHz, MeOH-d_4) 7.38 (d, 1H, $J=15.6$ Hz, H_β), 7.01 (d, 1H, $J=1.8$ Hz, H_2), 6.90 (dd, 1H, $J=8.2$, 1.8 Hz, H_6), 6.76 (d, 1H, $J=8.2$ Hz, H_5), 6.41 (d, 1H, $^3J=15.6$ Hz, H_α), 3.73 (unresolved signal, 1H, $H_{3'}$), 3.34 (unresolved signal, 2H, $H_{4'}$), 1.48 (s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4/D_2O: 1/1) 181.8 ($C_{1'}$), 169.8 (CONH), 148.9 (C_4), 146.8 (C_3), 142.3 (C_β), 128.1 (C_1), 122.3 (C_6), 118.2 (C_α), 117.2 (C_5), 115.5 (C_2), 76.0 ($C_{2'}$), ($C_{3'}$), 42.7 ($C_{4'}$), 23.4 ($C_{5'}$); IR (cm^{-1}) 3630–2640, 1645, 1595, 1285, 1125, 1080; HR MS (ES^-): *m/z* Calcd for $C_{14}H_{16}NO_7K$ $[M-K]^-$ 310.1, found 310.1$[M-K]^-$, 100%).

3.4.3. 4-[[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methyl butanoate potassium salt 1. *β-syn*. Yellow-green solid, 87.0 mg, 92%, mp 135–137 °C, $[\alpha]_D^{22}$ +1.67 (*c* 0.24 50% MeOH aq.). ^1H NMR (400 MHz, MeOH-d_4/D_2O: 1/1) 7.38 (d, 1H, $J=15.6$ Hz, $H_{\beta\beta}$), 7.09 (d, 1H, $J=1.7$ Hz, H_2), 7.02 (dd, 1H, $J=8.2$, 1.7 Hz, H_6), 6.85 (d, 1H, $J=8.2$ Hz, H_5), 6.45 (d, 1H, $J=15.6$ Hz, H_α), 3.74 (unresolved signal, 1H, $H_{3'}$), 3.23 (unresolved signal, 2H, $H_{4'}$), 1.47 (large s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4/D_2O: 1/1) 181.8 ($C_{1'}$), 169.3 (CONH), 147.9 (C_4), 145.3 (C_3), 142.7 (C_β), 128.1 (C_1), 123.2 (C_6), 118.6 (C_α), 117.1 (C_5), 115.5 (C_2), 78.0 ($C_{2'}$), 75.5 ($C_{3'}$), 42.5 ($C_{4'}$), 23.4 ($C_{5'}$).

3.4.4. 4-[[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methyl butanoate potassium salt 1. *α-anti*. Brown-yellow solid, 88.0 mg, 93%, $[\alpha]_D^{22}$ −4.0 (*c* 0.24 50% MeOH aq.). ^1H NMR (400 MHz, MeOH-d_4) 7.36 (d, 1H, $^3J=15.8$ Hz, H_β), 7.02 (enlarged s, 1H, H_2), 6.88 (enlarged d, 1H, $J=8.2$ Hz, H_6), 6.75 (d, 1H, $J=8$ Hz, H_5), 6.40 (d, 1H, $J=15.8$ Hz, H_α), 3.80 (m, 1H, $H_{3'}$), 3.43 (unresolved m, 2H, $H_{4'}$), 1.37 (s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4) 181.9 ($C_{1'}$), 170.0 (CONH), 149.9 (C_4), 147.0 (C_3), 142.3 (C_β), 128.2 (C_1), 122.3 (C_6), 118.6 (C_α), 116.6 (C_5), 115.1 (C_2), 77.7 ($C_{2'}$), 76.1 ($C_{3'}$), 42.9 ($C_{4'}$), 23.3 ($C_{5'}$).

3.4.5. 4-[[(2*E*)-3-(3,4-Dihydroxyphenyl)-1-oxo-2-propenyl]amino]-2,3-dihydroxy-2-methyl butanoate potassium salt 1. *β-anti*. Brown solid, 93.0 mg, 98%, $[\alpha]_D^{22}$ +5.4 (*c* 0.24 50% MeOH aq.). ^1H NMR (400 MHz, MeOH-d_4/D_2O: 1/1) 7.37 (d, 1H, $J=15.7$ Hz, H_β), 7.08 (d, 1H, $J=1.9$ Hz, H_2), 7.00 (dd, 1H, $J=8.2$, 1.9 Hz, H6), $\delta=6.84$ (d, 1H, $J=8.2$ Hz, H_5), 6.44 (d, 1H, $J=15.7$ Hz, H_α), 3.82 (m, 1H, $H_{3'}$), 3.37 (unresolved m, 2H, $H_{4'}$), 1.36 (s, 3H, $H_{5'}$). $^{13}C/\{^1H\}$ NMR (100 MHz, MeOH-d_4/D_2O: 1/1) 181.5 ($C_{1'}$), 170.0 (CONH), 147.9 (C_4), 145.7 (C_3), 142.0 (C_β), 128.5 (C_1), 123.0 (C_6), 118.5 (C_α), 117.0 (C_5), 115.5 (C_2),

78.0 ($C_{2'}$), 75.5 ($C_{3'}$), 42.5 ($C_{4'}$), 23.5 ($C_{5'}$); IR (cm^{-1}) 3635–2640, 1655, 1600, 1280, 1120, 1080; HR MS (ES^-): *m/z* Calcd for $C_{14}H_{16}NO_7K$ $[M-K]^-$ 310.1, found 310.1$[M-K]^-$, 100%).

3.4.6. Preparation of Mosher's esters 7b/7′b. Dry pyridine (1.2 mL) and (*S*)-(+)-α-Methoxy-α-(trifluoromethyl)-phenylacetyl chloride [(*S*)-MTPA-Cl] were dissolved in 5 mL of dry CH_2Cl_2 and appropriate *t*-butyl-4-[*N*-(Benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methylbutanoate **4b** (80 mg, 0.235 mmol) was added. The reaction mixture was stirred for 48 h, then diluted with 20 mL of CH_2Cl_2, successively washed with 1 N aq. HCl (2×5 mL), sat. aq. $NaHCO_3$ (3×5 mL), sat. aq. NaCl (3×5 mL), dried over $MgSO_4$ and evaporated to give the crude product as an oil.

7b/7′b *β-anti*. Colourless syrup, 89.0 mg, 68.0%, R_f 0.84 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, $CDCl_3$) 7.62–7.31 (m, 10H, Ph), 5.41 (dd, 1H, $^3J_{HH}$= 7.9 Hz, $^3J_{HH}$=4.0 Hz, CH), 5.08 (m, 2H, CH_2Ph), 4.93–5.10 (m, 1H, NH), 3.49 (s, 3H, OCH_3), 3.37–3.71 (m, 2H, CH_2), 3.42 (s, 1H, OH), 1.50 (s, 9H, $C(CH_3)_3$), 1.28 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.77 (s, 3F, CF_3). *Diastereomer 2*: ^1H NMR (250 MHz, $CDCl_3$): 7.62–7.31 (m, 10H, Ph), 5.36–5.46 (m, 1H, CH), 5.08 (m, 2H, CH_2Ph), 4.56–5.76 (m, 1H, NH), 3.57 (s, 3H, OCH_3), 3.37–3.52 (m, 2H, CH_2), 3.42 (s, 1H, OH), 1.50 (s, 9H, $C(CH_3)_3$), 1.30 (s, 1H, $C(CH_3)$), ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.87 (s, 3F, CF_3), $^{13}C/\{^1H\}$ NMR (62.9 MHz, CH_3OD) 179.7 (*C*(O)), 175.6 (*C*(O)O-*t*-Bu), 158.2 (NH*C*(O)), 129.9 (Ph), 128.6 (Ph), 128.3 (Ph), 127.6 (Ph), 84.6 (*C*(OH)), 77.8 (*C*F_3), 75.3 (*C*H(O)), 67.1 (Ph–*C*H_2) 55.8, 55.6 (O*C*H_3 from dia. 1 and 2), 41.4 (NH*C*H_2), 27.9 (C(*C*$H_3)_3$), 23.6, 23.3 (C(*C*H_3)) from dia. 1 and 2).

7b/7′b *α-anti*. Colourless syrup, 94.0 mg, 72.0%, R_f 0.84 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, $CDCl_3$) 7.60–7.20 (m, 10H, Ph), 5.41 (m, 1H, CH), 5.08 (m, 2H, CH_2Ph), 4.86 (m, 1H, NH), 3.55 (s, 3H, OCH_3), 3.42 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.41 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.74 (s, 3F, CF_3). *Diastereomer 2*: ^1H NMR (250 MHz, $CDCl_3$) 7.28 (m, 10H, Ph), 5.15 (m, 1H, CH), 5.08 (m, 2H, CH_2Ph), 4.86 (m, 1H, NH), 3.49 (s, 3H, OCH_3), 3.42 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.26 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −72.07 (s, 3F, CF_3). MS (FAB^+): *m/z* Calcd for $C_{27}H_{32}F_3NO_8$ $[M]^+$ 555.2, found 556.2 $[M+1]^+$ (100%).

7b/7′b *β-syn*. Colourless syrup, 91.0 mg, 70.0%, R_f 0.90 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, $CDCl_3$) 7.63–7.25 (m, 10H, Ph), 5.48 (m, 1H, CH), 5.08 (m, 2H, CH_2Ph), 4.86 (m, 1H, NH), 3.52 (s, 3H, OCH_3), 3.12–3.24 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.46 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.43 (s, 3F, CF_3). *Diastereomer 2*: ^1H NMR (250 MHz, $CDCl_3$) 7.28 (m, 10H, Ph), 5.38 (m, 1H, CH), 5.08 (m, 2H, CH_2Ph), 4.86 (m, 1H, NH), 3.49 (s, 3H, OCH_3), 3.12–3.24 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.41 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.61 (s, 3 F, CF_3). MS (FAB): *m/z* Calcd for $C_{27}H_{32}F_3NO_8$ $[M]^+$ 555.2, found 556.1 $[M+1]^+$ (100%).

7b/7′b *α-syn*. Colourless syrup, 90.0 mg, 69.0%, R_f 0.90 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, $CDCl_3$) 7.58–7.21 (m, 10H, Ph), 5.47 (m, 1H, CH), 5.05 (m, 2H, CH_2Ph), 3.41 (s, 3H, OCH_3), 3.56–3.58 (m, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.36 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.58 (s, 3F, CF_3). *Diastereomer 2*: ^1H NMR (250 MHz, $CDCl_3$) 7.29 (m, 10H, Ph), 5.47 (m, 1H, CH), 5.05 (m, 2H, CH_2Ph), 3.41 (s, 3H, OCH_3), 3.19–3.06 (m, 2H, CH_2), 1.49 (s, 9H, $C(CH_3)_3$), 1.29 (s, 1H, $C(CH_3)$). ^{19}F NMR (235.4 MHz, $CDCl_3$) −71.89 (s, 3F, CF_3), IR (cm^{-1}) 3580–3150, 1750, 1720, 1515, 1250, 1170, 1070.

3.4.7. Preparation of dipeptides 8b/8′b. To a solution of 4-[*N*-(Benzyloxycarbonyl)amino]-2,3-dihydroxy-2-methylbutanoic acid (440 mg, 1.55 mmol) in dry CH_2Cl_2 (25 mL), were added successively Et_3N (0.22 mL, 1.55 mmol), BOP (680 mg, 1.55 mmol) and H-Leu-OMe·HCl (310 mg, 1.705 mmol). The mixture was stirred for 5 min and Et_3N (∼1 equiv) was added up to obtain pH 9–10. Stirring was continued for 2 h, before the reaction mixture was evaporated to dryness to provide a crude oil which was purified by column chromatography (Hexane/EtOAc 2:1, then EtOAc) to obtain pure product **8b**.

8b/8′b *β-anti*. White solid, 520.0 mg, 82.0%, R_f 0.21 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, acetone-d_6) 7.76 (bs, 1H, N*H*–CH–C(O)), 7.30 (m, 5H, Ph), 6.48 (bs, 1H, N*H*–CH_2–Ph), 5.08 (s, 2H, CH_2Ph), 4.50 (m, 2H, NH–C*H* and O*H*), 3.89 (bs, 1H, C*H*), 3.70 (s, 3H, OCH_3), 3.18 (m, 3H, NH–CH_2 and O*H*), 1.45 (m, 3H, CH_2C*H*), 1.45 (s, 3H, CH_3), 0.91 (m, 6H, (C$H_3)_2$). *Diastereomer 2*: ^1H NMR (250 MHz, acetone-d_6) 7.76 (bs, 1H, N*H*–CH–C(O)), 7.30 (m, 5H, Ph), 6.48 (bs, 1H, N*H*–CH_2–Ph), 4.86 (s, 2H, CH_2Ph), 4.50 (m, 2H, NH–C*H* and O*H*), 3.89 (bs, 1H, C*H*), 3.68 (s, 3H, OCH_3), 3.18 (m, 3H, NH–CH_2 and O*H*), 1.45 (m, 3H, CH_2C*H*), 1.43 (s, 3H, CH_3), 0.91 (m, 6H, (C$H_3)_2$). MS (FAB): *m/z* Calcd for $C_{20}H_{30}N_2O_7$ $[M]^+$ 410.2, found 411.3 $[M+1]^+$ (100%).

8b/8′b *α-anti*. White solid, 540.0 mg, 85.0%, R_f 0.21 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR (250 MHz, acetone-d_6) 7.76 (bs, 1H, N*H*–CH–C(O)), 7.30 (m, 5H, Ph), 6.48 (bs, 1H, N*H*–CH_2–Ph), 5.08 (s, 2H, CH_2Ph), 4.50 (m, 2H, NH–C*H* and O*H*), 3.89 (bs, 1H, C*H*), 3.70 (s, 3H, OCH_3), 3.18 (m, 3H, NH–CH_2 and O*H*), 1.45 (m, 3H, CH_2C*H*), 1.45 (s, 3H, CH_3), 0.91 (m, 6H, (C$H_3)_2$), ^{13}C NMR (62.9 MHz, acetone-d_6)175.5 (*C*(O)–NH), 173.1 (*C*(O)CH_3), 157.6 (*C*(O)CH_2Ph), 137.7 (Ph), 128.7 (Ph), 128.2 (Ph), 76.7 (*C*–CH_3), 74.7 (*C*HOH), 66.3 (*C*H_2–Ph), 52.0 (O–*C*H_3), 50.6 (*C*H–CO), 43.1 (*C*H_2CH(C$H_3)_2$), 40.6 (NH–*C*H_2), 25.0 (*C*H(C$H_3)_2$), 22.8 ((*C*$H_3)_2$), 21.3 (*C*H_3). *Diastereomer 2*: ^1H NMR (250 MHz, acetone-d_6) 7.76 (bs, 1H, N*H*–CH–C(O)), 7.30 (m, 5H, Ph), 6.48 (bs, 1H, N*H*–CH_2–Ph), 4.86 (s, 2H, CH_2Ph), 4.50 (m, 2H, NH–C*H* and O*H*), 3.89 (bs, 1H, C*H*), 3.68 (s, 3H, OCH_3), 3.18 (m, 3H, NH–CH_2 and O*H*), 1.45 (m, 3H, CH_2C*H*), 1.43 (s, 3H, CH_3), 0.91 (m, 6H, (C$H_3)_2$), ^{13}C NMR (62.9 MHz, acetone-d_6)175.5 (*C*(O)–NH), 173.1 (*C*(O)CH_3), 157.6 (*C*(O)CH_2Ph), 137.7 (Ph), 128.7 (Ph), 128.2 (Ph), 76.8 (*C*–CH_3), 74.7 (*C*HOH), 66.3 (*C*H_2–Ph), 52.0 (O–*C*H_3), 50.6 (*C*H–CO), 43.1 (*C*H_2CH(C$H_3)_2$), 40.6 (NH–*C*H_2), 25.0 (*C*H(C$H_3)_2$), 22.9 ((*C*$H_3)_2$), 21.30 (*C*H_3).

8b/8′b *β-syn*. White solid, 490.0 mg, 82.0%, R_f 0.50 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^1H NMR

(250 MHz, acetone-d_6) 7.60 (bs, 1H, N*H*–CH–C(O)), 7.31 (m, 5H, Ph), 6.27 (bs, 1H, N*H*–CH_2–Ph), 5.06 (s, 2H, CH_2Ph), 4.46 (m, 1H, NH–C*H*), 3.70 (m, 1H, C*H*), 3.67 (s, 3H, OCH_3), 3.58 (m, 1H, NH–CH_2), 3.12 (m, 1H, NH–CH_2), 1.64 (m, 3H, CH_2C*H*), 1.43 (s, 3H, CH_3), 0.89 (m, 6H, (CH_3)$_2$). *Diastereomer 2*: ^{1}H NMR (250 MHz, acetone-d_6) 7.60 (bs, 1H, N*H*–CH–C(O)), 7.31 (m, 5H, Ph), 6.27 (bs, 1H, N*H*–CH_2–Ph), 5.06 (s, 2H, CH_2Ph), 4.46 (m, 1H, NH–C*H*), 3.70 (m, 1H, C*H*), 3.67 (s, 3H, OCH_3), 3.58 (m, 1H, NH–CH_2), 3.12 (m, 1H, NH–CH_2), 1.64 (m, 3H, CH_2C*H*), 1.40 (s, 3H, CH_3), 0.89 (m, 6H, (CH_3)$_2$).

8b/8′b *α-syn*. White solid, 509.0 mg, 80.0%, R_f 0.50 (EtOAc/Hexane 1:1), *Diastereomer 1*: ^{1}H NMR (250 MHz, $CDCl_3$) 7.27 (m, 6H, N*H*–CH–C(O)) and Ph), 5.59 (bs, 1H, N*H*–CH_2–Ph), 5.03 (s, 2H, CH_2Ph), 4.50 (m, 1H, NH–C*H*), 4.26 (bs, 2H, O*H*), 3.49 (m, 1H, C*H*), 3.66 (s, 3H, OCH_3), 3.55 (m, 1H, NH–CH_2), 3.18 (m, 1H, NH–CH_2),1.64 (m, 3H, CH_2C*H*), 1.47 (s, 3H, CH_3), 0.89 (m, 6H, (CH_3)$_2$), ^{13}C NMR (62.9 MHz, acetone-d_6) 176.9 (*C*(O)–NH), 173.4 (*C*(O)CH$_3$), 157.8 (*C*(O)CH$_2$Ph), 137.5 (Ph), 128.30 (Ph), 128.2 (Ph), 76.0 (*C*–CH$_3$), 75.7 (*C*OH), 66.5 (*C*H$_2$–Ph), 52.3 (O–*C*H$_3$), 50.9 (*C*H–CO), 42.7 (*C*H$_2$CH(CH$_3$)$_2$), 40.7 (NH–*C*H$_2$), 25.0 (*C*H(CH$_3$)$_2$), 22.9 ((*C*H$_3$)$_2$), 21.4 (*C*H$_3$). *Diastereomer 2*: ^{1}H NMR (250 MHz, $CDCl_3$) 7.27 (m, 6H, N*H*–CH–C(O)) and Ph), 5.59 (bs, 1H, N*H*–CH_2–Ph), 5.03 (s, 2H, CH_2Ph), 4.50 (m, 1H, NH–C*H*), 4.26 (bs, 2H, O*H*), 3.49 (m, 1H, C*H*), 3.65 (s, 3H, OCH_3), 3.55 (m, 1H, NH–CH_2), 3.18 (m, 1H, NH–CH_2),1.64 (m, 3H, CH_2C*H*), 1.39 (s, 3H, CH_3), 0.89 (m, 6H, (CH_3)$_2$), ^{13}C NMR (62.9 MHz, acetone-d_6) 176.9 (*C*(O)–NH), 173.4 (*C*(O)CH$_3$), 157.8 (*C*(O)CH$_2$Ph), 137.5 (Ph), 128.3 (Ph), 128.2 (Ph), 76.0 (*C*–CH$_3$), 75.7 (*C*OH), 66.5 (*C*H$_2$–Ph), 52.3 (O–*C*H$_3$), 50.9 (*C*H–CO), 42.7 (*C*H$_2$-CH(CH$_3$)$_2$), 40.5 (NH–*C*H$_2$), 25.0 (*C*H(CH$_3$)$_2$), 22.9 ((*C*H$_3$)$_2$), 21.4 (*C*H$_3$). MS (FAB): *m*/*z* Calcd for $C_{20}H_{30}N_2O_7$ $[M]^+$ 410.2, found 411.2 $[M+1]^+$ (100%).

Acknowledgements

The authors thank the French Ministry of National Education (MENESR) for financial support. We are very grateful to Dr. A. van Dorsselaer, University Louis Pasteur, Strasbourg, France, for mass measurements.

References and notes

1. Ueda, M.; Hiraoka, T.; Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1999**, *40*, 6777–6780.
2. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
3. Fehrentz, J. A.; Castro, B. *Synthesis* **1983**, 676–678.
4. (a) Grison, C.; Coutrot, P.; Genève, S.; Didierjean, C.; Marraud, M. *J. Org. Chem.* in press. (b) Grison, C.; Genève, S.; Halbin, E.; Coutrot, P. *Tetrahedron* **2001**, *57*, 4903–4923.
5. (a) Yokokawa, F.; Hamada, Y.; Shioiri, T. *Synlett* **1992**, 703–705. (b) Gurjar, M. K.; Ghosh, L.; Jayasree, V. *Tetrahedron Lett.* **1994**, *35*, 8871–8872. (c) Reetz, M. T.; Strack, T. J.; Mutilis, F.; Goddard, R. *Tetrahedron Lett.* **1996**, *52*, 9293–9296. (d) Reetz, M. T.; Strack, T. J.; Mutilis, F.; Goddard, R. *Tetrahedron Lett.* **1996**, *37*, 9293–9296. (e) Broady, R.; Rexhausen, S. D.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1083–1094. (f) Chandrasekharan, S.; Ramachandar, T.; Reddy, M. V. *Synthesis* **2002**, 1867–1870. (g) Hulme, A. N.; Montgomery, C. H. *Tetrahedron Lett.* **2003**, *44*, 7649–7653. (h) Kwan, C. Y.; Zhang, W. B.; Miller, J.; Harrison, P. H. M.; Kassan, S. *J. Pharmacol. Sci.* **2003**, *92*, 203–208. (i) Dagonneau, C.; Denis, J. N.; Philouze, C.; Averbuch-Pouchot, M. T.; Vallée, Y. *Acta Cryst. E* **2004**, *60*, 510–512.
6. Claudel, S. Thesis, University of UHP, Nancy 1, France, 2004.
7. Grison, C.; Petek, S.; Finance, C.; Coutrot, P. *Carbohydr. Res.* **2005**, *340*, 529–537.
8. Chandrasekaran, S.; Kluge, A. F.; Edwards, J. A. *J. Org. Chem.* **1977**, *42*, 3972–3974.
9. Fujii, T.; Sugimoto, T.; Yamamura, S.; Ueda, M. *Tetrahedron Lett.* **2003**, *44*, 2497–2499.
10. Cifonelli, J. A.; Smith, F. *Anal. Chem.* **1954**, *26*, 1132–1134.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1799–1805
Tetrahedron

A synthesis of novel *N*-sulfonylated β-amino acids

Dirk Freitag[†] and Peter Metz*

Technische Universität Dresden, Institut für Organische Chemie, Bergstraße 66, D-01069 Dresden, Germany

Received 16 September 2005; revised 17 November 2005; accepted 21 November 2005

Available online 20 December 2005

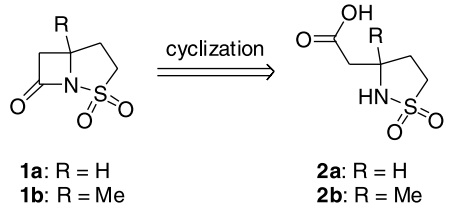
Abstract—Novel *N*-sulfonyl β-amino acids were efficiently prepared in a seven-step synthesis starting from Boc protected methanesulfonamide and terminal epoxides. A zinc-mediated allylation of cyclic *N*-sulfonyl imines readily derived from these building blocks served as a key operation of this sequence.

1. Introduction

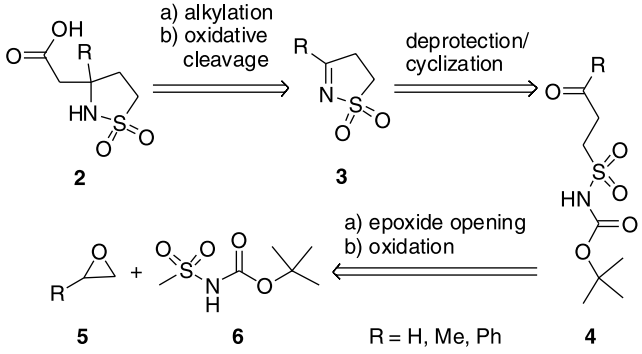
In the last decade, β-amino acids and their derivatives have been studied intensively.[1] They represent major structural features of a large number of bioactive compounds such as the antifungal agent jasplakinolide[2a] and the antitumor drug taxol.[2b] Moreover, β-amino acid derivatives are of high value as precursors for peptidomimetics[3a] and β-lactams,[3b–d] and the free amino acids can display useful biological effects as well.[4]

As part of a program launched into the development of novel methods for the preparation of cyclic sulfonic acid derivatives,[5] we have recently developed an access to a range of bicyclic β-lactam-sulfonamide hybrids[6] by ring closing metathesis and hydrogenation.[5a,b] However, the carbapenam–monobactam hybrids **1a**,**b** featuring a γ-sultam moiety were not available using this methodology. Since cyclization of β-amino acids **2** was envisioned as an alternative approach to **1** (Scheme 1), we investigated their synthesis. Here, we report an efficient protocol for the preparation of the *N*-sulfonylated β-amino acids **2a** and **2b**.

According to our retrosynthetic analysis (Scheme 2), acids **2** should be available by an allylation/oxidative cleavage sequence from cyclic *N*-sulfonyl imines **3**. Heterocycles **3** might be obtained by deprotection/condensation from carbonyl compounds **4**, which in turn should be accessible by regioselective ring opening of epoxides **5** with the dianion of **6** followed by oxidation.



Scheme 1. Envisaged access to β-lactam-sulfonamide hybrids **1** by cyclization of β-amino acids **2**.



Scheme 2. Retrosynthetic analysis for β-amino acids **2**.

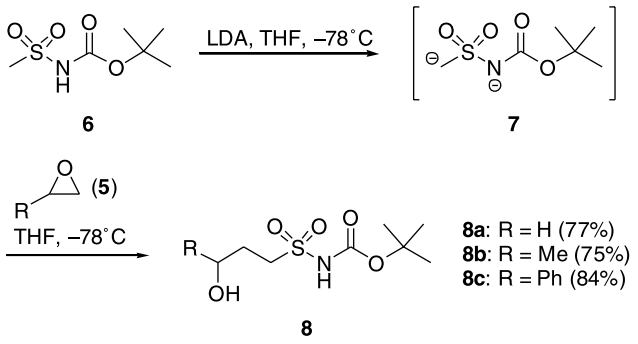
2. Results and discussion

2.1. Synthesis of cyclic *N*-sulfonyl imines 3

Deprotonation of Boc protected methanesulfonamide **6**[7] using an excess of LDA gave rise to dianion **7**,[8] which was used in ring opening reactions of ethylene oxide (**5a**), propylene oxide (**5b**), and styrene oxide (**5c**) (Scheme 3). Nucleophilic addition of **7** to **5** delivered primary alcohol **8a** and secondary alcohols **8b**,**c** in good yields.

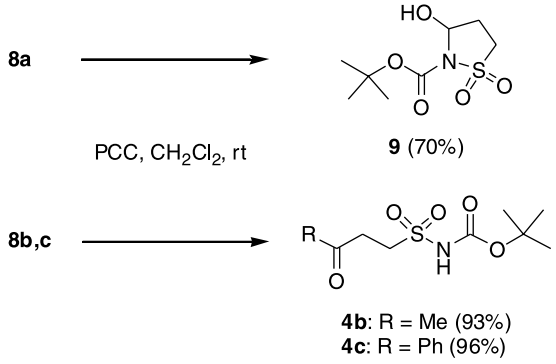
Keywords: β-Amino acids; γ-Sultams; Sulfonyl imines; Sulfonamides; Allylation; Oxidative cleavage.
* Corresponding author. Tel.: +49 351 463 37006; fax: +49 351 463 33162; e-mail: peter.metz@chemie.tu-dresden.de
[†] New address: Chemisches Labor für Umwelt- und Produktanalytik, Drebnitzer Weg 4, D-01877 Bischofswerda, Germany.

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.052



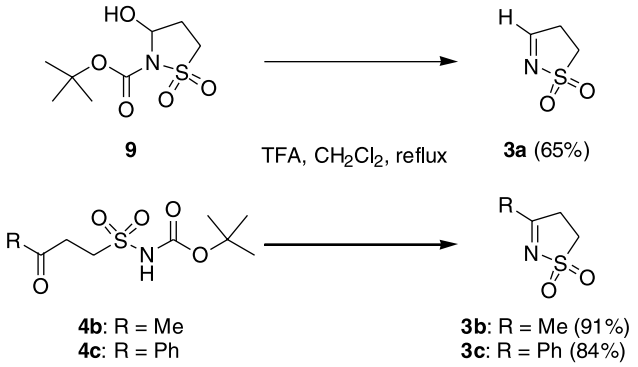
Scheme 3. Nucleophilic addition of dianion **7** to epoxides **5**.

For oxidation of alcohols **8**, the chromium reagent PCC[9] gave the best results (Scheme 4). While hemiaminal **9** was isolated after oxidation of **8a**, reactions of **8b** and **8c** with PCC smoothly afforded ketones **4b** and **4c**, respectively, in high yields.



Scheme 4. PCC oxidation of **8**.

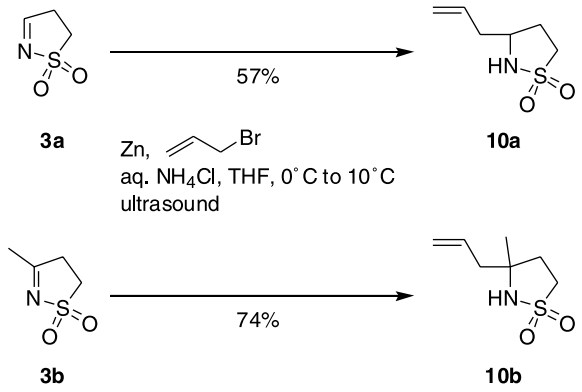
Trifluoroacetic acid (TFA) is a standard reagent for the cleavage of Boc protecting groups.[10] In our approach to heterocycles **3**, TFA has two additional functions as an acidic catalyst, namely to promote intramolecular nucleophilic attack at the carbonyl moiety of **4** as well as subsequent dehydration (Scheme 5). Much to our delight, all tasks were readily fulfilled by TFA, and the *N*-sulfonyl imines **3** could be isolated as crystalline compounds in good (**3a**) to excellent (**3b**,**c**) yields.[11] For deprotection/dehydration of **9**, the use of molecular sieves 4 Å was essential in order to achieve a synthetically useful yield of **3a**.



Scheme 5. Deblocking/dehydration to give cyclic *N*-sulfonyl imines **3**.

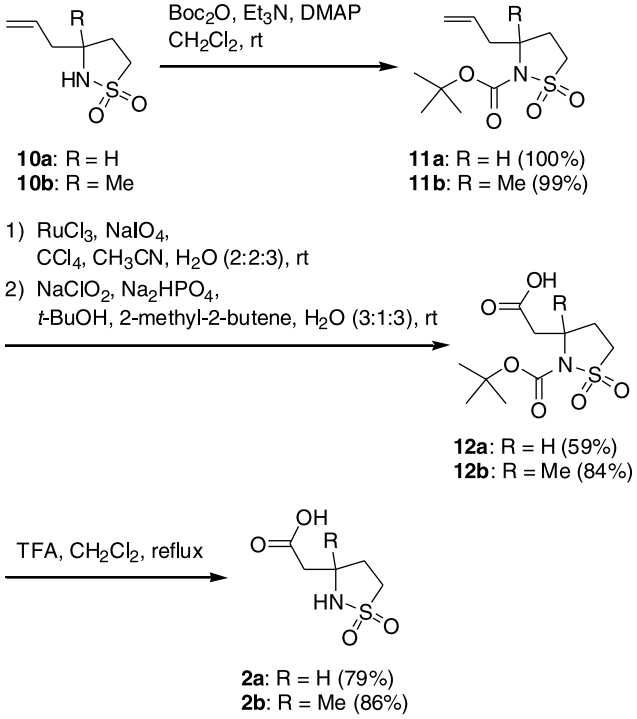
2.2. Allylation of cyclic *N*-sulfonyl imines 3 and oxidative cleavage

Among the large variety of reaction conditions for allylation of imines,[12] reactions in aqueous media are of particular importance,[13] since they are easily performed and environmentally friendly. We allylated imines **3** according to conditions published by Lu and Chan[14] using a large excess of zinc and allyl bromide (Scheme 6). Activation of the metal surface[15] by ultrasonication of the reaction mixture shortened the reaction times and improved the yields of γ-sultams **10a**,**b**.



Scheme 6. Allylation of cyclic *N*-sulfonyl imines **3a** and **3b**.

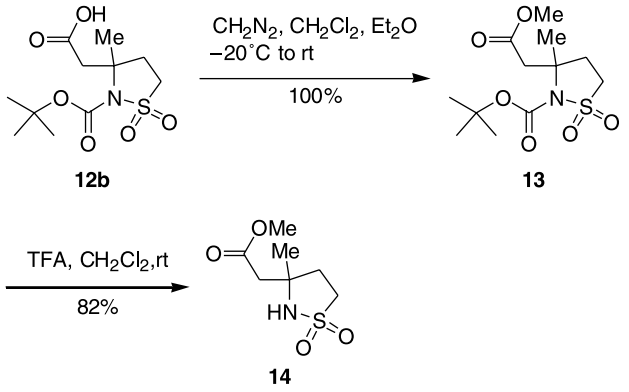
As anticipated, allylation of **3a** proceeded much faster than allylation of **3b**. Nevertheless, sultam **10b** was obtained in good yield. In contrast, phenylsubstituted analog **3c** was not allylated under these conditions, probably due to the steric hindrance caused by the phenyl substituent. Likewise, attempted alkylation of **3c** with other nucleophilic agents (MeMgBr, MeLi) met with no success.



Scheme 7. Formation of β-amino acids **2a** and **2b**.

The next step in our synthetic plan was oxidative cleavage of the alkene. Using a Lemieux–von-Rudloff oxidation[16] with ruthenium tetroxide generated in situ from ruthenium trichloride in the presence of excess sodium periodate, formation of the desired products was detected by mass spectrometric analysis of the reaction mixture. However, isolation of the very polar acids **2** from the aqueous reaction medium could not be achieved. This problem was eventually overcome by Boc protection of γ-sultams **10** to afford derivatives **11**. Lemieux–von-Rudloff oxidation of **11** and subsequent oxidation with sodium chlorite delivered Boc protected acids **12**. Finally, TFA promoted removal of the Boc protecting group gave rise to the desired acids **2a** and **2b** (Scheme 7).

Similar to the cyclization of β-amino acids, conversion of their methyl esters to β-lactams promoted by organometallic agents such as Grignard reagents[17] and organolithium compounds[18] is a commonly applied process. With this aim in mind, we also transformed the Boc protected β-amino acid **12b** into methyl ester **13**. Removal of the Boc protecting group by TFA then smoothly delivered β-amino acid methyl ester **14** (Scheme 8).



Scheme 8. Synthesis of β-amino acid methyl ester **14**.

Despite extensive experimentation, we were not able to find suitable conditions for cyclization of free acids **2a**,**b** or methyl ester **14** to give bicyclic β-lactams **1**. Apparently, the highly strained nature of the ring system to be formed and the low nucleophilicity of the sulfonamide moiety[19] in **2a**,**b** and **14** preclude β-lactam formation.

3. Conclusion

An efficient seven-step route to novel β-amino acids **2** bearing a γ-sultam moiety has been developed starting from Boc protected methanesulfonamide (**6**) and terminal epoxides **5** via a zinc-mediated allylation of cyclic *N*-sulfonyl imines **3** readily derived from building blocks **6** and **5**.

4. Experimental

4.1. General methods

All reactions were carried out under argon atmosphere using anhydrous solvents and flame-dried glassware. Commercially available compounds were used without further purification. Diazomethane was prepared as an approximately 0.35 M solution in diethyl ether from commercially available Diazald® according to a procedure published by Hudlicky.[20] Solvents were dried according to standard procedures. Analytical TLC was performed on precoated Merck Si 254 F plates, and the products were visualized with a solution of $KMnO_4$. Merck silica gel 60 (40–63 μm) was used for flash chromatography. Melting points were determined on a Kofler microscope desk. IR spectra were measured with a ThermoNicolet AVATAR 360 FT-IR. ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-300 using either $CDCl_3$ or DMSO-d_6 as the solvent and are reported in ppm downfield from TMS ($\delta=0$) for ^1H NMR and relative to the central $CDCl_3$ resonance ($\delta=77.7$) or DMSO-d_6 resonance ($\delta=40.8$) for ^{13}C NMR. ^{13}C multiplicities were determined using DEPT pulse sequences. Mass spectra were recorded with a Hewlett Packard Esquire-LC (LC/MS) and an Agilent GC 6890N coupled to an Agilent MSD 5973 (GC/MS). Elemental analysis were carried out with a EuroVector EA-3000.

4.2. Nucleophilic opening of epoxides 5

4.2.1. *tert*-Butyl-*N*-[(3-hydroxypropyl)sulfonyl]-carbamate (8a). To a cooled (−78 °C) solution of diisopropylamine (1.12 mL, 8.00 mmol) in THF (8 mL) was added *n*-BuLi (5.00 mL, 8.00 mmol, 1.6 M in *n*-hexane). After stirring the resulting mixture for 10 min, a solution of carbamate **6** (0.78 g, 4.00 mmol) in THF (8 mL) was added dropwise over a period of 20 min and stirring was continued for additional 20 min. The resulting white suspension was treated successively with 0.5 mL portions of a solution of ethylene oxide (**5a**) (0.22 g, 5.00 mmol) in THF (5 mL) over a period of 30 min. The reaction mixture was slowly warmed to 0 °C and stirred for 2 h. After additional stirring at ambient temperature for 2 h, the mixture was poured onto an ice-cold saturated aqueous NH_4Cl solution (10 mL). The resulting precipitate was dissolved by addition of water, and the mixture was acidified with 2 N HCl to pH 3. The aqueous layer was extracted 3× with CH_2Cl_2 (20 mL), and the organic extracts were dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was finally purified by flash chromatography (CH_2Cl_2/Et_2O 20:1) to afford **8a**. Yield 77% (735.0 mg, 3.08 mmol); white solid; mp 98–99 °C; R_f 0.21 (CH_2Cl_2/Et_2O 5:1); IR (neat) 3458, 1743, 1332, 1126 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9H), 2.08–2.15 (m, 2H), 3.54–3.59 (m, 2H), 3.81 (t, 2H, $J=5.9$ Hz); ^{13}C NMR ($CDCl_3$) δ 26.27, 27.94, 50.13, 60.27, 84.49, 149.65; MS (LC/MS) *m/z* (%) 278 (8) [M+K$^+$], 262 (100) [M+Na$^+$], 257 (7) [M+NH$_4^+$]. Anal. Calcd for $C_8H_7NO_5S$: C, 40.15; H, 7.16; N, 5.85; S, 13.40. Found: C, 40.25; H, 7.14; N, 5.87; S, 13.57.

4.2.2. *tert*-Butyl-*N*-[(3-hydroxybutyl)sulfonyl]-carbamate (8b). To a cooled (−78 °C) solution of diisopropylamine (5.60 mL, 40.0 mmol) in THF (40 mL) was added *n*-BuLi (25.0 mL, 40.0 mmol, 1.6 M in *n*-hexane). After stirring the resulting mixture for 10 min, a solution of carbamate **6** (3.90 g, 20.0 mmol) in THF (40 mL) was added dropwise over a period of 20 min and stirring was continued for additional 20 min. The resulting white suspension was treated with a solution of propylene oxide (**5b**) (1.75 mL, 25.0 mmol) in THF (25 mL) over a period of 30 min.

The reaction mixture was slowly warmed to ambient temperature (16 h) and poured onto an ice-cold saturated aqueous NH_4Cl solution (50 mL). The resulting precipitate was dissolved with water, and the mixture was acidified with 2 N HCl to pH 3. The aqueous layer was extracted 3× with CH_2Cl_2 (50 mL), and the organic extracts were washed with brine and dried over anhydrous $MgSO_4$. After concentration in vacuo, the residue was finally purified by flash chromatography (Et_2O) to afford **8b**. Yield 75% (3.80 g, 15.0 mmol); colorless oil; R_f 0.33 (Et_2O); IR (neat) 3513, 1734, 1340, 1127 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.26 (d, 3H, J=6.2 Hz), 1.51 (s, 9H), 1.85–2.08 (m, 2H), 3.56 (dt, 2H, J=6.5, 9.1 Hz), 3.96–4.02 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 23.41, 27.92, 32.16, 49.88, 65.90, 84.34, 149.86; MS (LC/MS) m/z (%)=271 (68) [M+NH_4^+], 254 (18) [M+H^+], 198 (100) [M−C_4H_8+H^+]. Anal. Calcd for $C_9H_{19}NO_5S$: C, 42.67; H, 7.56; N, 5.53; S, 12.66. Found: C, 42.48; H, 7.78; N, 5.64, S, 12.35.

4.2.3. *tert*-Butyl-*N*-[(3-hydroxy-3-phenylpropyl)-sulfonyl]-carbamate (8c). The reaction was performed as described for the preparation of **8b**; starting materials: **6** (3.90 g, 20.0 mmol) and styrene oxide (**5c**) (2.85 mL, 25.0 mmol), flash chromatography: CH_2Cl_2/Et_2O 20:1. Yield 84% (5.30 g, 16.8 mmol); white solid; mp 98–100 °C; R_f 0.53 (CH_2Cl_2/Et_2O 20:1); IR (neat) 3506, 1723, 1339, 1128 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.21–2.28 (m, 2H), 3.50–3.55 (m, 2H), 4.88 (t, 1H, J=6.4 Hz), 7.27–7.39 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.89, 32.44, 49.75, 72.01, 84.43, 125.61, 128.13, 128.76, 142.90, 149.62; MS (LC/MS) m/z (%)=653 (100) [2×M+Na^+], 333 (21) [M+NH_4^+]. Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.32; H, 6.71; N, 4.44; S, 10.17. Found: C, 53.41; H, 6.99; N, 4.39; S, 10.17.

4.3. Oxidation of alcohols 8

4.3.1. 3-Hydroxy-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (9). To a solution of **8a** (239.0 mg, 1.00 mmol) in CH_2Cl_2 (8 mL) was added PCC (453.0 mg, 2.10 mmol). The resulting dark-brown solution was stirred for 9 h at ambient temperature. After addition of Et_2O (5 mL) and additional stirring (15 min), the mixture was filtered (Et_2O) through a pad of silica gel. Concentration in vacuo afforded the analytically pure hemiaminal **9**. Yield 70% (167.0 mg, 0.70 mmol); white solid; mp 78–80 °C; R_f 0.43 (Et_2O); IR (neat) 3467, 1719, 1317, 1129 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56 (s, 9H), 2.30–2.38 (m, 1H), 2.47–2.58 (m, 1H), 3.31 (ddd, 1H, J=12.7, 2.6, 6.9 Hz), 3.60 (ddd, 1H, J=7.0, 7.0, 12.6 Hz), 3.95 (s, 1H), 5.65–5.68 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.16, 28.02, 46.94, 79.52, 85.30, 150.26; MS (LC/MS) m/z (%)=255 (100) [M+NH_4^+], 238 (9) [M+H^+]. Anal. Calcd for $C_8H_{15}NO_5S$: C, 40.50; H, 6.37; N, 5.90; S, 13.51. Found: C, 40.29; H, 6.39; N, 5.89; S, 13.46.

4.3.2. *tert*-Butyl-*N*-[(3-oxobutyl)sulfonyl]-carbamate (4b). To a solution of **8b** (3.80 g, 15.0 mmol) in CH_2Cl_2 (120 mL) was added PCC (6.90 g, 32.0 mmol). The resulting dark-brown solution was stirred for 3 h at ambient temperature. After addition of Et_2O (30 mL) and additional stirring (15 min), the mixture was filtered (Et_2O) through a pad of silica gel. Concentration in vacuo afforded the analytically pure ketone **4b**. Yield 93% (3.5 g, 14.0 mmol); white solid; mp 82–83 °C; R_f 0.40 (Et_2O); IR (neat) 1724, 1332, 1130 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.50 (s, 9H), 2.22 (s, 3H), 3.01 (t, 2H, J=7.2 Hz), 3.67 (t, 2H, J=7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 27.92, 29.79, 36.68, 47.71, 84.61, 149.53, 203.52; MS (LC/MS) m/z (%)=525 (100) [2×M+Na^+], 269 (32) [M+NH_4^+], 252 (9) [M+H^+]. Anal. Calcd for $C_9H_{17}NO_5S$: C, 43.01; H, 6.82; N, 5.57; S, 12.76. Found: C, 43.14; H, 6.92; N, 5.52; S, 12.77.

4.3.3. *tert*-Butyl-*N*-[(3-oxo-3-phenylpropyl)sulfonyl]-carbamate (4c). To a solution of **8c** (4.33 g, 13.8 mmol) in CH_2Cl_2 (120 mL) was added PCC (6.20 g, 28.8 mmol). The resulting dark-brown solution was stirred for 4.5 h at ambient temperature. After addition of Et_2O (100 mL) and additional stirring (15 min), the mixture was filtered (Et_2O) through a pad of silica gel. Concentration in vacuo afforded the analytically pure ketone **4c**. Yield 96% (4.15 g, 13.22 mmol); white solid; mp 103–104 °C; R_f 0.56 (CH_2Cl_2/MeOH 100:1); IR (neat) 1739, 1341, 1137 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 9H), 3.56–3.60 (m, 2H), 3.86–3.91 (m, 2H), 7.14 (s, 1H), 7.47–7.52 (m, 2H), 7.59–7.64 (m, 1H), 7.96–8.00 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.94, 32.31, 48.26, 84.68, 128.14, 128.84, 133.85, 135.79, 149.44, 195.15; MS (LC/MS) m/z (%)=649 (100) [2×M+Na^+], 336 (30) [M+Na^+], 280 (13) [M−C_4H_8+Na^+]. Anal. Calcd for $C_{14}H_{19}NO_5S$: C, 53.66; H, 6.11; N, 4.47; S, 10.23. Found: C, 53.78; H, 6.11; N, 4.49; S, 10.35.

4.4. Synthesis of cyclic *N*-sulfonyl imines 3

4.4.1. 4,5-Dihydro-isothiazole 1,1-dioxide (3a). TFA (0.11 mL, 1.41 mmol) and molecular sieves 4 Å (100 mg) were added to a solution of **9** (111 mg, 0.47 mmol) in CH_2Cl_2 (14 mL). The resulting solution was heated to reflux for 16 h, cooled to ambient temperature and filtered (CH_2Cl_2/ethyl acetate 1:1) through a pad of silica gel. Concentration in vacuo and purification by flash chromatography (CH_2Cl_2/ethyl acetate 1:1) afforded imine **3a**. Yield 65% (36.4 mg, 0.31 mmol); white solid; mp 68–70 °C; R_f 0.41 (CH_2Cl_2/ethyl acetate 1:1); IR (neat) 1597, 1307, 1142 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.13–3.18 (m, 2H), 3.31–3.37 (m, 2H), 8.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.69, 40.70, 170.82; MS (GC/MS, EI, 70 eV) m/z (%) 119 (6) [M^+], 75 (5), 66 (8), 65 (13), 64 (97), 59 (8), 58 (7), 57 (7), 55 (22), 54 (26), 52 (25), 51 (20), 50 (9), 49 (7), 48 (100), 46 (13), 45 (13), 43 (7), 40 (15), 39 (29), 38 (19), 37 (11). Anal. Calcd for $C_3H_5NO_2S$: C, 30.24; H, 4.23; N, 11.76; S, 26.91. Found: C, 30.33; H, 4.19; N, 11.84; S, 26.96.

4.4.2. 3-Methyl-4,5-dihydro-isothiazole 1,1-dioxide (3b). TFA (4.70 mL, 63.6 mmol) was added to a solution of ketone **4b** (4.00 g, 15.9 mmol) in CH_2Cl_2 (150 mL). The solution was heated to reflux for 48 h, and EtOH (20 mL) was added. Concentration of the reaction mixture in vacuo to a volume of approximately 10 mL and subsequent crystallization at −20 °C afforded imine **3b**. Yield 91% (1.93 g, 14.5 mmol); white solid; mp 81 °C; R_f 0.30 (CH_2Cl_2/ethyl acetate 1:1); IR (neat) 1618, 1308, 1146 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 3.11–3.23 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.90, 37.88, 44.33, 182.04; MS (GC/MS, EI, 70 eV) m/z (%) 133 (5) [M^+], 89 (2), 69

(75), 68 (9), 64 (9), 54 (7), 48 (15), 42 (100), 41 (11), 40 (8), 39 (7). Anal. Calcd for $C_4H_7NO_2S$: C, 36.08; H, 5.30; N, 10.52; S, 24.08. Found: C, 35.87; H, 5.34; N, 10.33; S, 24.19.

4.4.3. 3-Phenyl-4,5-dihydro-isothiazole 1,1-dioxide (3c). TFA (3.00 mL, 40.4 mmol) was added to a solution of **4c** (4.14 g, 13.2 mmol) in CH_2Cl_2 (100 mL). The solution was heated to reflux for 35 h, cooled to ambient temperature and filtered (CH_2Cl_2) through a pad of silica gel. After concentration in vacuo and purification by flash chromatography (CH_2Cl_2), imine **3c** was isolated. Yield 84% (2.16 g, 11.1 mmol); white solid; mp 175 °C; R_f 0.32 (CH_2Cl_2); IR (neat) 1592, 1310, 1141 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.35–3.40 (m, 2H), 3.59–3.63 (m, 2H), 7.42–7.48 (m, 2H), 7.55–7.61 (m, 1H), 7.94 (dd, 2H, $J=1.2$, 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 33.47, 44.23, 129.03, 129.13, 130.87, 134.50, 175.86; MS (GC/MS, EI, 70 eV) *m/z* (%) 195 (15) [M^+], 131 (8), 104 (15), 103 (100), 77 (9), 76 (12), 51 (6). Anal. Calcd for $C_9H_9NO_2S$: C, 55.37; H, 4.65; N, 7.17; S, 16.42. Found: C, 55.31; H, 4.77; N, 6.94; S, 16.40.

4.5. Allylation of cyclic *N*-sulfonyl imines 3

4.5.1. 3-Allyl-isothiazolidine-1,1-dioxide (10a). Imine **3a** (0.40 g, 3.38 mmol) was dissolved in a mixture of THF (7 mL) and saturated aqueous NH_4Cl solution (33 mL). To the solution was added Zn powder (1.10 g, 16.8 mmol), and the mixture was ultrasonicated for 30 s. Then allyl bromide (0.89 mL, 10.1 mmol) was added, and the temperature of the mixture was carefully adjusted to 0–10 °C with ice-cooling. After 30 min of ultrasonication, the mixture was warmed to ambient temperature, the resulting precipitate was dissolved with water, and remaining Zn was removed by filtration. To the filtrate 1 N H_3PO_4 (0.5 mL) and CH_2Cl_2 (25 mL) were added, and the mixture was carefully acidified with 2 N HCl. The layers were separated, and the aqueous layer was extracted 5× with CH_2Cl_2 (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo, and the residue was purified by flash chromatography (CH_2Cl_2/ethyl acetate 4:1) to afford γ-sultam **10a**. Yield 57% (308.0 mg, 1.91 mmol); colorless oil; R_f 0.53 (CH_2Cl_2/ethyl acetate 4:1); IR (neat) 3261, 1289, 1137 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.10–2.20 (m, 1H), 2.37 (dd, 2H, $J=6.8$, 6.8 Hz), 2.45–2.56 (m, 1H), 3.07–3.25 (m, 2H), 3.68 (ddd, 1H, $J=6.4$, 12.9, 14.5 Hz), 4.12 (s, 1H), 5.16–5.22 (m, 2H), 5.70–5.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 28.76, 39.84, 47.74, 53.95, 119.18, 132.77; MS (GC/MS, EI, 70 eV) *m/z* (%) 162 (0.2) [$M^+ + 1$], 122 (11), 121 (12), 120 (100), 68 (7), 56 (48), 54 (7). Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69; S, 19.89. Found: C, 44.83; H, 6.92; N, 8.77; S, 19.77.

4.5.2. 3-Allyl-3-methyl-isothiazolidine-1,1-dioxide (10b). Imine **3b** (1.94 g, 14.5 mmol) was dissolved in a mixture of THF (30 mL) and saturated aqueous NH_4Cl solution (140 mL). To the solution was added Zn powder (4.70 g, 71.8 mmol), and the mixture was ultrasonicated for 30 s. Then allyl bromide (3.80 mL, 43.5 mmol) was added, and the temperature of the mixture was carefully adjusted to 0–10 °C with ice-cooling. After 30 min of ultrasonication, additional amounts of Zn powder (2.40 g, 36.7 mmol) and allyl bromide (2.00 mL, 22.9 mmol) were added, and this was repeated 4× in 30 min intervals. Then ultrasonication was stopped, the mixture was warmed to ambient temperature, the resulting precipitate was dissolved with water, and remaining Zn was removed by filtration. To the filtrate 1 N H_3PO_4 (2 mL) and CH_2Cl_2 (100 mL) were added, and the mixture was carefully acidified with 2 N HCl. The layers were separated, and the aqueous layer was extracted 5× with CH_2Cl_2 (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, concentrated in vacuo, and the residue was purified by flash chromatography (Et_2O) to afford γ-sultam **10b**. Yield 74% (1.87 g, 10.7 mmol); colorless oil; R_f 0.36 (Et_2O); IR (neat) 3265, 1293, 1136 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.29 (s, 3H), 2.10–2.20 (m, 1H), 2.25–2.35 (m, 3H), 3.06–3.20 (m, 2H), 4.31 (s, 1H), 5.09–5.17 (m, 2H), 5.69–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 27.34, 34.54, 46.27, 47.63, 59.31, 120.25, 132.19; MS (GC/MS, EI, 70 eV) *m/z* (%) 176 (0.1) [$M^+ + 1$], 136 (9), 135 (11), 134 (100), 70 (33), 54 (4). Anal. Calcd for $C_7H_{13}NO_2S$: C, 47.97; H, 7.48; N, 7.99; S, 18.30. Found: C, 47.99; H, 7.43; N, 8.14; S, 18.63.

4.6. Conversion of 10 to β-amino acids 2

4.6.1. Typical procedure for protection of γ-sultams 10. To a solution of γ-sultam **10b** (1.87 g, 10.7 mmol) in CH_2Cl_2 (30 mL) were added triethylamine (1.70 mL, 11.7 mmol) and DMAP (127.0 mg, 1.07 mmol) followed by dropwise addition of a solution of Boc_2O (2.66 g, 12.3 mmol) in CH_2Cl_2 (20 mL) over 30 min. The reaction mixture was stirred for 3 h and filtered (CH_2Cl_2) through a pad of silica gel. After evaporation in vacuo, the crude product was purified by flash chromatography (Et_2O) to give **11b**.

4.6.1.1. 3-Allyl-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (11a). Starting material: **10a** (270.0 mg, 1.68 mmol), flash chromatography: Et_2O. Yield 100% (438.0 mg, 1.68 mmol); colorless oil; R_f 0.59 (Et_2O); IR (neat) 1716, 1309, 1134 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.55 (s, 9H), 2.11–2.21 (m, 1H), 2.35–2.52 (m, 2H), 2.60–2.68 (m, 1H), 3.21–3.89 (m, 2H), 4.13–4.21 (m, 1H), 5.18 (dd, 1H, $J=1.3$, 15.8 Hz), 5.18 (dd, 1H, $J=1.1$, 11.4 Hz), 5.70–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.29, 28.04, 37.48, 47.62, 55.79, 84.19, 119.42, 132.39, 149.70; MS (LC/MS) *m/z* (%) 545 (100) [$2\times M+Na^+$], 279 (88) [$M+NH_4^+$], 262 (6) [$M+H^+$], 223 (16) [$M-C_4H_8+NH_4^+$], 206 (57) [$M-C_4H_8+H^+$]. Anal. Calcd for $C_{11}H_{19}NO_4S$: C, 50.55; H, 7.33; N, 5.36; S, 12.27. Found: C, 50.65; H, 7.36; N, 5.33; S, 12.20.

4.6.1.2. 3-Allyl-3-methyl-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (11b). Yield 99% (2.90 g, 10.5 mmol); colorless oil; R_f 0.53 (Et_2O); IR (neat) 1717, 1309, 1143 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.51 (s, 3H), 1.53 (s, 9H), 2.00 (ddd, 1H, $J=6.8$, 6.8, 13.6 Hz), 2.39 (ddd, 1H, $J=8.1$, 8.1, 14.4 Hz), 2.48 (dd, 1H, $J=7.7$, 14.0 Hz), 2.83 (dd, 1H, $J=7.0$, 14.0 Hz), 3.20–3.28 (m, 2H), 5.12–5.20 (m, 2H), 5.66–5.80 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 24.97, 28.06, 30.13, 42.71, 46.34, 63.37, 83.98, 119.97, 132.06, 149.41; MS (LC/MS) *m/z* (%) 298 (33) [$M+Na^+$], 242 (100) [$M-C_4H_8+Na^+$]. Anal. Calcd for $C_{12}H_{21}NO_4S$: C, 52.34; H, 7.69; N, 5.09; S, 11.64. Found: C, 52.54; H, 7.74; N, 5.25; S, 11.44.

4.6.2. Lemieux–von-Rudloff oxidation of 11.

4.6.2.1. 3-Carboxymethyl-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (12a). Boc protected γ-sultam **11a** (412.0 mg, 1.91 mmol) was dissolved in a mixture of CCl_4 (4 mL), CH_3CN (4 mL), and H_2O (5.5 mL). To the vigorously stirred solution $NaIO_4$ (1.63 g, 7.64 mmol) and $RuCl_3$ (13.5 mg, 0.065 mmol) were added. After stirring for 4 h, the resulting black mixture was filtered, and H_2O (20 mL) and ethyl acetate (20 mL) were added. The layers were separated, and the aqueous layer was extracted 3× with ethyl acetate (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The black residue was dissolved in CH_2Cl_2 (2 mL), *t*-BuOH (6 mL), and 2-methyl-2-butene (2 mL). To the resulting mixture a solution of Na_2HPO_4 (0.65 g, 4.70 mmol) and $NaClO_2$ (0.65 g, 7.18 mmol) in H_2O (6 mL) was added, and stirring was continued for 16 h. After addition of 1 N H_3PO_4 (35 mL) and CH_2Cl_2 (20 mL), the layers were separated, and the aqueous layer was extracted 3× with CH_2Cl_2 (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in CH_2Cl_2 (20 mL), H_2O (10 mL) was added, and the pH was adjusted to 10 with a saturated aqueous Na_2CO_3 solution. The aqueous layer was extracted 3× with CH_2Cl_2 (20 mL), acidified with 2 N HCl to pH 2 and extracted again 3× with CH_2Cl_2 (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and subsequent evaporation in vacuo afforded pure acid **12a**. Yield: 59% (316.0 mg, 1.13 mmol); white solid; IR (neat) 2981, 2876, 2740, 1721, 1710, 1310, 1133 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.42 (s, 9H), 2.02–2.16 (m, 1H), 2.42–2.49 (m, 1H), 2.66 (d, 2H, J=6.8 Hz), 3.45–3.62 (m, 2H), 4.27–4.30 (m, 1H), 12.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 23.09, 27.47, 36.86, 46.49, 52.96, 82.92, 148.94, 171.26; MS (LC/MS) *m/z* (%) 297 (100) [M+NH_4^+], 280 (5) [M+H^+], 241 (17) [M−C_4H_8+NH_4^+], 224 (48) [M−C_4H_8+H^+], 180 (27) [M−C_4H_8–CO_2+H^+]. Anal. Calcd for $C_{10}H_{17}NO_6S$: C, 43.00; H, 6.13; N, 5.01; S, 11.48. Found: C, 43.02; H, 6.04; N, 5.06; S, 11.13.

4.6.2.2. 3-Carboxymethyl-3-methyl-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (12b). Boc protected γ-sultam **11b** (2.90 g, 10.6 mmol) was dissolved in a mixture of CCl_4 (20 mL), CH_3CN (20 mL), and H_2O (30 mL). To the vigorously stirred solution $NaIO_4$ (9.05 g, 42.3 mmol) and $RuCl_3$ (75.0 mg, 0.36 mmol) were added. After stirring for 4 h, the resulting black mixture was filtered, and H_2O (50 mL) and ethyl acetate (50 mL) were added. The layers were separated, and the aqueous layer was extracted 3× with ethyl acetate (50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated in vacuo. The black residue was purified by filtration (Et_2O) over a short pad of silica gel, the filtrate was evaporated in vacuo, and the crude product was dissolved in *t*-BuOH (30 mL) and 2-methyl-2-butene (10 mL). To the resulting mixture a solution of Na_2HPO_4 (3.60 g, 26.0 mmol) and $NaClO_2$ (3.60 g, 39.8 mmol) in H_2O (30 mL) was added, and stirring was continued for 16 h. After addition of 1 N H_3PO_4 (200 mL) and Et_2O (20 mL), the layers were separated, and the aqueous layer was extracted 5× with Et_2O (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated. The residue was dissolved in Et_2O (50 mL), H_2O (20 mL) was added, and the pH was adjusted to 10 with a saturated aqueous Na_2CO_3 solution. The aqueous layer was extracted 3× with Et_2O (20 mL), acidified with 2 N HCl to pH 2 and extracted again 3× with Et_2O (20 mL). The combined organic extracts were dried over anhydrous $MgSO_4$, and subsequent evaporation in vacuo afforded pure acid **12b**. Yield: 84% (2.60 g, 8.87 mmol); white solid; IR (neat) 3243, 1719, 1314, 1125 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.54 (s, 9H), 1.66 (s, 3H), 2.30 (ddd, 1H, J=7.0, 7.0, 14.0 Hz), 2.70 (ddd, 1H, J=7.7, 7.7, 13.9 Hz), 2.97 (d, 1H, J=15.0 Hz), 3.12 (d, 1H, J=15.0 Hz), 3.22–3.35 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 24.79, 28.03, 30.49, 42.16, 46.16, 61.35, 84.59, 149.35, 175.00; MS (LC/MS) *m/z* (%) 311 (76) [M+NH_4^+], 294 (7) [M+H^+], 260 (39) [M−C_4H_8+Na^+], 238 (57) [M−C_4H_8+H^+], 216 (11) [M−C_4H_8–CO_2+Na^+], 194 (100) [M−C_4H_8–CO_2+H^+]. Anal. Calcd for $C_{11}H_{19}NO_6S$: C, 45.04; H, 6.53; N, 4.77; S, 10.93. Found: C, 45.02; H, 6.78; N, 4.79; S, 10.58.

4.6.3. Deprotection of Boc derivatives 12.

4.6.3.1. (1,1-Dioxo-1λ⁶-isothiazolidin-3-yl)-acetic acid (2a). Boc protected acid **12a** (294.0 mg, 1.05 mmol) was suspended in CH_2Cl_2 (15 mL), and TFA (0.33 mL, 4.50 mmol) was added. The clear solution was heated to reflux for 24 h, cooled to ambient temperature, and all volatile components were removed in high vacuo. The resulting yellow oil was dissolved in a mixture of CH_2Cl_2 (10 mL) and H_2O (10 mL) and stirred for 5 min. The layers were separated, and the aqueous layer was evaporated completely to afford pure β-amino acid **2a**. Yield: 79% (148 mg, 0.83 mmol); colorless oil; IR (neat) 3214, 1700, 1301, 1135 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.84–1.97 (m, 1H), 2.43–2.63 (m, 3H), 2.94–3.04 (m, 1H), 3.13–3.21 (m, 1H), 3.75 (dd, 1H, J=6.9, 13.6 Hz), 6.97 (d, 1H, J=6.3 Hz), 12.37 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.68, 39.92, 47.15, 50.29, 171.72; MS (LC/MS) *m/z* (%) 197 (12) [M+NH_4^+], 180 (100) [M+H^+]. Anal. Calcd for $C_5H_9NO_4S$: C, 33.51; H, 5.06; N, 7.82; S, 17.89. Found: C, 33.41; H, 5.14; N, 7.66; S, 17.59.

4.6.3.2. (3-Methyl-1,1-dioxo-1λ⁶-isothiazolidin-3-yl)-acetic acid (2b). Boc protected acid **12b** (2.93 g, 10.0 mmol) was dissolved in CH_2Cl_2 (140 mL), and TFA (3.33 mL, 45.0 mmol) was added. The mixture was heated to reflux for 48 h, cooled to ambient temperature, and all volatile components were removed in high vacuo to afford pure β-amino acid **2b**. Yield: 86% (1.66 g, 8.60 mmol); white solid; mp 110 °C; IR (neat) 3214, 1700, 1301, 1135 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.32 (s, 3H), 2.14 (ddd, 1H, J=7.0, 7.0, 13.9 Hz), 2.37 (ddd, 1H, J=6.4, 6.4, 14.5 Hz), 2.48–2.56 (m, 2H), 3.08–3.25 (m, 2H), 6.98 (s, 1H), 12.31 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 26.68, 33.95, 45.47, 46.66, 56.88, 171.54; MS (LC/MS) *m/z* (%) 409 (96) [2×M+Na^+], 216 (19) [M+Na^+], 211 (29) [M+NH_4^+], 194 (100) [M+H^+], 176 (27) [M−H_2O+H^+]. Anal. Calcd for $C_6H_{11}NO_4S$: C, 37.30; H, 5.74; N, 7.25; S, 16.60. Found: C, 37.03; H, 5.72; N, 7.20; S, 16.44.

4.7. Preparation of methyl ester 14

4.7.1. 3-Methoxycarbonylmethyl-3-methyl-1,1-dioxo-1λ⁶-isothiazolidine-2-carboxylic acid *tert*-butyl ester (13). Boc protected acid **12b** (1.47 g, 5.00 mmol) was

dissolved in CH_2Cl_2 (20 mL), and the solution was cooled to −20 °C. Diazomethane (ca. 0.35 M in diethyl ether) was added until the mixture turned constantly yellow. The mixture was warmed to ambient temperature and stirred until the color completely faded. The solvents were removed in vacuo, and the residue was purified by flash chromatography (Et_2O) to afford methyl ester **13**. Yield: 100% (1.53 g, 4.98 mmol); colorless oil; R_f 0.38 (Et_2O); IR (neat) 1720, 1313, 1137 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (s, 9H), 1.74 (s, 3H), 2.24 (ddd, 1H, J=7.0, 7.0, 14.0 Hz), 2.67 (ddd, 1H, J=7.7, 7.7, 13.9 Hz), 2.96 (s, 2H), 3.18–3.31 (m, 2H), 3.68 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 25.07, 28.03, 30.47, 42.19, 46.14, 51.90, 61.51, 84.31, 149.34, 170.29; MS (LC/MS) *m/z* (%) 330 (24) [M+Na^+], 274 (80) [M−C_4H_8+Na^+], 230 (100) [M−C_4H_8–CO_2+Na^+]. Anal. Calcd for $C_{12}H_{21}NO_6S$: C, 46.89; H, 6.89; N, 4.56; S, 10.43. Found: C, 47.01; H, 6.99; N, 4.68; S, 10.17.

4.7.2. (3-Methyl-1,1-dioxo-1λ^6-isothiazolidin-3-yl)-acetic acid methyl ester (14). Ester **13** (2.61 g, 8.50 mmol) was dissolved in CH_2Cl_2 (100 mL), and TFA (3.90 mL, 51.0 mmol) was added. The resulting mixture was stirred for 30 h at ambient temperature, diluted with CH_2Cl_2 (100 mL) and carefully washed with saturated aqueous $NaHCO_3$ solution. After evaporation of the organic layer in vacuo and purification of the crude product by flash chromatography (CH_2Cl_2/MeOH 40:1), methyl ester **14** was isolated. Yield: 82% (1.45 g, 7.00 mmol); pale yellow oil; R_f 0.37 (ethyl acetate); IR (neat) 1727, 1294, 1131 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3H), 2.22–2.39 (m, 2H), 2.60 (AB pattern, 2H, J=15.9 Hz, $\Delta\delta$=41.0 Hz), 3.07–3.21 (m, 2H), 3.66 (s, 3H), 5.12 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 27.36, 34.94, 45.05, 46.75, 51.95, 57.19, 171.07; MS (GC/MS, EI, 70 eV) *m/z* (%) 192 (12), 160 (6), 136 (4), 135 (6), 134 (100), 128 (22), 96 (5), 74 (11), 70 (9), 43 (7), 42 (17), 41 (5). Anal. Calcd for $C_7H_{13}NO_4S$: C, 40.57; H, 6.32; N, 6.76; S, 15.47. Found: C, 40.76; H, 6.43; N, 6.86; S, 15.05.

Acknowledgements

Financial support of this work by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie is gratefully acknowledged.

References and notes

1. For reviews, see: (a) *Enantioselective Synthesis of β-Amino Acids*, 2nd ed.; Juaristi, E., Soloshonok, V. A., Eds. Wiley-VCH: New York, 2005. (b) Liu, M.; Sibi, M. P. *Tetrahedron* **2002**, *58*, 7991–8035. (c) Abele, S.; Seebach, D. *Eur. J. Org. Chem*. **2000**, 1–15. (d) Juaristi, E.; López-Ruiz, H. *Curr. Med. Chem*. **1999**, *6*, 983–1004. (e) For a recent paper, see: Ege, M.; Wanner, K. T. *Org. Lett*. **2004**, *20*, 3553–3556.
2. (a) Crews, P.; Manes, L. V.; Boehler, M. *Tetrahedron Lett.* **1986**, *27*, 2797–2800. (b) Rowinsky, E. K.; Donehower, R. C. *Pharmacol. Ther.* **1991**, *52*, 35–84.
3. (a) Steer, D. L.; Lew, R. A.; Perlmutter, P.; Smith, A. I.; Aquilar, M.-I. *Curr. Med. Chem*. **2002**, *9*, 811–822. (b) *Chemistry and Biology of β-Lactam Antibiotics*, Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982: Vol. 1–3. (c) For a recent review on the synthesis and chemistry of azetidinones, see: Singh, G. S. *Tetrahedron* **2003**, *59*, 7631–7649. (d) For a recent review on non-classical β-lactams, see: Gómez–Gallego, M.; Mancheño, M. J.; Sierra, M. A. *Tetrahedron* **2000**, *56*, 5743–5774.
4. (a) Shinagawa, S.; Kanamaru, T.; Harada, S.; Asai, M.; Okazaki, H. *J. Med. Chem.* **1987**, *30*, 1458–1463. (b) Casiraghi, G.; Colombo, L.; Rassu, G.; Spanu, P. *J. Org. Chem.* **1991**, *56*, 6523–6527.
5. (a) Freitag, D.; Schwab, P.; Metz, P. *Tetrahedron Lett.* **2004**, *45*, 3589–3592. (b) Karsch, S.; Freitag, D.; Schwab, P.; Metz, P. *Synthesis* **2004**, *10*, 1696–1712. (c) Merten, S.; Fröhlich, R.; Kataeva, O.; Metz, P. *Adv. Synth. Catal.* **2005**, *347*, 754–758. (d) Freitag, D.; Drees, M.; Goutal, S.; Strassner, T.; Metz, P. *Tetrahedron* **2005**, *61*, 5615–5621.
6. Turos and co-workers also reported several non-conventionally fused β-lactam-sulfonamide hybrids: (a) Ren, X.-F.; Konaklieva, M. I.; Shi, H.; Dickey, S.; Lim, D. V.; Gonzalez, J.; Turos, E. *J. Org. Chem.* **1998**, *63*, 8898–8917. (b) Turos, E.; Konaklieva, M. I.; Ren, R. X.-F.; Shi, H.; Gonzalez, J.; Dickey, S.; Lim, D. *Tetrahedron* **2000**, *56*, 5571–5578.
7. Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379–380.
8. Campbell, J. A.; Hart, D. J. *J. Org. Chem.* **1993**, *58*, 2900–2903.
9. Piancatelli, G.; Scettri, A.; D'Auria, M. *Synthesis* **1982**, 245–258.
10. (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley: New York, 1999. (b) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, 2004.
11. For a review on *N*-sulfonyl imines, see: Weinreb, S. M. *Top. Curr. Chem.* **1997**, *190*, 131–184.
12. (a) For a review, see: Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207–2293. (b) For catalytic asymmetric allylation of imines, see: Fernandes, R. A.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 735–738.
13. For a review on reactions in aqueous media, see: Li, C. J. *Chem. Rev.* **2005**, *105*, 3095–3165.
14. Lu, W.; Chan, T. H. *J. Org. Chem.* **2000**, *65*, 8589–8594.
15. For a review on metal-activation, see: Fürstner, A. *Angew. Chem.* **1993**, *105*, 171–197. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 164–189.
16. Lemieux, R. U.; von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1701–1709.
17. (a) Kametani, T.; Huang, S.-P.; Yokohama, S.; Suzuki, Y.; Ihara, M. *J. Am. Chem. Soc.* **1980**, *102*, 2060–2065. (b) Salzmann, T. N.; Ratcliffe, R. W.; Christensen, B. G.; Bouffard, F. A. *J. Am. Chem. Soc.* **1980**, *102*, 6161–6163. (c) Shono, T.; Tsubata, K.; Okinaga, N. *J. Org. Chem.* **1984**, *49*, 1056–1059. (d) Colvin, E. W.; McGarry, D.; Nugent, M. J. *Tetrahedron* **1988**, *44*, 4157–4172. (e) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555–3557.
18. (a) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1987**, *28*, 4331–4334. (b) Gennari, C.; Venturini, I.; Gislon, G.; Schimperna, G. *Tetrahedron Lett.* **1987**, *28*, 227–230. (c) Kobayashi, S.; Furuta, T.; Sugita, K.; Oyamada, H. *Synlett* **1998**, *9*, 1019–1022.
19. For a successful cyclization of an *N*-sulfonyl β-amino acid to give a monocyclic β-lactam, see: Vassiliou, S.; Dimitropoulos, C.; Magriotis, P. A. *Synlett* **2003**, 2398–2400.
20. Hudlicky, M. *J. Org. Chem.* **1980**, *45*, 5377–5378.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1806–1816
Tetrahedron

Molecular receptors for monosaccharides: di(pyridyl)naphthyridine and di(quinolyl)naphthyridine

Weibing Lu,[a] Li-He Zhang,[a] Xin-Shan Ye,[a,*] Jiachun Su[b] and Zhixiang Yu[b]

[a]*State Key Laboratory of Natural and Biomimetic Drugs, School of Pharmaceutical Science, Peking University, Xue Yuan Road 38, Beijing 100083, China*
[b]*College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, China*

Received 12 September 2005; revised 18 November 2005; accepted 21 November 2005

Available online 19 December 2005

Abstract—The recognition capabilities of two molecular receptors 2,7-di(3′-pyridyl)-1,8-naphthyridine (DPN) and 2,7-di(3′-quinolyl)-1,8-naphthyridine (DQN) toward monosaccharides in chloroform were evaluated. Both DPN and DQN possess a naphthyridine core moiety, in which two pyridinic nitrogen atoms serve as the proton acceptors. Attached to the C2 and C7 positions of naphthyridine are two identical arms, each of which consists of pyridine (DPN) or quinoline (DQN) moiety that also acts as the proton acceptor. The arrangement of hydroxyl groups in monosaccharides offers the proton donors complementary to the proton acceptors of DPN (or DQN) to form a quadruply hydrogen bonds complex. The binding processes were studied by UV–vis, fluorescence and ^{1}H NMR spectrophotometric titrations as well as electrospray ionization mass spectroscopy. The binding strength between DPN (or DQN) and examined monosaccharides was comparable to that for many other hydrogen-bonding host molecules previously reported.

1. Introduction

Because of the importance of carbohydrate recognition in nature, the design of effective and selective receptors for carbohydrates is an actively investigated subject in supramolecular and biomimetic chemistry.[1] These studies are of particular importance due to the key roles sugar molecules play in a wide range of biological processes, including various intermolecular recognition processes, such as cell adhesion, cell infection and many aspects of the immune response.[2]

Artificial receptors provide model systems for studying the molecular basis of carbohydrate recognition, which in turn may lead to the development of new chemosensors or therapeutics. Given the complexity of recognition of carbohydrates, currently the attention has been mainly focused on monosaccharides or short oligosaccharides.

So far, there are two types of sensors developed for saccharide recognition. One is using boronic acids or their derivatives as receptors, in which sensing of saccharides is via the covalent formation of boronic esters between the receptors and saccharides. This kind of receptors is required to have a well-defined geometry.[3] The other depends on multiple point noncovalent interactions between receptors and guests, such as hydrogen bonding, van der Waals interactions, or weak metal coordination. This noncovalent recognition towards saccharides affords the superiority of the geometrical flexibility of hosts in complexation.[1c,4]

In the past years, a number of studies on synthetic receptors and their biding properties toward saccharide guests in organic solvents have become available.[5–21] Although some interesting results have been obtained, due to the three-dimensional complexity of sugar structures, the comprehension of the principles underlying recognition and the search for ease synthetically, efficient, selective receptors are still challenging goals.

Shinkai et al.[16b] reported a receptor based on a naphthyridine core which binds cationic monosaccharides in methanol with high affinity. Fang et al.[19] reported the binding behavior of two receptors with a naphthyridine core for monosaccharides in chloroform. In this paper, we report two relatively simple receptors based on a naphthyridine core: 2,7-di(3′-pyridyl)-1,8-naphthyridine (DPN, Figures 1a and 2) and 2,7-di(3′-quinolyl)-1,8-naphthyridine (DQN, Fig. 1b), both of which possess a well-defined cleft with flexibility suited to an efficient multiple hydrogen bonds formation with various guest saccharides. The isomer of

Keywords: Molecular recognition; Receptors; Spectrophotometric titrations; Binding strength; Hydrogen-bonding.
* Corresponding author. Tel.: +86 10 82801570; fax: +86 10 62014949; e-mail: xinshan@bjmu.edu.cn

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.048

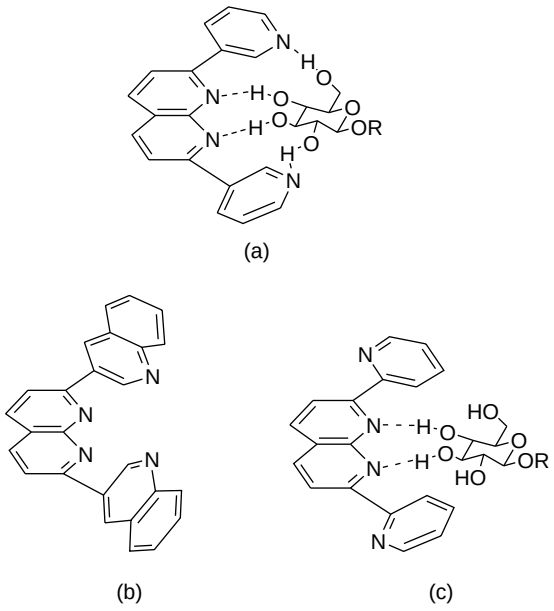


Figure 1. (a) Complexation of DPN with alkyl β-D-glucopyranoside via quadruply hydrogen bondings. (b) Structure of DQN with two quinoline rings in lieu of the pyridine rings in DPN. (c) Complexation of DPN′ with alkyl β-D-glucopyranoside via binary hydrogen bondings.

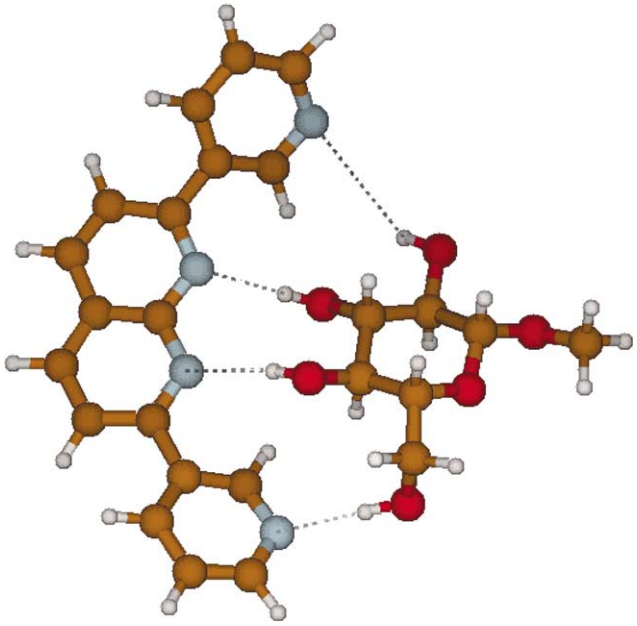


Figure 2. Energy-minimized structure of the 1:1 complex formed between receptor DPN and methyl β-D-glucopyranoside derived by the B3LYP/6-31G** method (the dashed lines show the hydrogen bonds).

DPN, 2,7-di(6′-pyridyl)-1,8-naphthyridine (DPN′, Fig. 1c) was used as a reference receptor. Although receptors DPN and DQN had a much simpler structure and could be synthesized readily, the binding strength between DPN (or DQN) and examined saccharides was comparable to that for many other hydrogen-bonding host molecules previously reported.

Both DPN and DQN possess a naphthyridine core moiety, in which two pyridinic nitrogen atoms serve as the proton acceptors. Attached to the C2 and C7 positions of naphthyridine are two identical arms, each of which consists of pyridine (DPN) or quinoline (DQN) moiety that also acts as the proton acceptor. The arrangement of hydroxyl groups in monosaccharides offers the proton donors complementary to the proton acceptors of DPN (or DQN) to form a quadruply hydrogen bonds complex. DPN′ also contains a naphthyridine core, in which two identical pyridine arms are attached to the C2 and C7 positions. Owing to the nitrogens pointing outward, DPN′ can form only a binary hydrogen bonds complex with saccharide guests. The binding processes were studied by UV–vis, fluorescence and ^{1}H NMR spectrophotometric titrations as well as electrospray ionization mass spectroscopy.

2. Results and discussion

2.1. Synthesis and characterization of molecular receptors: DPN, DQN and DPN′

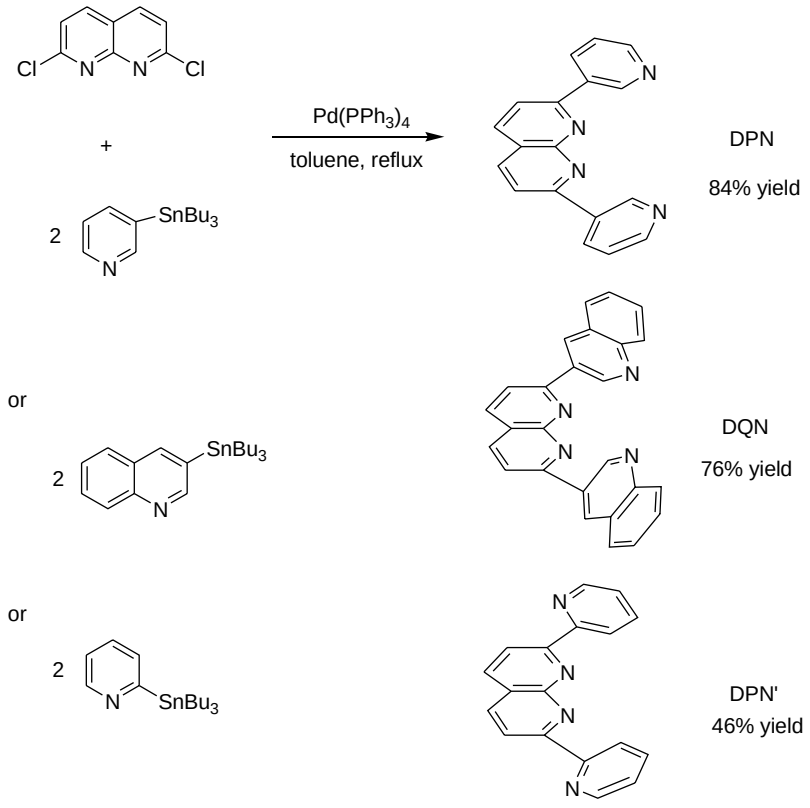
The molecular sensors DPN and DQN were prepared by $Pd(PPh_3)_4$-catalyzed Stille coupling of 2,7-dichloro-1,8-naphthyridine[22] and corresponding tin reagents[23] as outlined in Scheme 1. DPN′ was also synthesized in the same way by using 2-(1′,1′,1′-tributylstannyl)pyridine as the starting material. For the preparation of DPN′, ^{1}H NMR of the solid purified by column chromatography revealed the existence of two isomers with a molar ratio approximately of 10:1. But careful recrystallization from CH_2Cl_2/*n*-hexane yielded DPN′ as a pure isomer.

The six proton peaks and ten ^{13}C signals of DPN indicated that DPN had a symmetric structure. Similarly, the eight ^{1}H peaks and fourteen ^{13}C signals indicated the symmetric structure of DQN.

The NMR spectra of DPN′ exhibited six proton peaks and ten ^{13}C signals, indicating a symmetric structure. A single-crystal structure analysis of DPN′ revealed that the DPN′ molecule had a well-behaved V-shaped cleft (Fig. 3). The two pyridine rings disposed their nitrogen atoms as the outward conformation, the pyridine rings and the naphthyridine core were almost in a coplanar geometry. The receptors DPN and DQN were assumed to possess the same well-defined cleft as DPN′ except for the different pointing direction of nitrogens on pyridine (or quinoline) moieties.

2.2. UV–vis spectra of the DPN and DQN complexes with saccharides

The absorption spectra of receptor DPN in the presence of octyl β-D-glucopyranoside with different concentrations were shown in Figure 4. The maximum wavelength (λ_{max}=251 nm, ε=40500 $M^{-1}\,cm^{-1}$ and 345 nm, ε=17520 $M^{-1}\,cm^{-1}$) did not change but its intensity increased gradually with increasing the concentration of guest. The Job plot at 251 nm indicated a 1:1 stoichiometry between the host and guest. According to Benesi-Hildebrand method,[24] the binding constants between the receptor DPN and octyl β-D-glucopyranoside as well as other guests were determined (Table 1).



Scheme 1. Synthesis of DPN, DQN and DPN′.

Figure 5 gave the absorption spectra of receptor DQN with increasing concentrations of octyl β-D-glucopyranoside. The UV–vis spectrum of DQN in $CHCl_3$ showed the absorption maxima at 317 nm ($\varepsilon = 57800\ M^{-1}\ cm^{-1}$) and 375 nm ($\varepsilon = 46240\ M^{-1}\ cm^{-1}$). As the amounts of the octyl β-D-glucopyranoside increased, new absorption maxima at 337 and 409 nm appeared with a gradual increase of the absorbance, whereas the absorptions at 317 and 375 nm for the free DQN receptor decreased concomitantly. The occurrence of isosbestic points at 331 and 390 nm throughout the titration supported the formation of DQN–saccharide complex in equilibrium with free DQN. The Job plot at 409 nm also indicated a 1:1 stoichiometry between the host and guest. Complexation of receptor DQN with other saccharides also displayed similar spectral features in the UV–vis titration. By using the Benesi-Hildebrand equation, the binding constants between DQN and the guests were determined (Table 2).

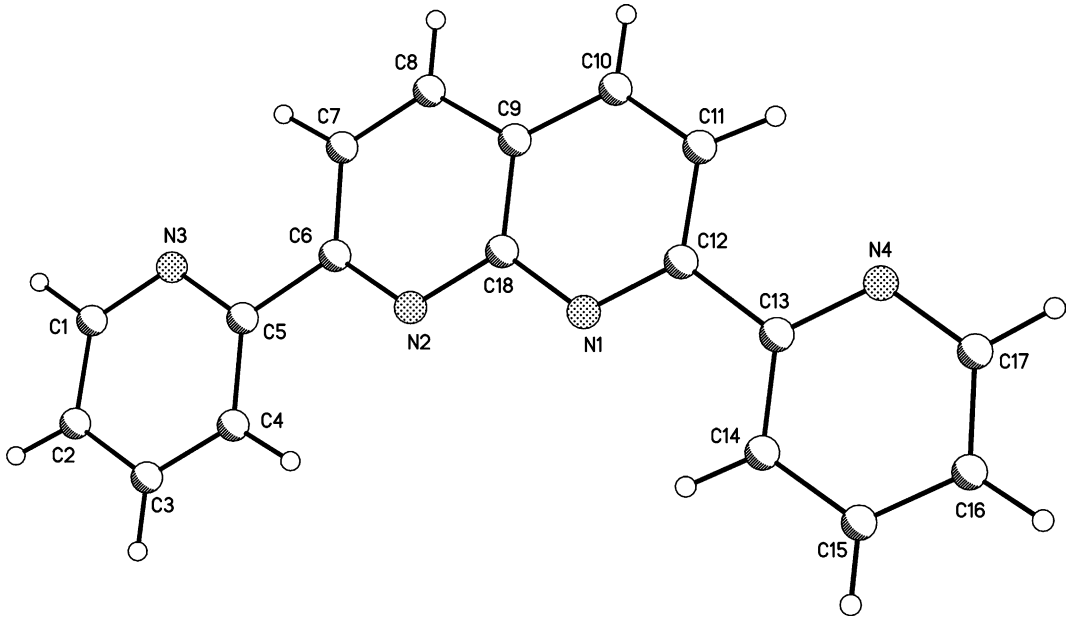


Figure 3. ORTEP drawing of DPN′ shows a V-shaped cleft.

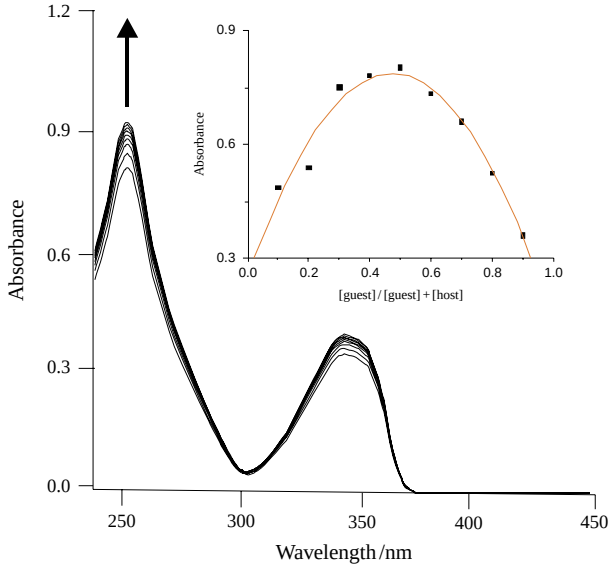


Figure 4. UV–vis titration of receptor DPN with octyl β-D-glucopyranoside in $CHCl_3$ at 298 K; [DPN]$=2.0\times10^{-6}$ M; [octyl β-D-glucopyranoside]$=0$, 0.04, 0.06, 0.08, 0.10, 0.12, 0.2, 0.5, 1.0×10^{-3} M. The inset gives the Job plot indicating a maximum at a mol fraction of 0.5 (i.e., 1:1 stoichiometry).

Table 1. Association constants for the binding of saccharides with receptor DPN in $CHCl_3$ at 298 K

	Ka (M^{-1})	
	Fluorescence	UV–vis
β-D-glucoside (**5**)	6320	6120
α-D-glucoside (**6**)	4510	3760
β-D-galactoside (**7**)	3970	3340
α-D-galactoside (**8**)	2150	1980
β-D-mannoside (**9**)	8840	8070
α-D-mannoside (**10**)	7950	7500
β-D-fructoside (**11**)	1070	810
α-D-riboside (**12**)	510	490

2.3. Fluorescence titration of DPN and DQN with saccharides

With 313 nm as the excitation wavelength, the fluorescence emission spectra of receptor DPN in $CHCl_3$ with various concentrations of octyl *β*-D-glucopyranoside were shown in Figure 6. The emission maximum (392 nm) did not change but the intensity diminished gradually with increasing concentration of the guest. The line of $F_0/(F_0-F)$ versus the inverse of the concentration of the guest revealed also a 1:1 stoichiometry.[25] Complexation of DPN with other saccharides also caused certain degrees of fluorescence quenching. According to Benesi-Hildebrand method,[24] the binding constants between the receptor DPN and the guests were determined (Table 1).

The fluorescence emission spectra of receptor DQN in the presence of octyl β-D-glucopyranoside with different concentrations were displayed in Figure 7. Upon excitation at 365 nm, DQN showed a fluorescence emission at 445 nm in $CHCl_3$ solution. On binding with octyl β-D-glucopyranoside in different concentrations, the fluorescence intensity at 445 nm decreased, accompanied with a growth of an emission band at 468 nm. An isosbestic point at 449 nm appeared. The plot of $F_0/(F-F_0)$ at 468 nm versus the inverse of the concentration of the guest reconfirmed a 1:1 DQN–saccharide complex. Complexation of receptor DQN with other saccharides also displayed similar dual spectral features in the fluorescence titration. By using the Benesi-Hildebrand equation, the binding constants between DQN and the guests were determined (Table 2).

2.4. NMR study of the binding modes of DPN, DQN and DPN′ with saccharides

When a stock solution of octyl β-D-glucopyranoside in $CDCl_3$ (1×10^{-3} M) was mixed with 1 equiv of DPN, the hydroxyl protons of the glucoside showed significant chemical-shift changes (Fig. 8). All of the four hydroxyl protons of the glucoside shifted downfield due to the formation of hydrogen bonds (Fig. 8b). The induced

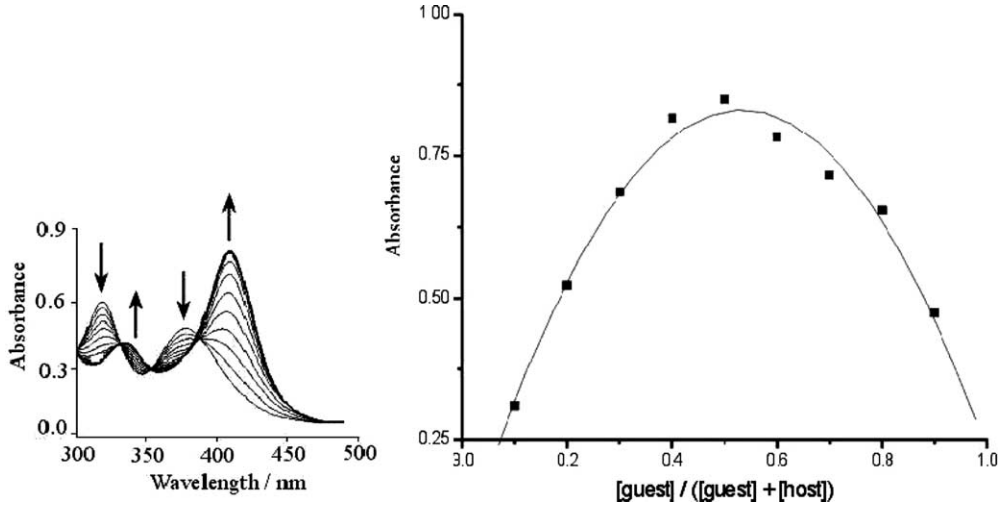


Figure 5. UV–vis titration of receptor DQN with octyl β-D-glucopyranoside in $CHCl_3$ at 298 K; [DQN]$=2.5\times10^{-6}$ M; [octyl β-D-glucopyranoside]$=0$, 0.04, 0.06, 0.08, 0.10, 0.12, 0.2, 0.5, 1.0×10^{-3} M. The Job plot at 409 nm indicating 1:1 stoichiometry.

Table 2. Association constants for the binding of saccharides with receptor DQN in $CHCl_3$ at 298 K

	Ka (M^{-1})	
	Fluorescence	UV–vis
β-D-glucoside (**5**)	7120	6560
α-D-glucoside (**6**)	4900	4740
β-D-galactoside (**7**)	5020	4690
α-D-galactoside (**8**)	3500	2890
β-D-mannoside (**9**)	10040	10030
α-D-mannoside (**10**)	9910	8520
β-D-fructoside (**11**)	1350	1010
α-D-riboside (**12**)	605	570

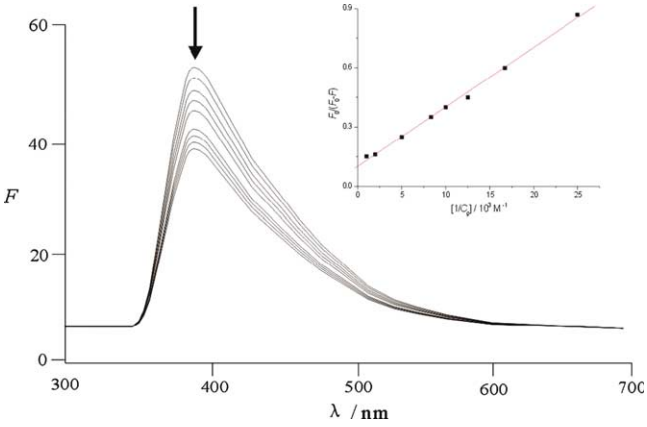


Figure 6. Fluorescence spectra of receptor DPN (2×10^{-6} M) in $CHCl_3$ at 298 K by adding various concentrations (C_g) of octyl β-D-glucopyranoside. The plot at 392 nm shows a linear relationship of $[F_0/(F_0-F)]$ vs $1/C_g$ indicating the 1:1 stoichiometry of DPN-glucoside complex.

chemical-shift changes of all the studied pyranosides (**5**–**11**) and furanoside (**12**) were collected in Tables 3 and 4. Upon addition of 1 equiv of DQN to a solution of octyl β-D-glucopyranoside in $CDCl_3$, all of the four hydroxyl protons of the glucoside shifted downfield due to the formation of hydrogen bonds (Fig. 8d). The induced chemical-shift changes of all the studied pyranosides (**5**–**11**) and furanoside (**12**) were collected in Tables 5 and 6. The similar chemical-shift changes revealed the similar binding modes of DPN and DQN with saccharide guests. When a stock solution of octyl β-D-glucopyranoside in $CDCl_3$ (5×10^{-4} M) was treated with 1 equiv of DPN′, only 3-and 4-OH hydroxyl protons of the glucoside shifted downfield due to the formation of hydrogen bonds while 2- and 6-OH hydroxyl protons remained almost unchanged (Fig. 8c). This phenomenon suggested only two hydrogen bonds were formed between receptor DPN′ and saccharide guest (Fig. 1c).

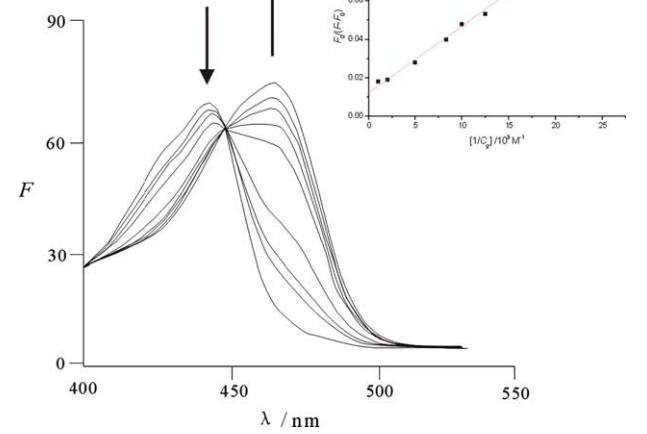
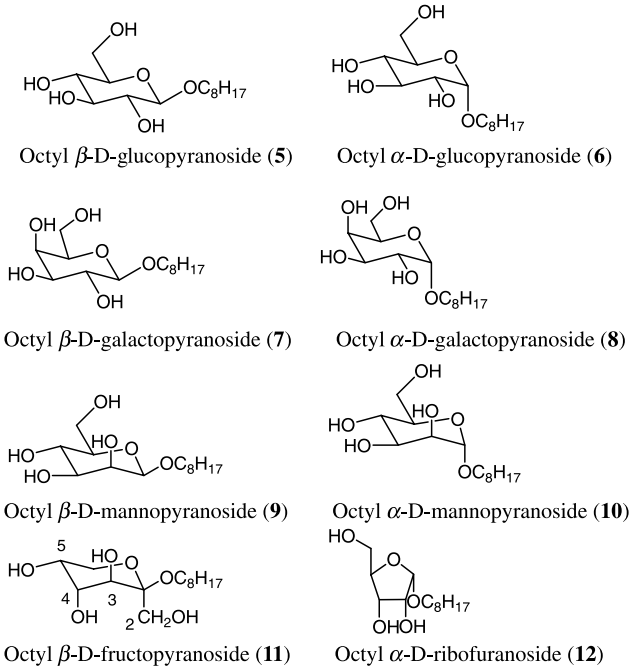


Figure 7. Fluorescence spectra of receptor DQN (2.5×10^{-6} M) in $CHCl_3$ at 298 K by adding various concentrations (C_g) of octyl β-D-glucopyranoside. The plot at 468 nm shows a linear relationship of $[F_0/(F-F_0)]$ vs $1/C_g$ indicating the 1:1 stoichiometry of DQN-glucoside complex.



2.5. MS study of the binding of DPN, DQN and DPN′ with saccharides

Electrospray ionization mass spectroscopy (ESI-MS) is a powerful tool for studying noncovalent biological complexes such as multiprotein assemblies and protein–ligand complexes. In addition to providing a rapid and sensitive method for detecting biomolecular complexes and directly establishing their binding stiochiometry, ESI-MS based methods hold tremendous promise for quantifying the noncovalent interactions. To our knowledge, studying on the interaction between saccharide with synthetic receptors through ESI-MS method has not been reported. We checked by electrospray ionization time-of-flight mass spectrometry (ESI-TOF-MS) for the formation of complexes of DPN and DQN with various saccharide guests in solution. Figure 9 gave the mass spectra of the mixture of DPN, DQN and DPN′ with octyl β-D-glucopyranoside in $CHCl_3$ with a molar ratio of 1:1. The designation of the MS peaks was given in the figure. The mass spectra reconfirmed the 1:1 stiochiometry of receptor–saccharide complex. All spectra displayed the receptor-saccharide peaks ascribed to the complex formation. The positive ion mode spectrum of DPN-β-glucoside in $CHCl_3$ showed major peaks at *m*/*z* 569, 577, 585, 591, 599, 607. The *m*/*z* 569 and 591 peaks came from DPN. The *m*/*z* 585 and 607 peaks came from β-glucoside. The *m*/*z* 577 and 599 peaks were belonged to

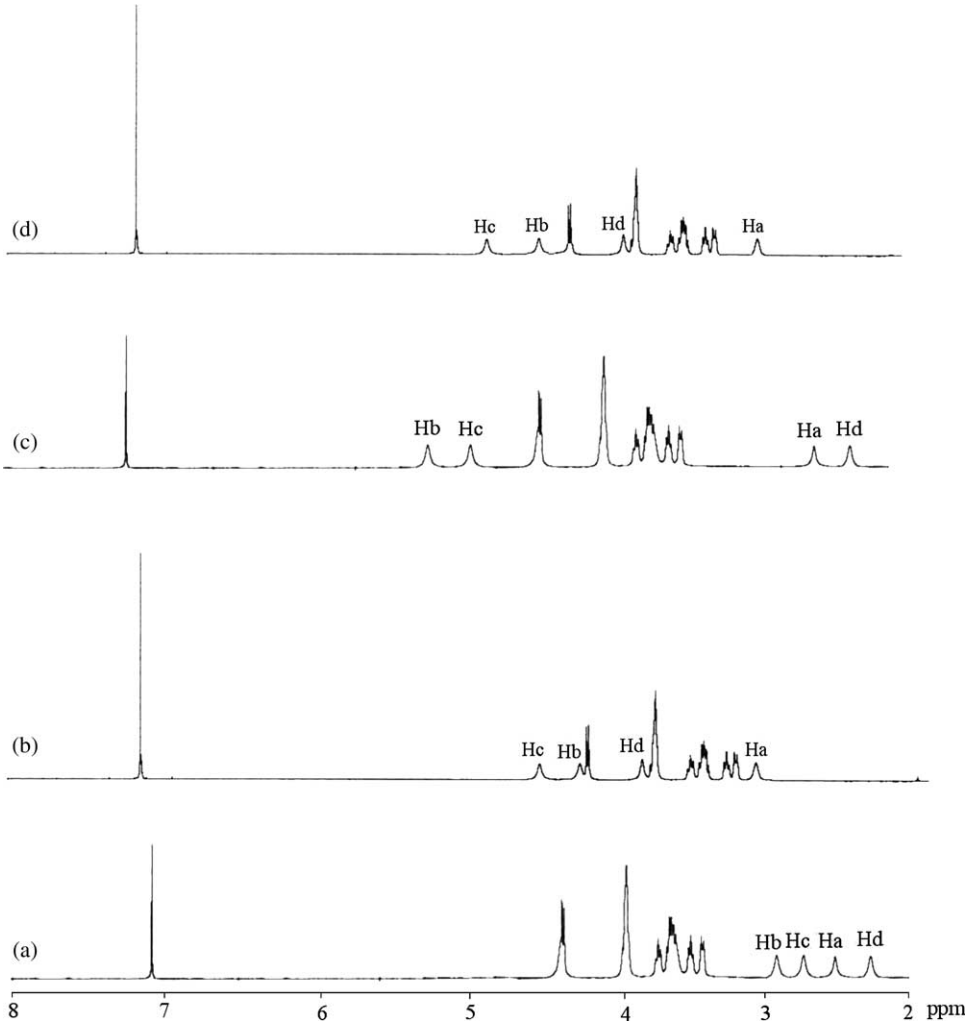


Figure 8. Induced ^{1}H NMR changes of octyl β-D-glucopyranoside on addition of DPN, DQN and DPN′. (a) free octyl β-D-glucopyranoside (1×10^{-3} M in $CDCl_3$, 298 K); (b) octyl β-D-glucopyranoside with DPN (1 equiv); (c) octyl β-D-glucopyranoside with DPN′ (1 equiv) and (d) octyl β-D-glucopyranoside with DQN (1 equiv). The hydroxyl protons at the C-2, C-3, C-4, and C-6 positions of the saccharide are designated as Ha, Hb, Hc and Hd, respectively. Signal assignments were made on the basis of ^{1}H–^{1}H COSY experiments.

Table 3. ^{1}H NMR complexation-induced shifts (Δδ/ppm) of alkyl monosaccharides upon complexation with DPN in $CDCl_3$ at 298 K

Guest	Δδ/ppm (δ of free guest/ppm)			
	5	**7**	**9**	**11**
2-OH	0.84 (2.25)	0.88 (2.39)	1.10 (2.48)	0.46 (2.17)
3-OH	1.39 (2.86)	1.49 (2.58)	1.79 (2.51)	1.00 (2.66)
4-OH	1.79 (2.69)	1.36 (2.71)	1.63 (2.43)	0.54 (2.58)
6-OH	1.62 (2.23)	1.32 (2.18)	1.84 (2.07)	0.53 (2.43)[a]

[a] 5-OH of octyl β-D-fructopyranoside (**11**).

Table 4. ^{1}H NMR complexation-induced shifts (Δδ/ppm) of alkyl monosaccharides upon complexation with DPN in $CDCl_3$ at 298 K

	Δδ/ppm (δ of free guest/ppm)			
	6	**8**	**10**	**12**
2-OH	0.72 (1.99)	0.74 (1.96)	1.07 (2.20)	0.54 (2.59)
3-OH	1.57 (2.42)	1.33 (2.57)	1.72 (2.41)	1.01 (2.38)
4-OH	1.44 (2.54)	1.25 (2.73)	1.56 (2.33)	0.63 (2.22)[a]
6-OH	1.06 (1.89)	1.14 (2.22)	1.87 (2.01)	

[a] 5-OH of octyl α-D-ribofuranoside (**12**).

Table 5. ^{1}H NMR complexation-induced shifts (Δδ/ppm) of alkyl monosaccharides upon complexation with DQN in $CDCl_3$ at 298 K

	Δδ/ppm (δ of free guest/ppm)			
	5	**7**	**9**	**11**
2-OH	0.70 (2.25)	0.91 (2.39)	1.18 (2.48)	0.55 (2.17)
3-OH	1.53 (2.86)	1.51 (2.58)	1.78 (2.51)	1.07 (2.66)
4-OH	2.08 (2.69)	1.38 (2.71)	1.73 (2.43)	0.66 (2.58)
6-OH	1.62 (2.23)	1.43 (2.18)	2.02 (2.07)	0.78 (2.43)[a]

[a] 5-OH of octyl β-D-fructopyranoside (**11**).

Table 6. ^{1}H NMR complexation-induced shifts (Δδ/ppm) of alkyl monosaccharides upon complexation with DQN in $CDCl_3$ at 298 K

Guest	Δδ/ppm (δ of free guest/ppm)			
	6	**8**	**10**	**12**
2-OH	0.59 (1.99)	0.75 (1.96)	1.16 (2.20)	0.59 (2.59)
3-OH	1.88 (2.42)	1.42 (2.57)	1.79 (2.41)	0.77 (2.38)
4-OH	1.61 (2.54)	1.37 (2.73)	1.69 (2.33)	0.84 (2.22)[a]
6-OH	1.34 (1.89)	1.39 (2.22)	1.99 (2.01)	

[a] 5-OH of octyl α-D-ribofuranoside (**12**).

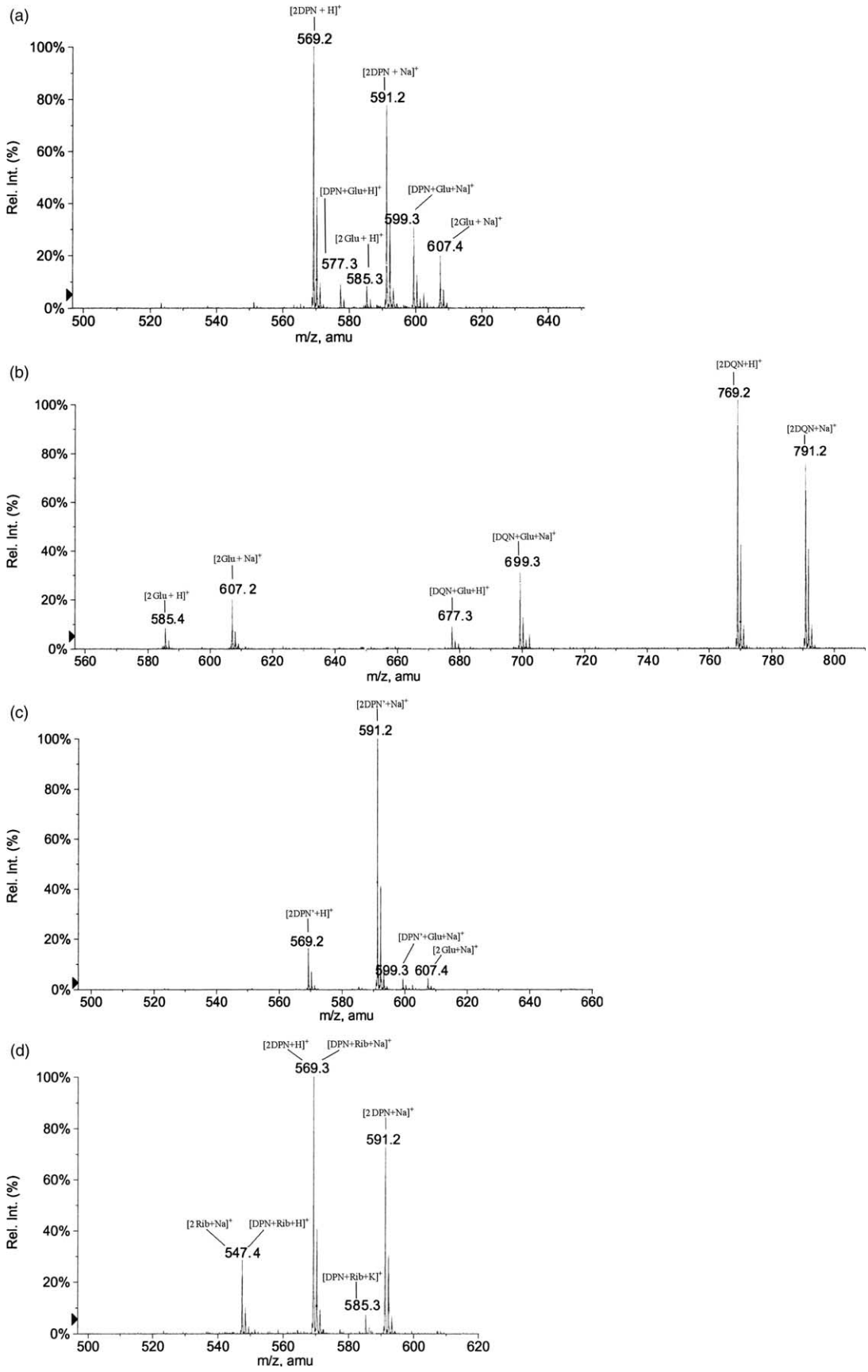


Figure 9. The ESI-MS spectra of receptor-saccharide complexes. The designation of the MS peaks was given. (a) DPN-octyl β-D-glucopyranoside; (b) DQN-octyl β-D-glucopyranoside; (c) DPN′-octyl β-D-glucopyranoside; (d) DPN-octyl α-D-ribofuranoside complex.

the DPN–glucopyranoside complex, $m/z=577$ for $[DPN+Glu+H]^+$ and $m/z=599$ for $[DPN+Glu+Na]^+$ (Fig. 9a). The spectrum of the complex of DPN–furanoside gave peaks at $m/z=547$ attributable to $[DPN+Rib+H]^+$, $m/z=569$ attributable to $[DPN+Rib+Na]^+$ and $m/z=585$ attributable to $[DPN+Rib+K]^+$ respectively (Fig. 9d). In Figure 9b, the peaks at $m/z=677$ for $[DQN+Glu+H]^+$ and $m/z=699$ for $[DQN+Glu+Na]^+$ were ascribed to the formation of DQN–glucopyranoside complex. The spectrum of DPN′-glucopyranoside also gave a peak at $m/z=599$ for $[DPN'+Glu+Na]^+$ with much lower relative intensity compared to DPN–glucopyranoside complex (Fig. 9c). This much lower relative intensity was in agreement with the much smaller binding constant of DPN′ to octyl β-D-glucopyranoside ($K_a=300\ M^{-1}$ and $K_a=270\ M^{-1}$ at 298 K in $CHCl_3$ determined by fluorescence and UV–vis titration method, respectively). We also recorded the mass spectra of the mixture of receptor and saccharide with molar ratio from 1:1 to 1:10, no obvious change in the mass peak pattern was observed, so it can be concluded that only 1:1 receptor–saccharide complex formed in the binding processes. The mass spectra of DPN and DQN with other saccharides **6–11** were all recorded and all of the spectra showed almost the same pattern as that of receptor–glucopyranoside complex, it can been concluded that although the binding constants of receptor and different saccharides differ from each other, the mass spectra are the same. In the current system, ESI-MS spectroscopy failed to study the difference of the binding ability of the receptors and saccharides, but this method directly proved the receptor–saccharide complex formation and rapidly gave the stoichiometry between the receptor and the examined saccharides.

2.6. Comparison of the binding strength of different saccharide complexes

The preferable 1:1 binding of each saccharide with receptor DPN and DQN was determined by UV–vis and fluorescence titrations as well as mass spectroscopy. The binding constants for various receptor DPN- and DQN–saccharide complexes were given in Table 1 and Table 2, respectively. Although the binding constant of each saccharide with receptor DPN and DQN determined by UV–vis and fluorescence titrations respectively was not the same, the results obtained from UV–vis and fluorescence titrations showed the similar trend of binding strength toward the examined monosaccharides, that is, (β-D-mannopyranoside, α-D-mannopyranoside)> β-D-glucopyranoside>(α-D-glucopyranoside, β-D-galactopyranoside)>α-D-galactopyranoside≫β-D-fructopyranoside>α-D-ribofuranoside. It is thus reasonable to assume that DPN and DQN molecules behave similarly to bind with various monosaccharides.

While the only structural difference between octyl β-D-galactopyranoside and octyl β-D-glucopyranoside is the spatial orientation of 4-OH, the binding constant for β-D-galactopyranoside is smaller than that of β-D-glucopyranoside on complexation with either DPN or DQN. As support evidence, the complexation-induced shift of 4-OH of galactopyranoside was smaller than that of 4-OH of glucopyranoside upon complexation with either DPN or DQN in $CDCl_3$. The binding of α-D-ribofuranoside was very weak presumably because the complexation could accommodate three hydrogen bondings. The binding constant of octyl α-D-glucopyranoside was less than that of the β-anomer. It was assumed that a cis-GAUCHE type hydrogen bonding occurred between the C-1 octoxy group and the C-2 hydroxyl group in the α-D-glucopyranoside, and thus rendered a less efficient hydrogen bonding between the 2-OH group and the pyridyl (or quinolyl) nitrogen of DPN (or DQN).[26] As support evidence, the ^1H NMR titration experiments indicated that the 2-OH group of octyl α-D-glucopyranoside showed a smaller chemical-shift change than the β-anomer on complexation with DPN and DQN. A similar selectivity for octyl β-D-galactopyranoside over its α-anomer was observed. Among the examined saccharides, octyl β-D-mannopyranoside and octyl α-D-mannopyranoside exhibited the highest affinity toward DPN and DQN. The 2-OH group in mannoside was free from the intramolecular hydrogen bonding with octoxy group, and thus exerted a strong hydrogen bonding with the pyridyl (or quinolyl) nitrogen of DPN (or DQN).[26] No selectivity was observed for octyl β-D-mannopyranoside and its α-anomer. As support evidence, the ^1H NMR titration experiments indicated that the 2-OH group of octyl β-D-mannopyranoside showed almost the same chemical-shift change as that of α-anomer on complexation with DPN and DQN. Furthermore, complexation-induced shift of 2-OH of octyl β- and α-D-mannopyranoside was much greater than that of 2-OH of the other examined monosaccharides.

3. Conclusion

The binding of octyl monosaccharides to DPN and DQN bearing naphthyridine and pyridyl (or quinolyl) group as hydrogen bond forming groups was reported. The binding mode was studied by UV–vis, fluorescence, ^1H NMR and ESI-TOF-MS spectrometric titrations. To the best of our knowledge, it is the first time to study the binding of saccharides with synthetic receptors with ESI-MS spectroscopy. Although in the current system, ESI-MS spectroscopy failed to study the difference of the binding ability of the receptors and saccharides, this method directly proved the receptor–saccharide complex formation and rapidly gave the stoichiometry between the receptor and the examined saccharides. The binding strength between DPN (or DQN) and examined saccharides was comparable to that for many other hydrogen-bonding host molecules previously reported. However, receptors DPN and DQN we designed had a much simpler structure and were readily synthesized. This study could be advanced by designing the water-soluble analogues of DPN/DQN receptors for direct sensing of sugars without prior derivatization to alkyl saccharides.

4. Experimental

4.1. General

^1H NMR spectra were recorded on an INOVA 500 spectrometer at 500 MHz for ^1H NMR and 125 MHz for

^{13}C NMR. Chemical shifts were reported in parts per million relative to TMS. Ultraviolet–visible spectroscopy was performed with a Varian CARY 300 UV–Visible spectrophotometer with a thermostatted compartment. Fluorescence spectroscopy was performed on a Varian CARY Eclipse Fluorescence spectrophotometer with a thermostatted compartment. All spectra were corrected for the background spectrum of the solvent. Elemental analyses were determined with a Vario EL III elemental analyzer. ESI-MS spectra were taken on a MDS SCIEX QSTAR mass spectrometer. $CHCl_3$ containing amylene as a stabilizer was purchased from Aldrich (A.C.S. HPLC grade, 99.9%) and was used in titration experiments. $CDCl_3$ used in NMR experiments was stored over activated molecular sieves and deacidified with alumina.

4.1.1. 2,7-Di(3′-pyridyl)-1,8-naphthyridine (DPN). A mixture of 2,7-dichloro-1,8-naphthyridine[22] (139 mg, 0.7 mmol), 3-(tri-*n*-butylstannyl)pyridine[23a] (1.0 g, 2.7 mmol), $Pd(PPh_3)_4$ (120 mg) and freshly distilled toluene (40 mL) was refluxed for 36 h under nitrogen. The reaction mixture was passed through a short plug of diatomaceous earth and washed with CH_2Cl_2. The combined organic phase was evaporated to dryness under reduced pressure to give a pale yellow solid. This solid was dissolved in CH_2Cl_2 and chromatographed on silica gel column with a mixture of dichloromethane–acetone (1/4) as an eluent. Recrystallization from CH_2Cl_2/*n*-hexane afforded 2,7-di(3′-pyridyl)-1,8-naphthyridine (167 mg, 84% yield) as a light yellow solid. mp 164–165 °C; R_f (CH_2Cl_2/acetone=1/4): 0.42; UV–vis(in $CHCl_3$), (ε, $M^{-1}\,cm^{-1}$): 251 (4.05×10^4), 345 (1.75×10^4) nm; ^{1}H NMR ($CDCl_3$): 9.43 (d, 2H, J=2.0 Hz), 8.76 (dd, 2H, J=4.5, 1.5 Hz), 8.70 (dt, 2H, J=3.0, 2.0 Hz), 8.38 (d, 2H, J=8.5 Hz), 8.05 (d, 2H, J=8.5 Hz), 7.48–7.54 (m, 2H); ^{13}C NMR ($CDCl_3$): 158.8, 156.1, 150.9, 149.0, 138.1, 135.6, 134.2, 123.7, 121.1, 119.7; ESI MS: *m*/*z* 285 $(M+H)^+$, 307 $(M+Na)^+$. Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.06; H, 4.23; N, 19.72. Found: C, 75.79; H, 4.43; N, 19.43.

4.1.2. 2,7-Di(3′-quinolyl)-1,8-naphthyridine (DQN). The same procedure as described for DPN was followed with 3-(tri-*n*-butylstannyl)quilonine[23b] taking the place of 3-(tri-*n*-butylstannyl)pyridine. Yield: 76%; mp 214–216 °C; R_f (CH_2Cl_2/acetone=1/5): 0.52; UV–vis(in $CHCl_3$), (ε, $M^{-1}\,cm^{-1}$): 317 (5.78×10^4), 375 (4.62×10^4) nm; ^{1}H NMR ($CDCl_3$): 9.84 (d, 2H, J=2.5 Hz), 9.32 (d, 2H, J=3.0 Hz), 8.75 (d, 2H, J=8.5 Hz), 8.58 (d, 2H, J=8.5 Hz), 8.20 (d, 2H, J=2.5 Hz), 8.14 (d, 2H, J=3.0 Hz), 7.89 (td, 2H, J=7.0, 1.5 Hz), 7.69–7.77 (m, 2H); ^{13}C NMR ($CDCl_3$): 158.8, 156.5, 154.9, 149.1, 147.5, 139.1, 137.6, 136.9, 134.6, 125.2, 123.0, 122.7, 122.5, 121.2; ESI MS: *m*/*z* 385 $(M+H)^+$. Anal. Calcd for $C_{26}H_{16}N_4$: C, 81.25; H, 4.17; N, 14.58. Found: C, 81.56; H, 4.06; N, 14.26.

4.1.3. 2,7-Di(6′-pyridyl)-1,8-naphthyridine (DPN′). A mixture of 2,7-dichloro-1,8-naphthyridine (139 mg, 0.7 mmol), 2-(tri-*n*-butylstannyl)pyridine[23c] (1.0 g, 2.7 mmol), $Pd(PPh_3)_4$ (120 mg) and freshly distilled toluene (40 mL) was refluxed for 48 h under nitrogen. The reaction mixture was passed through a short plug of diatomaceous earth and washed with CH_2Cl_2. The combined organic phase was evaporated to dryness under reduced pressure to give a light yellow solid. This solid was dissolved in CH_2Cl_2 and chromatographed on silica gel column with a mixture of dichloromethane–acetone (10/1) as an eluent. ^{1}H NMR of the resultant solid revealed the existence of two isomers with a molar ratio about 10/1. The solid was then recrystallized twice from CH_2Cl_2/*n*-hexane to afford 2,7-di(6′-pyridyl)-1,8-naphthyridine (91 mg, 46% yield) as a white solid. Mp 224–225 °C; R_f (CH_2Cl_2/acetone=4/1): 0.68; UV–vis(in $CHCl_3$), (ε, $M^{-1}\,cm^{-1}$): 280 (1.81×10^4), 343 (1.55×10^4), 358 (1.57×10^4) nm; ^{1}H NMR ($CDCl_3$): 8.89 (d, 2H, J=8.0 Hz), 8.76–8.77 (m, 2H), 8.75 (d, 2H, J=8.5 Hz), 8.37 (d, 2H, J=8.5 Hz), 7.92 (td, 2H, J=7.5, 2.0 Hz), 7.39–7.43 (m, 2H); ^{13}C NMR ($CDCl_3$): 159.7, 155.5, 155.4, 149.1, 137.7, 136.9, 124.6, 123.0, 122.7, 120.2; ESI MS: *m*/*z* 285 $(M+H)^+$, 307 $(M+Na)^+$. Anal. Calcd for $C_{18}H_{12}N_4$: C, 76.06; H, 4.23; N, 19.72. Found: C, 75.95; H, 4.29; N, 19.54. Slow evaporation of the DPN′ solution in CH_2Cl_2/*n*-hexane gave single crystal suitable for X-ray diffraction analysis. The crystal structure has been deposited in the Cambridge Crystallographic Data Center with the deposition number CCDC 265286.

4.2. Synthesis of alkyl monosaccharides

The examined octyl monosaccharides **5–12** were either commercially available or prepared following the reported procedures.[27]

4.3. UV–vis spectrophotometric titrations

UV–vis spectrophotometric titrations were carried out in $CHCl_3$ at a sensor concentration of 2.0×10^{-6} mol L^{-1} for DPN and 2.5×10^{-6} mol L^{-1} for DQN. Dilution experiments show that receptors do not self-aggregate in the used concentration range. Cells containing the samples were equilibrated at 298 K for 5 min. Absorbance titrations were conducted with concentrated stock solutions of a saccharide. The binding constants *Ka* for the receptor–saccharide complexes were determined from the absorbance changes at the absorption band maxima using the Benesi-Hildebrand equation assuming a 1:1 stiochiometry and that the guest concentration was significantly higher than the receptor concentration. The solution of the receptor and the saccharide were mixed to a standard volume with varying molar ratios of the two components and the stiochiometry was confirmed by the Job method of continuous variations. Absorbance changes were recorded to determine the binding constants. UV–vis titration for receptor DPN and DQN with each saccharide was repeated for three times and the binding constant was averaged in triplicate runs.

4.4. Fluorescence spectrophotometric titrations

Fluorescence spectroscopy was also utilized for the binding studies. The fluorescence spectra were taken using the same samples employed in the UV–vis studies, that is, transferring the same cuvette from the UV–vis spectrophotometer to the fluorescence spectrophotometer for each incremental addition of the analyte. With λ_{exc}=313 nm for DPN and 365 nm for DQN respectively, the emission spectra of DPN and DQN were recorded. The fluorescence intensity changes were analyzed using the Benesi-Hildebrand equation to reveal a 1:1 stiochiometry. Fluorescence titration for receptor DPN and DQN with each saccharide

was repeated for three times and the binding constant was averaged in triplicate runs.

4.5. ^{1}H NMR titration studies

A typical experiment was performed as follows. A solution of saccharide in $CDCl_3$ was prepared (1×10^{-3} M), and a 0.4 mL portion was transferred into a 5-mm NMR tube. A small aliquot of the $CDCl_3$ solution (0.02 M) containing DPN or DQN was introduced to the examined saccharide solution to keep the saccharide and the receptor with a 1:1 molar ratio. Their corresponding spectra were recorded and the chemical shift of the hydroxyl protons of the examined saccharides was monitored.

4.6. ESI-TOF-MS complexation studies

10 μL of 5×10^{-3} M solutions of the receptor and guests with a 1:1 molar ratio were mixed and diluted to 8×10^{-5} M. Mass spectrometric detection was carried out using a MDS SCIEX QSTAR hybrid LC/MS/MS system operating in the positive Turbo-Ion-Spray mode. The auxiliary gas (N_2) was at 40 psi and the curtain gas was at 30 psi. The ion spray voltage was at 3800 V. The injection volume was 2 μL onto the column. The mobile phase consisted of 70% methanol and 30% water and the flow rate was 0.1 mL/min.

4.7. X-ray diffraction analysis

The crystals were mounted on glass fiber and the crystal data were collected on a Rigaku RAXIS RAPID IP device installed with graphite-monochromatized Mo Kα radiation (λ=0.71073 Å) at 293(2) K. Refinement was carried out by full-matrix least-squares on F^2. Computer program used was SHELXL-97 software package.[28]

Acknowledgements

This work was financially supported by the National Natural Science Foundation of China and Peking University.

References and notes

1. (a) Dam, T. K.; Brewer, C. F. *Chem. Rev.* **2002**, *102*, 387–429. (b) Mellet, C. O.; Defaye, J.; García Fernández, J. M. *Chem. Eur. J.* **2002**, *8*, 1982–1990. (c) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978–2996. (d) Lee, y. c.; Lee, R. T. *Acc. Chem. Res.* **1995**, *28*, 321–327.
2. (a) Feizi, T.; Mulloy, B. *Curr. Opin. Struct. Biol.* **2001**, *11*, 585–586. (b) Bertozzi, C. R.; Kiessling, L. L. *Science* **2001**, *291*, 2357–2364. (c) Williams, S. J.; Davies, G. J. *Trends Biotechnol.* **2001**, *19*, 356–362. (d) Feizi, T.; Mulloy, B. *Curr. Opin. Struct. Biol.* **2003**, *13*, 602–604.
3. (a) James, T. D.; Sandanayake, K. R. A. S.; Shinkai, S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1911–1922. (b) James, T. D.; Shinkai, S. *Top. Curr. Chem.* **2002**, *218*, 159–200. (c) Wang, W.; Gao, X. M.; Wang, B. H. *Curr. Org. Chem.* **2002**, *6*, 1285–1317. (d) Striegler, S. *Curr. Org. Chem.* **2003**, *7*, 81–102.
4. deSilva, A. P.; Gunaratne, H. Q. N.; Gunnlaugsson, T.; Huxley, A. J. M.; McCoy, C. P.; Rademacher, J. T.; Rice, T. E. *Chem. Rev.* **1997**, *97*, 1515–1566.
5. (a) Kikuchi, Y.; Tanaka, Y.; Sutarto, S.; Kobayashi, K.; Toi, H.; Aoyama, Y. *J. Am. Chem. Soc.* **1992**, *114*, 10302–10306. (b) Aoyama, Y.; Tanaka, Y.; Sugahara, S. *J. Am. Chem. Soc.* **1989**, *111*, 5397–5404.
6. (a) Bonar-Law, R. P.; Ladomenou, K. *Chem. Commun.* **2002**, 2108–2109. (b) Bonar-Law, R. P.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1995**, *117*, 259–271.
7. (a) Velasco, T.; Lecollinet, G.; Ryan, T.; Davis, A. P. *Org. Biomol. Chem.* **2004**, *2*, 645–647. (b) Lecollinet, G.; Domoney, A. P.; Velasco, T.; Davis, A. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 4093–4096. (c) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1998**, *37*, 2270–2273. (d) Bonar-Law, R. P.; Davis, A. P.; Murray, B. A. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1407–1408. (e) Klein, E.; Crump, M. P.; Davis, A. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 298–302.
8. (a) Welti, R.; Diederich, F. *Helv. Chim. Acta* **2003**, *86*, 494–503. (b) Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243–2289. (c) Bähr, A.; Felber, B.; Schneider, K.; Diederich, F. *Helv. Chim. Acta* **2000**, *83*, 1346–1376. (d) Smith, D. K.; Diederich, F. *Chem. Commun.* **1998**, 2501–2502. (e) Bähr, A.; Droz, A. S.; Püntener, M.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1998**, *81*, 1931–1963. (f) Anderson, S.; Neidlein, U.; Gramlich, V.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1596–1600.
9. (a) Das, G.; Hamilton, A. D. *Tetrahedron Lett.* **1997**, *38*, 3675–3678. (b) Das, G.; Hamilton, A. D. *J. Am. Chem. Soc.* **1994**, *116*, 11139–11140.
10. (a) Kim, Y.-H.; Hong, J.-I. *Angew. Chem., Int. Ed.* **2002**, *41*, 2947–2950. (b) Kim, H.-J.; Kim, Y.-H.; Hong, J.-I. *Tetrahedron Lett.* **2001**, *42*, 5049–5052. (c) Lee, J.-D.; Greene, N. T.; Rushton, G. T.; Shimizu, K. D.; Hong, J.-I. *Org. Lett.* **2005**, *7*, 963–966.
11. Bitta, J.; Kubik, S. *Org. Lett.* **2001**, *3*, 2637–2640.
12. (a) Rusin, O.; Lang, K.; Král, V. *Chem. Eur. J.* **2002**, *8*, 655–663. (b) Král, V.; Rusin, O.; Charvátová, J.; Anzenbacher, P., Jr.; Fogl, J. *Tetrahedron Lett.* **2000**, *41*, 10147–10151. (c) Rusin, O.; Král, V. *Chem. Commun.* **1999**, 2367–2368. (d) Král, V.; Rusin, O.; Schmidtchen, F. P. *Org. Lett.* **2001**, *3*, 873–876. (e) Rusin, O.; Hub, M.; Král, V. *Mater. Sci. Eng. C* **2001**, *18*, 135–140.
13. (a) Inouye, M.; Takahashi, K.; Nakazumi, H. *J. Am. Chem. Soc.* **1999**, *121*, 341–345. (b) Inouye, M.; Chiba, J.; Nakazumi, H. *J. Org. Chem.* **1999**, *64*, 8170–8176. (c) Abe, H.; Aoyagi, Y.; Inouye, M. *Org. Lett.* **2005**, *7*, 59–61.
14. (a) Mazik, M.; Sicking, W. *Tetrahedron Lett.* **2004**, *45*, 3117–3121. (b) Mazik, M.; Radunz, W.; Sicking, W. *Org. Lett.* **2002**, *4*, 4579–4582. (c) Mazik, M.; Sicking, W. *Chem. Eur. J.* **2001**, *7*, 664–670. (d) Mazik, M.; Bandmann, H.; Sicking, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 551–554.
15. Mizutani, T.; Kurahashi, T.; Murakami, T.; Matsumi, N.; Ogoshi, H. *J. Am. Chem. Soc.* **1997**, *119*, 8991–9001.
16. (a) Ishi-I, T.; Mateos-Timoneda, M. A.; Timmerman, P.; Crego-Calama, M.; Reinhoudt, D. N.; Shinkai, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2300–2305. (b) Tamaru, S.-i.; Yamamoto, M.; Shinkai, S.; Khasanov, A. B.; Bell, T. W. *Chem. Eur. J.* **2001**, *7*, 5270–5276.
17. Liu, R.; Still, W. C. *Tetrahedron Lett.* **1993**, *34*, 2573–2576.

18. (a) Segura, M.; Bricoli, B.; Casnati, A.; Munoz, E. M.; Sansone, F.; Ungaro, R.; Vicent, C. *J. Org. Chem.* **2003**, *68*, 6296–6303. (b) Sansone, F.; Chierici, E.; Casnati, A.; Ungaro, R. *Org. Biomol. Chem.* **2003**, *1*, 1802–1809.
19. (a) Liao, J.-H.; Chen, C.-T.; Chou, H.-C.; Cheng, C.-C.; Chou, P.-T.; Fang, J.-M.; Slanina, Z.; Chou, T. J. *Org. Lett.* **2002**, *4*, 3107–3110. (b) Fang, J.-M.; Selvi, S.; Liao, J.-H.; Slanina, Z.; Chen, C.-T.; Chou, P.-T. *J. Am. Chem. Soc.* **2004**, *126*, 3559–3566.
20. Vacca, A.; Nativi, C.; Cacciarini, M.; Pergoli, R.; Roelens, S. *J. Am. Chem. Soc.* **2004**, *126*, 16456–16465.
21. Chen, Y.-Q.; Wang, X.-Z.; Shao, X.-B.; Hou, J.-L.; Chen, X.-Z.; Jiang, X.-K.; Li, Z.-T. *Tetrahedron* **2004**, *60*, 10253–10260.
22. Newkome, G. R.; Garbis, S. J.; Majestic, V. K.; Fronczek, F. R.; Chiari, G. *J. Org. Chem.* **1981**, *46*, 833–839.
23. (a) Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165–2173. (b) Yamamoto, Y.; Yanagi, A. *Chem. Pharm. Bull.* **1982**, *30*, 1731–1737. (c) Zhang, H. C.; Tse, M. K.; Chan, K. S. *Synth. Commun.* **2001**, *31*, 1129–1139.
24. Benesi, H. A.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
25. Chou, P.-T.; Wu, G.-R.; Wei, C.-Y.; Cheng, C.-C.; Chang, C.-P.; Hung, F.-T. *J. Phys. Chem. B* **2000**, *104*, 7818–7829.
26. (a) López de la Paz, M.; Ellis, G.; Pérez, M.; Perkins, J.; Jiménez-Barbero, J.; Vicent, C. *Eur. J. Org. Chem.* **2002**, 840–855. (b) Baggett, N.; Bukhari, M. A.; Foster, A. B.; Lehmann, J.; Webber, J. M. *J. Chem. Soc.* **1963**, 4157–4160. (c) Alonso, J. L.; Wilson, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 1248–1251.
27. (a) Pathak, A. K.; Pathak, V.; Maddry, J. A.; Suling, W. J.; Gurcha, S. S.; Besra, G. S.; Reynolds, R. C. *Bioorg. Med. Chem.* **2001**, *9*, 3145–3151. (b) Zhang, X. D.; Kamiya, T.; Otsubo, N.; Ishida, H.; Kiso, M. *J. Carbohydr. Chem.* **1999**, *18*, 225–239. (c) Ferrières, V.; Benvegnu, T.; Lefeuvre, M.; Plusquellec, D.; Mackenzie, G.; Watson, M. J.; Haley, J. A.; Goodby, J. W.; Pindak, R.; Durbin, M. K. *J. Chem. Soc., Perkin Trans. 2* **1999**, 951–959. (d) Konstantinović, S.; Dimitrijević, B.; Radulović, V. *Indian J. Chem. B* **2002**, *41*, 598–603. (e) Kikuchi, Y.; Toi, H.; Aoyama, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1856–1858. (f) Droz, A. S.; Neidlein, U.; Anderson, S.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **2001**, *84*, 2243–2289. (g) Kaur, K. J.; Hindsgaul, O. *Glycoconjugate J.* **1991**, *8*, 90–94.
28. Sheldrick, G. M. *SHEELXL-97*: *Program for the Refinement of Crystal Structures*; University of Göttingen: Göttingen, Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1817–1822

Malbrancheamide, a new calmodulin inhibitor from the fungus *Malbranchea aurantiaca*☆

Sergio Martínez-Luis,[a] Rogelio Rodríguez,[b] Laura Acevedo,[a] María C. González,[c] Alfonso Lira-Rocha[a] and Rachel Mata[a,*]

[a]*Departamento de Farmacia, Facultad de Química, Universidad Nacional Autónoma de México, DF 04510 México, Mexico*
[b]*Departamento de Bioquímica, Facultad de Química, Universidad Nacional Autónoma de México, DF 04510 México, Mexico*
[c]*Instituto de Biología, Universidad Nacional Autónoma de México, DF 04510 México, Mexico*

Received 5 October 2005; revised 17 November 2005; accepted 18 November 2005

Available online 20 December 2005

Abstract—Bioassay-directed fractionation of an ethyl acetate extract (mycelia and broth) of the fungus *Malbranchea aurantiaca* led to the isolation of the novel phytotoxic alkaloid (5a*S*,12a*S*,13a*S*)-8,9-dichloro-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,6*H*-5a,13a (epiminomethano)indolizino[7,6b]carbazol-14-one (**1**) of the brevianamide series. The phytotoxin was given the trivial name of malbrancheamide (**1**). The structure of **1** was unequivocally established by UV, NMR, MS and X-ray studies. The absolute configuration was established by X-ray analysis according to the method of Flack. According to the conformational studies using molecular mechanics analyses, **1** exists in one preferred conformation, which was optimized by DFT calculations. Compound **1** caused moderate inhibition of radicle growth of *Amaranthus hypochondriacus* ($IC_{50}=0.37$ μM) and inhibited the activation of the calmodulin-dependent enzyme PDE1 ($IC_{50}=3.65\pm0.74$ μM). This effect was comparable to that of chlorpromazine ($IC_{50}=2.75\pm0.87$ μM) a well characterized CaM antagonist. The inhibition mechanism of **1** was competitive with respect to CaM according to a kinetic analysis.

1. Introduction

Continuing with our search of fungal phytotoxins with calmodulin-inhibitor properties,[1–4] we have investigated a new culture of the ascomycete *Malbranchea aurantiaca* Sigler and Carmich (Myxotrichaceae). Previously we described the isolation, structure elucidation and the phytotoxic effect of 1-hydroxy-2-oxoeremophil-1(10),7(11),8(9)-trien-12(8)-olide and penicillic acid from this species.[4] Herein, we report the isolation, structure, absolute configuration and calmodulin inhibitors properties of (5a*S*,12a*S*,13a*S*)-8,9-dichloro-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6b]carbazol-14-one (**1**) from this fungi. Compound **1** is a new member of the brevianamides type of alkaloids and was given the trivial name of malbrancheamide (**1**) (Fig. 1). The brevianamides as well as the allied aspergamides, macfortines, paraherquamides, sclerotamides and stephacidins belongs to a rare type of indol alkaloids possessing an unusual bicyclo [2.2.2] diazaoctane ring system.[5–19] These alkaloids are biosynthesized from tryptophan, proline or lysine, and at least one isoprene unit. It has been proposed that the bicyclo [2.2.2] diazaoctane ring arises via an intramolecular Diels–Alder reaction of a suitable intermediate.[20–21] Since their discovery in 1969, these natural products have been isolated periodically to the present from different strains of fungi of the genera *Aspergillus* and *Penicillium*. Their pharmacological action, synthesis and biosynthesis have been the subject of several elegant investigations.[5–21]

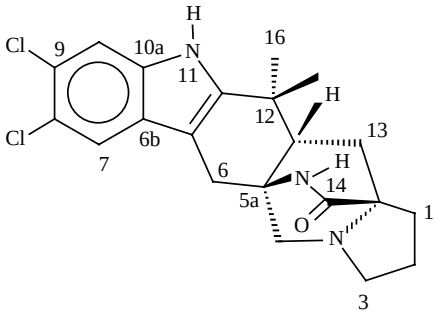


Figure 1. Structure of malbrancheamide (**1**).

☆ Taken in part from the PhD thesis of Sergio Martínez-Luis.

Keywords: *Malbranchea aurantiaca*; *Amaranthus hypochondriacus*; Calmodulin; *c*AMP phosphodiesterase; Brevianamides; Malbrancheamide.
* Corresponding author at present address: Colonia Parque San Andres, Inglaterra 102, 4040 Coyoacan, Mexico.
Tel.: +525 55 622 5289; fax: +525 55 622 5329;
e-mail: rachel@servidor.unam.mx

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.047

2. Results and discussion

2.1. Isolation and structure elucidation

Column chromatography of a phytotoxic (against *Amaranthus hypochondriacus* seedlings, $IC_{50}=195.0$ μg/mL) extract (mycelium and broth) of *M. aurantiaca* led to the isolation of a novel indole alkaloid, which was given the trivial name of malbrancheamide (**1**). The novel compound **1** was isolated as a colorless crystalline solid. Its molecular formula was determined as $C_{21}H_{23}ON_3Cl_2$ by HRMS. The compound showed a positive color reaction with Dragendorff's and Erlich's reagents. This information as well as the UV absorption maxima at 233 and 293 nm suggested that **1** was an indole alkaloid. The presence of two chlorine atoms in the molecule was consistent with the relative abundance of the [M+2] and [M+4] peaks with respect to the molecular ion [M] in the mass spectrum (approximately two-third and one-tenth, respectively, of the intensity of the molecular ion peak). The IR spectrum showed typical absorption bands for lactams at 3299 and 1659 cm^{-1}. In the ^1H NMR spectrum (Table 1) of **1**, two singlets signals showed the existence of a tetrasubstituted aromatic ring. Also apparent in the ^1H NMR spectrum were resonances for two methyl, one aliphatic methine and six methylene groups. The ^{13}C NMR spectrum (Table 1) revealed 21 carbon-resonances, interpreted from multiplicity-edited HSQC data as ten quaternary, three methine, six methylene, and two methyl carbons; this spectrum also supported the presence of a lactam functionality and an indole group in **1**. The chemical shift of the resonances at δ_C 125.4 and 128.2 were consistent with the placement of the chlorines at C-8 and C-9. The above-mentioned structural fragments accounted for seven of the 11 degrees of unsaturation required for the molecular formula, therefore there must be four additional rings in the structure of compound **1**. Detailed 2D-NMR spectra analyses (COSY, HETCOR, HMBC, and NOESY) led to the establishment of the connectivity of functional groups and, in turn, of the molecular structure. The position of the functional groups along the pentacyclic moiety was corroborated by an HMBC experiment (Table 1). Thus, the correlations C-10a/H-7, C-6b/H-10, C-6a/H-6, H-7, C-5a/H-12a, C-12a/H-6, H-16, H-17 and C-11a/H-6, H-16, H-17 corroborated the position of the chlorine atoms and the fusion of the indole nucleus to the dimethyl cyclohexane ring throughout C-6a and C-11a. On the other hand, the cross peaks C-5a/H-6, H-12a, H-13, H-5; C-12a/H-5 and C-13a/H-13, H-1, H-3, H-5 indicated that the bicyclo [2.2.2] diazaoctane ring system has the same arrangement than the one observed in alkaloids (−) VM55599 [17] and stephacidin A.[19]

Table 1. ^1H (500 MHz) and ^{13}C (125 MHz) NMR data for compound **1** in MeOD

Position	δ ^{13}C	δ ^1H	HMBC
1	28.1	A 2.52m B 1.46m	H_2, H_3, H_{13}
2	23.6	1.87m	H_1, H_3
3	55.3	A 3.05m B 2.15q 2, 5	H_1, H_2, H_5
5	59.4	A 2.25dd 2, 10 B 3.42d	H_3, H_6, H_{12a}
5a	57.5		H_5, H_6, H_{12a}, H_{13}, H_{16}
6	30.0	A 2.86m B 2.85m	
6a	104.8		H_6, H_7
6b	123.3		H_7, H_{10}
7	119.6	7.47s	H_6, H_{10}
8	125.4		H_7, H_{10}
9	128.2		
10	113.1	7.39s	H_7
10a	137.3		H_7, H_{10}
11a	145.2		H_6, H_{16}, H_{17}
12	35.5		H_{12a}, H_{13}, H_{16}, H_{17}
12a	48.5	2.14m	H_5, H_6, H_{13}, H_{16}, H_{17}
13	32.5	A 1.99m B 1.94m	H_1, H_2
13a	66.1		H_1, H_3, H_5, H_{13}
14	176.7		H_1, H_{13}
16	30.6	1.32s	H_{12a}, H_{17}
17	24.2	1.42s	H_{12a}, H_{16}

On the basis of the above data, the structure of **1** was elucidated as depicted and corroborated by X-ray analysis (Fig. 2). In the bicyclo [2.2.2] diazaoctane system, ring C (carbocyclic) adopts a boat conformation whereas ring F (lactam) an envelope conformation. Ring D was also observed as an envelope while ring E adopts a twisted envelope conformation. The atoms C13a–C1–C2–C3 are located in the ring plane while N4 is out-of the plane. Finally, the absolute configuration was determined applying the Flack's method.[22]

In order to gain a better understanding about the conformational behavior, a high level density functional theory (DFT) investigation was performed. The initial structure was built from standard fragments and minimized using molecular mechanics analysis as implemented in the SPARTAN'04 program. This initial study revealed a minimum energy conformer ($E=137.77$ kcal/mol) which was fully optimized by DFT (B3LYP/G31G*).[23] In the DFT optimized structure ($E=-1973.98$ kcal/mol) ring E displays an envelope conformation and the atoms N4–C13a–C1–C2 are located in the plane while the C3 is out-of the ring-plane (Fig. 3).

As previously proposed for the brevianamides, it is highly probable that the biogenesis of malbrancheamide (**1**) proceed from L-tryptophan, L-proline and one isoprene unit,[6,7,21] being the bicyclo [2.2.2] ring system arising through an intramolecular Diels–Alder reaction.[21,22]

From the structural point of view, it is important to point out that malbrancheamide is the first chlorinated indole alkaloid possessing a bicyclo [2.2.2] ring. The brevianamides, paraherquamides, aspergamides and macfortines type of compounds possess a spiro-ψ-indoxyl system, while malbracheamide does not. On the other hand, the main difference between malbrancheamide and (−) VM55599[19] and stephacidin A[17] seems to be the relative configuration at C12a in the bicyclo [2.2.2] diazaoctane ring system. Altogether, these features make malbrancheamide (**1**) unique among these of complex indole alkaloid derivatives.

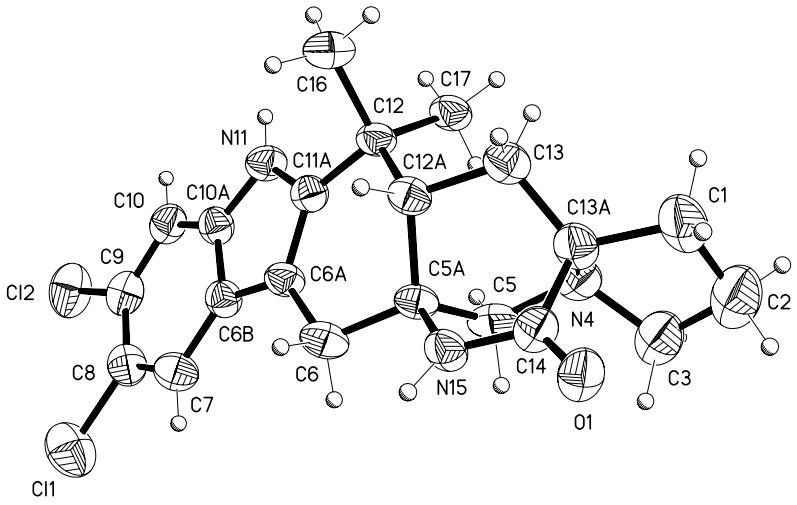


Figure 2. ORTEP view of malbrancheamide (**1**).

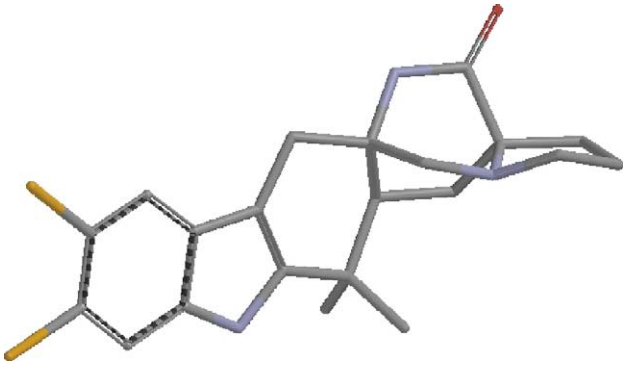


Figure 3. Optimized structure of compound **1** obtained by DFT analysis.

2.2. Biological testing

Compound **1** showed phytotoxic effects when tested against seedlings of *A. hypochondriacus* using a Petri dish bioassay.[1] Compound **1** ($IC_{50}=0.37$ μM) inhibited radicle growth of this species with a similar potency to 2,2-dichlorophenoxyacetic acid [2,4-D; $IC_{50}=0.18$ μM], which was used as a positive control.

The in vitro effect of the phytotoxin **1** on calmodulin (CaM)-sensitive PDE1 activity was investigated using a coupled enzymatic reaction. The PDE1 assay is well characterized and commonly used to detect CaM antagonists. The activity of PDE1 is correlated with the amount of inorganic phosphorous (Pi) released by the hydrolysis of *c*AMP in the presence of CaM and a nucleotidase. In turn, Pi was measured spectrophotocolorimetrically at 595 nm.[2–4,24] Compound **1** inhibited the activation of PDE1 in a concentration-dependent manner. The IC_{50} (concentration of the testing material inhibiting the activity of the enzyme by 50%) value calculated was 3.65 ± 0.74 μM. This effect was comparable to that of chlorpromazine ($IC_{50}=2.75\pm0.87$ μM) a well characterized CaM antagonist. During the course of these measurements **1** was found to have a mild but reproducible effect on the basal PDE1 activity in the presence of bovine-serum albumin (BSA), however, this last effect is unlikely to have physiological significance because its half-amplitude was above 200 μM, and was not pursued.

In order to obtain further evidence of the involvement of CaM in the inhibition of CaM-PDE1, a kinetic analysis of the inhibition of the activity of PDE1 was assessed using different amounts of CaM in the presence of different concentrations of **1** and in the absence of BSA. The BSA was eliminated in order to reduce, though not completely eliminate, the effect of the compound **1** on PDE1 itself. The results were analyzed by means of Dixon plots.[25] In this analysis, the vertical axes are the reciprocal of the PDE1 activity in the presence of each Ca^{2+}-CaM and **1** concentrations, and the horizontal axes are the **1** concentrations. Figure 4 shows the kinetic analysis of **1** induced inhibition of CaM-activated PDE1 by means of Dixon plots. These results suggested that **1** acts as competitive antagonist of CaM, thus competing with the formation of the CAM-PDE1 active complex. The estimated Ki (inhibition constant) value was 47.4 ± 5.63 μM. The difference between the IC_{50} and the Ki values can be explained by the difference in experimental conditions. In fact, an analysis of the impact of **1** on the assay indicated that the

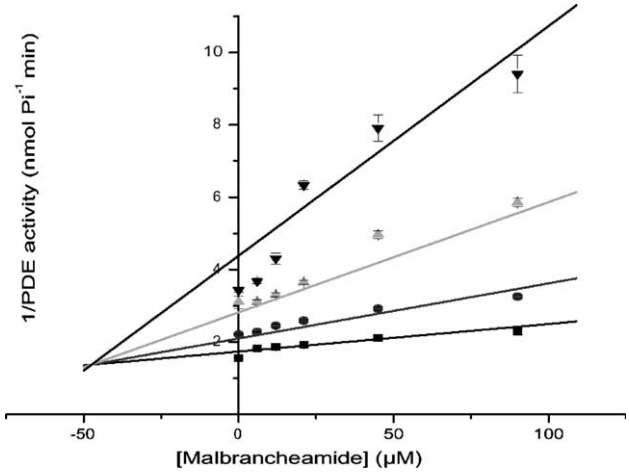


Figure 4. CaM-dependent PDE activity with constant concentrations of *c*AMP and $CaCl_2$. CaM concentration was held at 12.5 (▼), 25 (▲), 50 (●) and 100 (■) nM, and the concentration of **1** was varied. Error bars represent the standard error. Each point was repeated 6 to 12 times. The lines are the result of fitting all individual readings globally to a competitive inhibition model with CaM as essential activator and **1** as the inhibitor.

Ki value might be as much as three times lower than the IC_{50}, but never higher.

In conclusion, malbrancheamide (**1**) represents a novel type of CaM inhibitor although other natural indole alkaloids such as vincristine, vinblastine[26] and K-252a[27] as well as the synthetic compound DY-9760e[28] have been reported as CaM antagonists. The CaM antagonist effect of **1** might be related with its phytotoxic action and other pharmacological properties yet to be discovered. *M. aurantiaca* is very sensitive to light and temperature conditions. In dark and colder (25 °C) environments the fungi produce sesquiterpenes and polyketides but in warmer surroundings (32 °C) and under natural day-light cycles, malbrancheamide (**1**) is produced. The ecological significance of these variations remains an open question.

3. Experimental

3.1. General experimental procedures

Melting point determinations were carried out on a Fisher-Johns apparatus and are uncorrected. The optical rotation was recorded on a JASCO DIP 360 digital polarimeter. The CD spectrum was registered on a JASCO 720 spectropolarimeter at 25 °C in MeOH solution. The IR spectrum was obtained using KBr disk on a Perkin-Elmer 599B spectrophotometer. The UV spectrum was recorded on a Shimadzu 160 UV spectrometer in MeOH solution. NMR spectra including COSY, NOESY, HMBC and HMQC experiments were recorded in $CDCl_3$ on a Varian Unity Plus 500 spectrometer or on a Bruker DMX500 spectrometer at 500 MHz (^{1}H) or 125 MHz (^{13}C) NMR, using tetramethylsilane (TMS) as an internal standard. HREIMS was obtained on a JEOL JMS-AX505HA mass spectrometer. Column chromatography: silica gel 60 (70–230 mesh, Merck). TLC (analytical and preparative) was performed on precoated silica gel 60 F_{254} plates (Merck).

3.2. Fungal material and fermentation

The isolate of *Malbranchea aurantiaca* was obtained from bat guano collected at the Juxtlahuaca cave located in Ramal del Infierno, State of Guerrero, México, in 1998. A voucher specimen (24428) is deposited in the National Herbarium (MEXU), Instituto de Biología, Universidad Nacional Autónoma de México, Mexico City. Twelve 2-L Erlenmeyer flasks, each containing 1 L of PDB (Difco), were individually inoculated with one 1-cm^2 agar plug taken from a stock culture of *M. aurantiaca* maintained at 4 °C on potato dextrose agar (PDA). Flask cultures were incubated at environmental temperature and aerated by agitation on an orbital shaker at 200 rpm for 15 days.

3.3. Extraction and isolation of compound

After incubation, all flask contents were combined and filtered. The combined culture filtrate (10 L) was extracted exhaustively with AcOEt (3×10 L). The combined organic phase was filtered over anhydrous Na_2SO_4 and concentrated in vacuo to give a dark brown solid (3.5 g). The mycelium was macerated with AcOEt (3×2 L). After evaporating the solvent in vacuo, the combined mycelial and culture extract (4.0 g) was subjected to silica gel (400 g) open column chromatography eluting with a gradient of hexane–CH_2Cl_2 (10:0→0:10) and CH_2Cl_2:MeOH (9.9:0.1→1:1) to yield 10 major primary fractions (FI-FX). Bioactivity in the bioautographic bioassay showed one active pool: FVI (120 mg), eluted with CH_2Cl_2–AcOEt (7:3). From the active fraction crystallized a colorless solid, which was purified by re-crystallization from a mixture of MeOH–CH_2Cl_2 to yield 20 mg of **1**. Fraction FII, eluted with CH_2Cl_2–AcOEt (9:1), afforded 5 mg of each linoleic and oleic acids.[29]

3.3.1. Malbrancheamide (1). Crystalline colorless solid, mp 321–324 °C; $[\alpha]_D$ +42° (MeOH; *c*, 1). IR ν_{max} (KBr) cm^{-1}: 3299, 2959, 2924, 1739, 1659, 1460, 1317, 1241. UV λ_{max} (MeOH) nm (log ε): 233 (3.94), 293 (4.74) nm: CD (MeOH) λ_{max} nm ($\Delta\varepsilon$): 2.03×10^6 (245), 1.34×10^6 (218), 1.18×10^6 (227), 1.51×10^5 (296); ^{1}H and ^{13}C NMR, see Table 1; EIMS *m/z* (rel int.) 407 (1), 405 (3), 404 (1), 403 [M$^+$(5)], 363 (10.6), 361 (53.6), 359 (87.9), 345 (17.2), 325 (12.2), 264 (15.7), 262 (21.4), 240 (5), 228 (5), 180 (7), 164 (100), 163 (25), 135 (15.7), 120 (10) 96 (7); HREIMS *m/z* 403.1106 [M]$^+$ (calcd for $C_{21}H_{23}Cl_2N_3O$, 403.332).

3.4. X-ray crystal structure determination of 1

Single crystals suitable for X-ray analysis were obtained by recystallization from CH_2Cl_2–MeOH (8:2). A colorless prism crystal having approximate dimensions of 0.398×0.232×0.166 mm was mounted on a glass fiber. All measurements were made on a Bruker Smart Apex CCD diffractometer equipped with graphite-monochromated Mo Kα radiation (λ=1.54178 Å) at 293 K. Crystal data: $C_{21}H_{23}Cl_2N_3O$, 0.25*($C_4H_8O_2$), MW 426.35, tetragonal, space group $P4_32_12$, with unit cell parameters a=18.8877(7) Å, b=18.8877(7) Å, c=13.1336(9) Å, β=90°, V=4685.3 (4) Å^3, Z=8, $F(000)$=1792 and D_{calc}=1.209 g/cm^{-3}. Intensity data were collected in the range of $1.89<\theta<25.03°$ using a ω scan. Of the 37704 independent reflections collected, 4149 with $I>2\sigma(I)$ were considered observed and used in the calculations. The structure was solved by direct methods and refined by full matrix least-squares methods on F^2 using SHELXTL V 6.12[32] to give a final *R*-factor of 0.0751 ($wR2$=0.2101), confirming the reported configuration, with a data-restrains-parameters ratio of 4149/2/254. The absolute configuration was determined from the refined value of the Flack *x* parameter (0.05(9)).[22] Crystallographic data for the structure reported in this paper have been deposited with the Cambridge Crystallograpic Data Center (CCDC 285932). Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

3.5. Molecular modeling calculations

Minimum energy structures were generated using the MMF94 (Monte Carlo protocol) as implemented in the SPARTAN'04 Program (Wavefunction, Inc. Irvine, CA). The conformational search was carried out by exploring torsional internal degrees of freedom of dihedral angles selected by the automatic set up procedure. The torsional

angles considered were: C12a–C13–C13a, C13a–C1–C2, C1–C2C–3, C2–C3–N4, N4–C5–C5a. The rotation angle was 30°. The minimum energy conformer was fully optimized by DFT. DFT calculations were carried out at the B3LYP/G31G* level.

3.6. Phytogrowth-inhibitory bioassays

The phytogrowth-inhibitory activity of the crude extract, fractions and pure compounds was evaluated on seeds of *Amaranthus hypochondriacus* using a Petri dish bioassay.[1–4] In addition, a bioautographic phytogrowth inhibitory bioassay was employed to guide secondary fractionation.[1–4] Seeds of *A. hypochondriacus* were purchased from Mercado de Tulyehualco, Mexico City. The results were analyzed by ANOVA ($p<0.05$) and IC_{50} values were calculated by probit analysis based on percent of radicle growth or germination inhibition. Samples were evaluated at 10, 100 and 1000 μg ml^{-1}. 2,4-D was used as the positive control. The bioassays were performed at 28 °C.

3.7. Cyclic nucleotide phosphodiesterase assay

Phosphodiesterase activity was measured according to the method described by Sharma and Wang[30] with some modifications. Bovine brain CaM (44 ng) was incubated with 0.015 units of CaM-deficient-CaM-dependent *c*AMP from bovine brain during 40 min in 40 μL of assay solution containing 0.3 units of 5′-nucleotidase, 45 mM Tris–HCl, 5.6 mM magnesium acetate, 45 mM imidazole, 2.5 mM calcium chloride, and 10 μM bovine serum albumin (BSA), pH 7.0. Compounds were then added to the assay medium at 1, 2, 4, 7, 13, 20, 32, 50 and 65 μM in ACN, and the samples were incubated during 30 min. Then, 10 μL of 10.8 μM *c*AMP was added to start the assay. After 15 min, the assay was stopped by the addition of 190 μL of malachite green solution. All the above steps were carried out at 30 °C. The phosphodiesterase reaction was coupled to the 5′-nucleotidase (*Crotalus atrox* venom from Sigma) reaction; the amount of inorganic phosphate released, measured spectrophotometrically at 595 nm, correlated with the activity of the PDE1. The experiments to determine *Ki* values were performed as described above but in the presence of four different concentrations of CaM (10, 20, 40 and 80 ng/mL), and in the absence of BSA. All the results are expressed as the mean of at least six experiments ±SEM. The IC_{50} (concentration inhibiting by 50% the activity of the enzyme) values were determined by non-linear regression analysis by fitting to hyperbolic inhibition. The Ki was calculated from a global fit of data against inhibitor and CaM concentration using the simple competitive inhibition equation:

$$v = \frac{V_{MAX}[S]}{K_{MA}\left(1+\frac{[I]}{K_I}\right)+[S]}$$

where V_{MAX}=Activity at saturating CaM concentration; K_{MA}=Dissociation constant of CaM-PDE1 complex; I=Concentration of the inhibitor and S=Concentration of CaM.

Non-linear regression was performed with the program Origin 3.0 (Microcal) or with the SigmaStat 2-0 statistical package (Jendel Scientific). Both programs rendered very similar estimates. Chlorpromazine was used as a positive control.

Acknowledgements

This work was supported by Facultad de Química and PAEP-2005, Posgrado en Ciencias Químicas, UNAM and CONACYT 45814-Q. We also are grateful to the following people: Marisela Gutierrez and Georgina Duarte for recording UV, IR and mass spectra; Isabel Rivero-Cruz for technical assistance; and Blanca Rivero-Cruz for her valuable help in the CaM assays.

References and notes

1. Macías, M.; Ulloa, M.; Gamboa, A.; Mata, R. *J. Nat. Prod.* **2000**, *63*, 757–761.
2. Mata, R.; Gamboa, A.; Macías, M.; Santillan, S.; Ulloa, M.; González, M. C. *J. Agric. Food Chem.* **2003**, *51*, 4559–4562.
3. Rivero-Cruz, J. F.; Macías, M.; Cerda-García-Rojas, C. M.; Mata, R. *J. Nat. Prod.* **2003**, *66*, 511–514.
4. Martínez-Luis, S.; González, M. C.; Ulloa, M.; Mata, R. *Phytochemistry* **2005**, *66*, 1012–1016.
5. Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644–645.
6. Birch, A. J.; Wright, J. J. *Tetrahedron* **1970**, *26*, 2329–2344.
7. Birch, A. J.; Russell, R. A. *Tetrahedron* **1972**, *28*, 2999–3008.
8. Coetzer, J. *Acta Crystallogr.* **1974**, *B30*, 2254–2256.
9. Fenical, W.; Jensen, P. R.; Cheng, X. C. 2000, U.S. Patent 6,066,635; *Chem. Abstr.* **2000**, *132*, 346709.
10. Yutaka, S.; Hideo, H.; Taisuke, I.; Masaru, I.; Yoon-Jeong, K.; Yasuhiro, K.; Tatsuo, S.; Shinichi, S.; Akemi, S.; Yumiko, S.; Lori, B.; Joan, D.; Liang-Hsiung, H.; Joyce, S.; Nakao, K. *J. Antibiot.* **2001**, *54*, 911–916.
11. Polonsky, J.; Merrien, M-A. ; Prange, T.; Pascard, C. *J. Chem. Soc., Chem. Commun.* **1980**, 601–602.
12. Prange, T.; Buillion, M-A. ; Vuilhorgne, M.; Pascard, C.; Polonsky, J. *Tetrahedron Lett.* **1980**, *22*, 1977–1980.
13. Yamazaki, M.; Okuyama, E.; Kobayashi, M.; Inoue, H. *Tetrahedron Lett.* **1981**, *22*, 135–136.
14. Ondeyka, J. G.; Goegelman, R. T.; Schaeffer, J. M.; Kelemen, L.; Zitano, L. *J. Antibiot.* **1990**, *43*, 1375–1379.
15. Liesch, J. M.; Wichmann, C. F. *J. Antibiot.* **1990**, *43*, 1380–1386.
16. Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Manger, B. R.; Reading, C. *J. Antibiot.* **1991**, *44*, 492–497.
17. Blanchflower, S. E.; Banks, R. M.; Everett, J. R.; Reading, C. *J. Antibiot.* **1993**, *46*, 1355–1363.
18. Whyte, A. C.; Gloer, J. B. *J. Nat. Prod.* **1996**, *59*, 1093–1095.
19. Qian-Cutrone, J.; Huang, S.; Shu, Y. Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556–14557.
20. Stocking, E. M.; Willians, R. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 3078–3115 and references cited therein.
21. Williams, R.; Cox, R. J. *Acc. Chem. Res.* **2003**, *36*, 127–139 and references cited therein.
22. Flack, H. D. *Acta Crystallogr. A* **1983**, *39*, 876–881.
23. Lee, G-Y.; Jun, M-S. *Bull. Korean Chem. Soc.* **2001**, *22*, 11–12.

24. Sharma, R. K.; Wang, J. H. In Greengard, P., Robinson, G. A., Eds.; Advances in Cyclic Nucleotide Research; Raven: New York, 1979; Vol. 10, pp 187–198.
25. Dixon, M. *Biochem. J.* **1953**, *55*, 170–171.
26. Vertessy, B. G.; Ramat, V.; Böcskei, Z.; Náray-Szabó, G.; Orosz, F.; Ovádi, J. *Biochemistry* **1998**, *37*, 15300–15310.
27. Matsuda, Y.; Nakanishi, S.; Nagasawa, K.; Iwahashi, K.; Kase, H. *Biochem. J.* **1988**, *256*, 75–80.
28. Sogimura, M.; Sato, T.; Nakayama, W.; Morishima, Y.; Fukunaga, K.; Omitsu, M.; Miyamoto, E.; Shirasaki, Y. *Eur. J. Pharm.* **1997**, *336*, 99–106.
29. Dilika, F.; Bremner, P. D.; Meyer, J. J. M. *Fitoterapia.* **2000**, *71*, 450–452.
30. Sheldrick, G. M. *SHELXTL97*: *Program for Refinement of Crystal Structures*; University of Gottingen: Gottingen, Germany, 1997.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1823–1827

Silphos [$PCl_{3-n}(SiO_2)_n$]: a heterogeneous phosphine reagent for the conversion of epoxides to β-bromoformates or alkenes

Nasser Iranpoor,* Habib Firouzabadi* and Arezu Jamalian

Department of Chemistry, College of Sciences, Shiraz University, Shiraz 71454, Iran

Received 3 October 2005; revised 2 November 2005; accepted 17 November 2005

Available online 13 December 2005

Abstract—Silphos [$PCl_{3-n}(SiO_2)_n$] as a heterogeneous phosphine reagent is efficiently applied for the transformation of epoxides to β-bromoformates in the presence of bromine or *N*-bromosuccinimide in dimethyl formamide at 0 °C. The combination of Silphos and iodine was also found suitable for the room temperature preparation of alkenes. The use of Silphos provides the advantage of easy separation of the phosphine oxide by-product from the reaction mixture.

1. Introduction

Epoxides, as strained three-membered heterocyclic intermediates, play an increasingly important role in organic synthesis[1] and their nucleophilic ring opening reactions under mild conditions are of great interest.[2–4] On the other hand, synthetic transformation of different functionalities by using the combination of PPh_3 and molecular halogens or reagents carrying electrophilic halogens have been widely investigated.[5,6] It has been reported that applying these reagents in dry DMF provides a useful method for the formylation of hydroxyl groups.[7,8] We have also applied PPh_3/Br_2 or PPh_3/NBS in DMF for the synthesis of β-bromoformates from epoxides.[9] Despite the novelty of the reported method, this procedure along with other synthetic methods using homogeneous phosphine reagents as oxophile, have a common limitation, which is the formation of stoichiometric amount of phosphine oxide by-product in which its separation from the reaction mixture is usually a difficult task and requires time consuming techniques. As a solution to this problem, various heterogeneous or polymeric supported phosphine reagents have been presented and used for different synthetic purposes. Polystyrene supported triphenylphosphine,[10] ROMPgel-supported triphenylphosphine,[11] 4-diphenylphosphanyl-benzoic acid 2-trimethylsilanyl ethyl ester,[12] non-cross-linked polystyrene triphenylphosphine[13] and polymer-supported triphenylphosphine resin[14] are some of the recently reported examples of the useful phosphines, which are not easily prepared and available reagents.

Recently, we have introduced a cheap and easily prepared heterogeneous phosphine reagent, Silphos [$PCl_{3-n}(SiO_2)_n$], and used it for bromination and iodination of alcohols and thiols,[15] deoxygenation of sulfoxides, reductive coupling of sulfonyl chlorides[16] and formylation and acetylation of alcohols and amines.[17] Now, we report on the ability of this reagent for the synthesis of β-bromoformates from epoxides in the presence of Br_2 or NBS at 0 °C in DMF (Fig. 1).

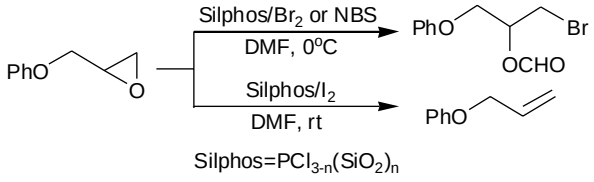


Figure 1. Conversion of epoxides to their corresponding β-bromoformates and alkenes in the presence of Silphos [$PCl_{3-n}(SiO_2)_n$] and halogenating agents.

The reaction of 2,3-epoxypropylphenyl ether with different ratios of *N*-bromosuccinimide (NBS), Br_2 and I_2 in combination with Silphos [$PCl_{3-n}(SiO_2)_n$] in dry DMF were studied. The data are summarized in Table 1. As shown, in the presence of 1.5 g of Silphos, the ratio of 1.2 for Br_2/epoxide was sufficient to complete the reaction. However, under this condition, a mixture of products (β-bromohydrin, β-bromoformate, and alkene) was produced (Table 1, entry 2). Increasing the amount of bromine did not show any considerable difference in the distribution of the products obtained. Refluxing the reaction mixture favoured the formation of alkene over bromoformate (Table 1, entry 4).

Keywords: Silphos; Heterogeneous phosphine reagent; Epoxides; β-Bromoformates; Alkenes.
* Corresponding authors. Tel.: +98 711 2287600; fax: +98 711 2280926; e-mail addresses: iranpoor@chem.susc.ac.ir; firouzabadi@chem.susc.ac.ir

0040–4020/$ - see front matter © 2006 Published by Elsevier Ltd.
doi:10.1016/j.tet.2005.11.042

Table 1. Reactions of 2,3-epoxypropylphenyl ether with 1.5 g of Silphos [$PCl_{3-n}(SiO_2)_n$] and different ratios of Br_2, NBS or 1.0 g of Silphos in the presence of different mmol of molecular iodine

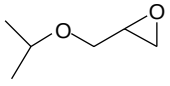
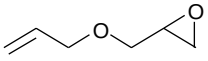
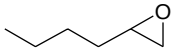
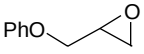
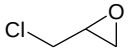
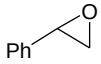
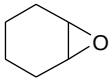
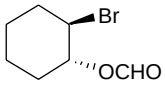
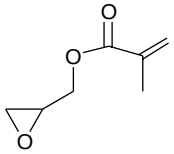
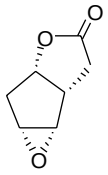
Entry	Reagent	Substrate/reagent	Reaction temperature	Time (h)	Conversion (%)
1	Br_2	1:1	rt	5	80[a]
2	Br_2	1:1.2	rt	3	100[a]
3	Br_2	1:1.4	rt	1	100[a]
4	Br_2	1:1.4	Reflux	0.3	100[b]
5	Br_2	1:1.4	0 °C	1	100
6	NBS	1:1.4	0 °C	3.5	100
7	I_2	1:1.8	rt	1	80[c]
8	I_2	1:2	rt	<10 min	100[d]

[a] Mixture of bromohydrin, bromoformate and alkene was produced in almost equal amounts.
[b] The amount of produced alkene was ~45%.
[c] The products were found to be iodohydrine and alkene with the ratio of 30:70 by NMR analysis.
[d] Conversion to 3-phenoxy propene was observed.

The best reaction condition was obtained when the reaction mixture was cooled down to 0 °C, in which 2,3-epoxypropylphenyl ether was quantitatively converted to its corresponding β-bromoformate in 1 h (Table 1, entry 5). Replacing molecular bromine with NBS required more reaction time (~3.5 h) for the above transformation (Table 1, entry 6). In this study, it was also observed that increasing the molar ratio of molecular iodine up to 2, converts 2,3-epoxypropylphenyl ether quantitatively to 3-phenoxy propene (Table 1, entry 8).

Applying 1.5 g of Silphos with 1.4 mmol of bromine or NBS to 1.0 mmol of different epoxides in dry DMF yielded the corresponding β-bromoformates (Table 2). The results show that epoxides carrying either electron-donating or withdrawing groups reacts under these conditions and yields the corresponding β-bromoformates in good to high yields. For entries 8 and 9 of Table 2, the conversion was not complete and a mixture of unidentified products was observed.

Table 2. Conversion of epoxides to β-bromoformates in the presence of 1.5 g of Silphos [$PCl_{3-n}(SiO_2)_n$] and 1.4 mmol of Br_2 or NBS in DMF at 0 °C

Entry	Substrate	Silphos/Br_2		Silphos/NBS		Product[a]
		Time (min)	Yield (%)	Time (h)	Yield (%)	
1		35	91	1	93	$Me_2CHOCH_2CH(OCHO)CH_2Br$
2		40	92	3	90	$CH_2{=}CHCH_2OCH_2CH(OCHO)CH_2Br$
3		20	85	1	90	$Me(CH_2)_3CH(OCHO)CH_2Br$
4		60	96	3.5	92	$PhOCH_2CH(OCHO)CH_2Br$
5		40	88	3	85	$ClCH_2CH(OCHO)CH_2Br$
6		15	58	0.5	60	$PhCH(Br)CH_2OCHO$
7		20	70	1	74	
8		3 h	—	24	—	—[b]
9		24 h	—	24	—	—[c]

[a] For entries 1–5, a trace amount of their corresponding alkene was produced. In the case of styrene oxide, entry 6, a mixture of products, styrene (10%), 2-bromo-2-phenyl ethanol (20%) were also obtained. 2-Bromo-2-phenyl ethanol has a primary hydroxyl group and cannot be formylated.[8b] For entry 7, ~15% of cyclohexene and trace amount of unidentified products were produced.
[b] The conversion was 50% and a mixture of unidentified products was produced.
[c] The conversion was 40% and a mixture of unidentified products was produced.

On the basis of literature,[7b,c,9] a similar mechanism is proposed for bromformylation of epoxides with Silphos (Fig. 2).

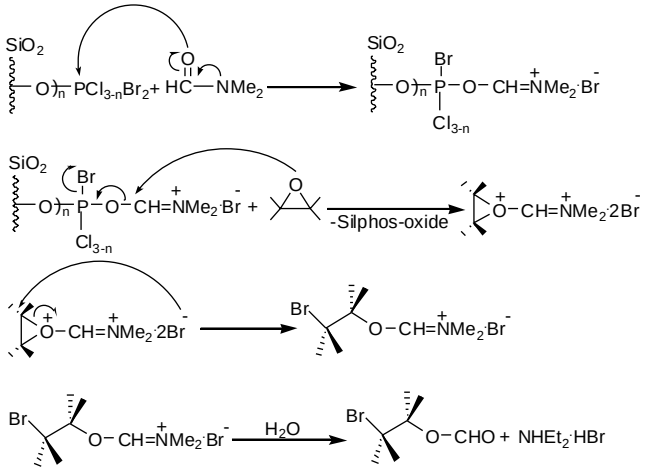


Figure 2. Mechanism proposed for the conversion of epoxides to their corresponding β-bromoformates in the presence of Silphos $[PCl_{3-n}(SiO_2)_n]$.

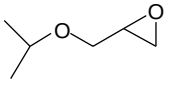
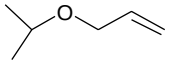
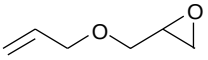
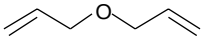
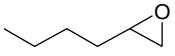
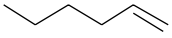
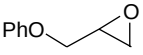
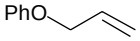
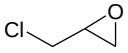
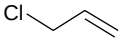
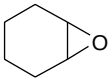
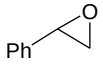
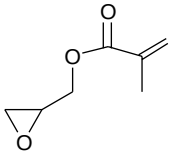
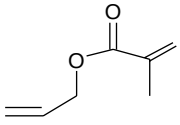
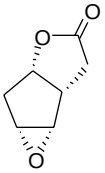
Deoxygenation of epoxides to alkenes enables epoxides to be introduced as protecting groups for double bonds.[18] A number of methods using phosphine reagents have been reported for removing oxygen from epoxides,[19] which mostly require expensive reagents, harsh reaction conditions and have problems for the separation of the phosphine oxide by-product from the reaction mixture, for example, the use of PPh_3/I_2 has the problem for the isolation of alkene from the reaction mixture and only conversion yield is reported.[9]

In continuation of our study, we optimized the reaction conditions for the conversion of epoxides to alkenes by applying different quantities of Silphos and I_2 in various solvents such as benzene, CH_2Cl_2, CH_3CN, and DMF at various temperatures. We observed that in the presence of Silphos (1.0 g) and 2.0 mmol of iodine, 1.0 mmol of epoxide can be quantitatively converted to its alkene in dry DMF at room temperature. Any change in the ratio of substrate and reagents produces a mixture of products. The results obtained from deoxygenation of structurally different classes of epoxides by the Silphos/I_2 system in dry DMF are shown in Table 3. The advantage of using Silphos/I_2 system is that the produced alkenes can be easily isolated from the reaction mixture.

2. Conclusion

In this study, we have introduced a new application for Silphos $[PCl_{3-n}(SiO_2)_n]$ as a cheap, efficient and easily

Table 3. Conversion of 1.0 mmol of epoxides to their corresponding alkenes by 1.0 g of Silphos $[PCl_{3-n}(SiO_2)_n]$ and 2.0 mmol of I_2 in DMF at room temperature

Entry	Substrate	Time (min)	Product	Yield (%)
1		5		77
2		15		88
3		15		80
4		<10		93
5		25		74
6		10		79
7		<5		89
8		3 h[a]		90
9		24 h	—	—[b]

[a] 1.5 g of Silphos was used.
[b] The conversion was 50% and mixture of products was produced after 24 h in reflux condition.

prepared heterogeneous phosphine reagent for the conversion of epoxides to their corresponding β-bromoformates or alkenes. The Silphos-oxide produced from the reaction can be removed with a filtration and offers a very simple and practical work-up.

3. Experimental

3.1. General

Chemicals were either prepared in our laboratory or were purchased from Fluka and Merck companies. The purity determination of the products was accomplished by GC on a Shimadzu model GC-14A instrument or by TLC on silica gel polygram SIL G/UV 254 plates. Mass spectra were run on a Shimadzu GC-Mass-QP 1000 EX at 20 eV. The IR spectra were recorded on a Perkin-Elmer 781 spectrophotometer. The NMR spectra were recorded on a Bruker Avance DPX 250 MHz spectrometer using tetramethylsilane as internal standard.

3.1.1. General procedure for the conversion of epoxides to β-bromoformates by Silphos $[PCl_{3-n}(SiO_2)_n]/Br_2$ or NBS in DMF. To a heterogeneous solution containing 1.5 g of Silphos $[PCl_{3-n}(SiO_2)_n]$ in 5 mL of dry DMF at 0 °C 1.4 mmol (0.07 mL) bromine or 0.25 g of NBS was added. 1.0 mmol of the epoxide was added after 5 min. The progress of the reaction was monitored by TLC and GC analysis. The epoxide disappeared in less than 10 min with formation of the corresponding β-bromoformate as the major product and some bromohydrin. The reaction mixture was stirred until the complete conversion of the bromohydrin to its corresponding β-bromoformate. The reaction mixture was then filtered to separate the Silphos-oxide. The filtrate was poured into saturated brine and the product was extracted by 2×30 mL of ether. The organic layer was washed with 2×20 mL of an aqueous solution of 10% sodium thiosulfate and 2×15 mL of water, respectively. The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under rotary evaporator gave the corresponding β-bromoformate. The obtained β-bromoformates were identified by comparison of their spectral data with those reported in the literature.[9] The spectral data of formic acid 1-bromomethyl-2-phenoxy-ethyl ester as a typical product is as follows: IR (neat): 3430, 3075, 3060, 3035, 2925, 2867, 1711, 1594, 1487, 1234, 1140, 751 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$): δ (ppm)=8.10 (s, 1H), 7.15–7.28 (m, 2H), 6.80–6.90 (m, 3H), 5.31 (m, 1H), 4.07–4.17 (m, 2H), 3.52–3.64 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$); δ (ppm)= 160.1, 157.9, 129.7, 122.0, 115.1, 70.7, 66.8, 30.0; MS (20 eV), *m/e* (%): 260 (4), 258 (4), 167 (96.2), 165 (100), 133 (23.5), 94 (32.3), 57 (31.4). Anal. Calcd for $C_{10}H_{11}BrO_3$: C, 46.36; H, 4.28. Found: C, 46.47, H, 4.17.

3.1.2. General procedure for the conversion of epoxides to alkenes by Silphos $[PCl_{3-n}(SiO_2)_n]/I_2$ in DMF. To a heterogeneous solution containing 1.0 g of Silphos $[PCl_{3-n}(SiO_2)_n]$ in 3 mL of dried DMF at room temperature 2.0 mmol (0.5 g) of iodine was added. 1.0 mmol of the epoxide was added after 5 min. The progress of the reaction was monitored by TLC and GC analysis. The reaction mixture was stirred until the complete conversion of the epoxide to alkenes. The reaction mixture was then filtered to separate the Silphos-oxide. The filtrate was poured into saturated brine and the product was extracted by 2×30 mL of ether. The organic layer was washed with 2×20 mL of an aqueous solution of 10% sodium thiosulfate and 2×15 mL of water, respectively. The combined organic layers were dried over anhydrous Na_2SO_4. Filtration and evaporation of the solvent under rotary evaporator gave the corresponding alkene. In the case of low boiling point alkenes (Table 3, entries 1–3, 5 and 6) liquid air cooled, bulb-to-bulb distillation was used for purification. The spectral data of the produced alkenes (3-*i*-propopoxy-propene, diallyl ether, 1-hexene, allyloxy benzene, 3-chloro-propene, cyclohexene, styrene, allyl methacrylate) were compared to those of authentic samples.[20]

Acknowledgements

We gratefully acknowledge the support of this study by the Management and Programming Organization of Iran and Shiraz University Research Council.

References and notes

1. See some of the latest publications: (a) Firouzabadi, H.; Iranpoor, N.; Jafarpour, M. *Tetrahedron Lett.* **2005**, *46*, 4107–4110. (b) Surendra, K.; Krishnaveni, N. S.; Rao, K. R. *Tetrahedron Lett.* **2004**, *45*, 6523–6526. (c) Kaboudin, B.; Norouzi, H. *Tetrahedron Lett.* **2004**, *45*, 1283–1285. (d) Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49–52. (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, Ch. S. *Tetrahedron Lett.* **2004**, *45*, 1291–1293. (f) Harfouche, J.; Hérault, D.; Tommasino, M. L.; Pellet-Rostaing, S.; Lemaire, M. *Tetrahedron: Asymmetry* **2004**, *15*, 3413–3418. (g) Tamami, B.; Kolahdoozan, M. *Tetrahedron Lett.* **2004**, *45*, 1535–1537. (h) Ramos, V. D.; Derouet, D.; Visconte, L. L. Y. *Polym. Test.* **2003**, *22*, 297–304. (i) Yoo, S. K.; Han, J. H.; Lee, S. J.; Ryu, J. Y.; Kim, C.; Jin, S. W.; Kim, Y.; Nam, W. *Inorg. Chem. Commun.* **2003**, *6*, 1148–1151. (j) Derouet, D.; Cauret, L.; Brosse, J. C. *Eur. Polym. J.* **2003**, *39*, 671–686.
2. For reviews, see: (a) Sander, M. *Chem. Rev.* **1966**, *66*, 297–339. (b) Smith, J. C. *Synthesis* **1984**, 629–656.
3. (a) Rosewsky, A. *Heterocyclic Compounds with Three and Four Membered Rings, Part I*; Interscience: New York, 1964; Chapter 1. (b) Sexton, A. R.; Britton, E. C. *J. Am. Chem. Soc.* **1948**, *70*, 3606–3607. (c) Gilman, H.; Fullhart, L. *J. Am. Chem. Soc.* **1949**, *71*, 1478–1481. (d) Bordwell, F. G.; Anderson, H. M. *J. Am. Chem. Soc.* **1953**, *75*, 495–496. (e) Goodman, L.; Benitez, A.; Baker, B. R. *J. Am. Chem. Soc.* **1958**, *80*, 1680–1687. (f) Bridger, R. F.; Russel, R. R. *J. Org. Chem.* **1960**, *25*, 863–866. (g) Christensen, B. G.; Strachan, R. G.; Trenner, N. R.; Arison, B. H.; Hir Schmann, R.; Chemerds, J. M. *J. Am. Chem. Soc.* **1960**, *82*, 3995–4000. (h) Brown, H. C.; Yoon, N. M. *J. Am. Chem. Soc.* **1966**, *88*, 1464–1472. (i) Sander, M. *Chem. Rev.* **1966**, *66*, 297–339. (j) Izydore, R. A.; Ghirardelli, G. R. *J. Org. Chem.* **1973**,

38, 1790–1793. (k) Norton, J. R.; Shenton, K. E.; Schwartz, J. *Tetrahedron Lett.* **1975**, 51–54. (l) Brown, H. C.; Krishnamurthy, S. *Tetrahedron* **1979**, *35*, 567–607.

4. (a) Iranpoor, N.; Mohammadpour Baltork, I. *Synth. Commun.* **1990**, *20*, 2789–2797. (b) Iranpoor, N.; Mohammadpour Baltork, I.; Shiriny, F. *Tetrahedron* **1991**, *47*, 9861–9866. (c) Iranpoor, N.; Mohammadpour Baltork, I. *Tetrahedron Lett.* **1990**, *31*, 735–738. (d) Iranpoor, N.; Owji, J. *Tetrahedron* **1991**, *47*, 149–154. (e) Safavi, A.; Iranpoor, N.; Fotuhi, L. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 2591–2594. (f) Iranpoor, N.; Tarrian, T.; Movahedi, Z. *Synthesis* **1996**, 1473–1476. (g) Iranpoor, N.; Kazemi, F. *Tetrahedron* **1997**, *53*, 11377–11382. (h) Iranpoor, N.; Tamami, B.; Niknam, K. *Can. J. Chem.* **1997**, *75*, 1913–1919. (i) Iranpoor, N.; Shakarriz, M.; Shiriny, F. *Synth. Commun.* **1998**, *28*, 347–366. (j) Katsuki, H.; Shimanouchi, T.; Ohshima, R.; Fujiwara, S. *Teterahedron* **1998**, *54*, 2709–2722. (k) Skupin, R.; Haufe, G. *J. Fluorine Chem.* **1998**, *92*, 157–165. (l) Prestat, G.; Baylon, C.; Heck, M.-P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829–3831. (m) Iranpoor, N.; Adibi, H. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 675–680. (n) Salomon, C. J. *Synlett* **2001**, 65–68. (o) Kamal, A.; Khana, G. B. R. *Tetrahedron: Asymmetry* **2001**, *12*, 405–410. (p) Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* **2001**, *42*, 8721–8724. (q) Sartillo-Piscil, F.; Quintero, L.; Villegas, C.; Santacruz-Juárez, E.; Parrodi, C. A. D. *Tetrahedron Lett.* **2002**, *43*, 15–17. (r) Chandrasekhar, S.; Reddy, Ch. R.; Babu, N.; Chandrasekhar, G. *Tetrahedron Lett.* **2002**, *43*, 3801–3803. (s) Tamami, B.; Mahdavi, H. *React. Funct. Polym.* **2002**, *51*, 7–13. (t) Tamami, B.; Mahdavi, H. *Tetrahedron Lett.* **2002**, *43*, 6225–6228. (u) Mirkhani, V.; Tangestaninejad, S.; Yadollahi, B.; Alipanah, L. *Tetrahedron* **2003**, *59*, 8213–8218. (v) Sharghi, H.; Nasseri, M. A.; Hassani Nejad, A. *J. Mol. Catal. A: Chem.* **2003**, *206*, 53–57. (w) Fox, D. L.; Robinson, A. A.; Frank, J. B.; Salvatore, R. N. *Tetrahedron Lett.* **2003**, *44*, 7579–7582. (x) Moghadam, M.; Tangestaninejad, S.; Mirkhani, V.; Shaibani, R. *Tetrahedron* **2004**, *60*, 6105–6111. (y) Kamal, A.; Adil, S. F.; Arifuddin, M. *Ultrason. Sonochem.* **2005**, *12*, 429–431.

5. (a) Horner, L.; Oediger, H.; Hofmann, H. *Liebigs Ann. Chem.* **1959**, *626*, 26–34. (b) Wiley, G. A.; Hershkowiz, R. L.; Rein, B. M.; Chung, B. C. *J. Am. Chem. Soc.* **1964**, *86*, 964–965. (c) Wiley, G. A.; Rein, B. M.; Hershkowitz, R. L. *Tetrahedron Lett.* **1964**, 2509–2513. (d) Kaplan, L. *J. Org. Chem.* **1966**, *31*, 3454. (e) Schaefer, J. P.; Weinberg, D. S. *J. Org. Chem.* **1965**, *30*, 2635–2639. (f) Brett, D.; Downie, I. M.; Lee, J. B. M.; Matough, F. S. *Chem. Lett.* **1969**, 1017–1018. (g) Arain, R. A.; Hargreaves, M. K. *J. Chem. Soc. C* **1970**, 67–70. (h) Sonnet, P. E.; Oliver, J. E. *J. Org. Chem.* **1976**, *41*, 3279–3284. (i) Hrubiec, R. T.; Smith, M. B. *J. Org. Chem.* **1984**, *49*, 431–435.

6. (a) Hanack, M.; Auchter, G. *J. Am. Chem. Soc.* **1985**, *107*, 5238–5245. (b) Sandr, J.; Viala, J. *Synth. Commun.* **1992**, *22*, 2945–2948. (c) Machinek, R.; Luttke, W. *Synthesis* **1975**, 255–256. (d) Hodge, P.; Khoshdel, E. *J. Chem. Soc., Perkin Trans. 1* **1984**, 195–198.

7. (a) Heer, M. E.; Johnson, R. A. *J. Org. Chem.* **1972**, *37*, 310–312. (b) Boeckman, R. K., Jr.; Ganem, B. *Tetrahedron Lett.* **1974**, *11*, 913–916. (c) Barluenga, J.; Campos, P. J.; Gonzalez-Nunez, E.; Asensio, G. *Synthesis* **1985**, 426–428.

8. Caputo, R.; Ferreri, C.; Palumbo, G. *Synth. Commun.* **1987**, *17*, 1629–1636.

9. Iranpoor, N.; Firouzabadi, H.; Chitsazi, M.; Jafari, A. A. *Tetrahedron* **2002**, *58*, 7037–7042.

10. Charette, A. B.; Boezio, A. A.; Janes, M. K. *Org. Lett.* **2000**, *2*, 3777–3779.

11. Årstad, E.; Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Org. Lett.* **2002**, *4*, 1975–1977.

12. Yoakim, C.; Guse, I.; O'Meara, J. A.; Thavonekham, B. *Synlett* **2003**, 473–476.

13. Charette, A. B.; Janes, M. K.; Boezio, A. A. *J. Org. Chem.* **2001**, *66*, 2178–2180.

14. Srivastava, R. R.; Collibee, S. E. *Tetrahedron Lett.* **2004**, *45*, 8895–8897.

15. Iranpoor, N.; Firouzabadi, H.; Jamalian, A.; Kazemi, F. *Tetrahedron* **2005**, *61*, 5699–5704.

16. Iranpoor, N.; Firouzabadi, H.; Jamalian, A. *Synlett* **2005**, 1447–1449.

17. Iranpoor, N.; Firouzabadi, H.; Jamalian, A. *Tetrahedron Lett.*, **2005**, *46*, 7963–7966.

18. (a) Kraus, G. A.; Thomas, P. J. *J. Org. Chem.* **1998**, *53*, 1395–1397. (b) Johnson, W. S.; Plummer, M. S.; Pulla Reddy, S.; Bartlett, W. R. *J. Am. Chem. Soc.* **1993**, *115*, 515–521.

19. Some of the more recent publications are: (a) Gable, K. P.; Brown, E. C. *Synlett* **2003**, 2243–2244. (b) Patra, A.; Bandyopadhyay, M.; Mal, D. *Tetrahedron Lett.* **2003**, *44*, 2355–2357. (c) Gable, K. P.; Brown, E. C. *Organometallics* **2000**, *19*, 944–946. (d) Antonioletti, R.; Bovicelli, P.; Fazzolari, E.; Righi, G. *Tetrahedron Lett.* **2000**, *41*, 9315–9318. (e) Righi, G.; Bovicelli, P.; Sperandio, A. *Tetrahedron* **2000**, *56*, 1733–1737.

20. http://www.aist.go.jp/RIODB/SDBS/cgi-bin/direct_frame_topcgi?lang=eng.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1828–1832

Cytotoxic terpenoids from *Dasyscyphus niveus*

Veronica Rojas de la Parra,[a] Viktor Mierau,[b] Timm Anke[b] and Olov Sterner[a,*]

[a]*Department of Organic Chemistry, University of Lund, PO Box 124, S-22100 Lund, Sweden*
[b]*TU Kaiserslautern, Department of Biotechnology, D-67663 Kaiserslautern, Germany*

Received 26 September 2005; revised 3 November 2005; accepted 17 November 2005

Available online 20 December 2005

Abstract—Three novel tetracyclic terpenoids, of which two possess potent cytotoxic activities towards various mammalian cell lines, were isolated from extracts of the fermentation broth of the ascomycete *Dasayscyphus niveus*. The structures of the compounds, named dasyscyphins A–C, were determined with spectroscopic techniques.

1. Introduction

During an ongoing screening of fungal extracts for metabolites with various biological activities, strong cytotoxic effects towards mammalian cell lines were shown by extracts of the ascomycete *Dasayscyphus niveus*. Bioassay-guided fractionation yielded an active fraction that contained three components in approximately equal amounts. Further purification by chromatography yielded the metabolites dasyscyphin A (**1**), B (**2**) and C (**3**), that possess a novel carbon skeleton, which could be imagined as based on a drimane sesquiterpene that has been fused with a benzoic acid derivative. Dasyscyphin A (**1**) is lacking cytotoxic and antimicrobial activities, while dasyscyphin B (**2**) and C (**3**) showed potent cytotoxic activities in several human cell lines and moderate antimicrobial activities. This paper reports the isolation and the structure determination of the three novel metabolites, while the fermentation of the producing strain and biological properties of the metabolites are reported elsewhere.[1]

2. Results and discussion

The structures of the dasyscyphins (see Fig. 1) were elucidated from data obtained by high-resolution mass spectrometry and 2D NMR spectroscopy (COSY, NOESY, HMQC and HMBC experiments). The pertinent HMBC and NOESY correlations observed with dasyscyphin A (**1**) is shown in Figure 2, as an example. High-resolution ESIMS experiments with dasyscyphin A (**1**) suggested that its elemental composition is $C_{22}H_{36}O_4$, and that is in agreement with the 1D NMR data. Signals for 33 protons are visible in the ^{1}H NMR spectra (see Tables 1 and 2 for 1D NMR data), and as the data suggest the presence of three oxygenated but saturated carbons it can be assumed that the compound contains three hydroxyl groups. Of the 5 unsaturations of **1** only one is accounted for by a double bond, a keto group, and the compound consequently has four rings. The HMBC correlations from the methyl groups 18-H_3, 19-H_3, 20-H_3 and 21-H_3, all appearing as singlets in the ^{1}H NMR spectrum, could be used to establish large parts of the two first rings. While 18-H_3 gave correlations with C-7, C-8, C-9 and C-17, 19-H_3 and 20-H_3 both gave correlations to C-3, C-4 and C-5 (as well as to each other), while 21-H_3 gave correlations to C-1, C-5, C-9 and C-10. The first ring could be closed with the COSY correlations from 1-H_2 via 2-H_2 to 3-H, confirmed by the HMBC correlations from 1-H_2 to C-3 and from 3-H to C-1, while the second ring could be closed with the COSY correlations from 5-H via 6-H_2 to 7-H_2, confirmed by the HMBC correlations from 5-H to C-7 and from 7-H_2 to C-5. Starting from 9-H, a ^{1}H spin system over 11-H_2, 12-H, 13-H, 14-H_2 and 15-H to 22-H_3 can be observed. HMBC correlations from 22-H_3 to C-14, C-15 and the carbonyl carbon show that the latter is C-16. By now all 22 carbons, 36 hydrogens and four oxygens have been included in the growing structure, and what remains is to connect the other side of the keto group, to connect C-12 once and to connect C-17 twice. This can only be made in one way, closing the third and fourth rings as shown in the structure for **1** in Figure 1, and this is confirmed by the HMBC correlations from 12-H to both C-16 and C-17. The relative configuration of dasyscyphin A (**1**) was shown to be as depicted in Figure 1 by the correlations observed in a NOESY spectrum. NOESY

Keywords: *Dasayscyphus niveus*; Terpenoids; Dasyscyphin; Cytotoxicity; Structure determination.
* Corresponding author. Tel.: +46 462228213; fax: +46 462228209; e-mail: olov.sterner@organic.lu.se

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.041

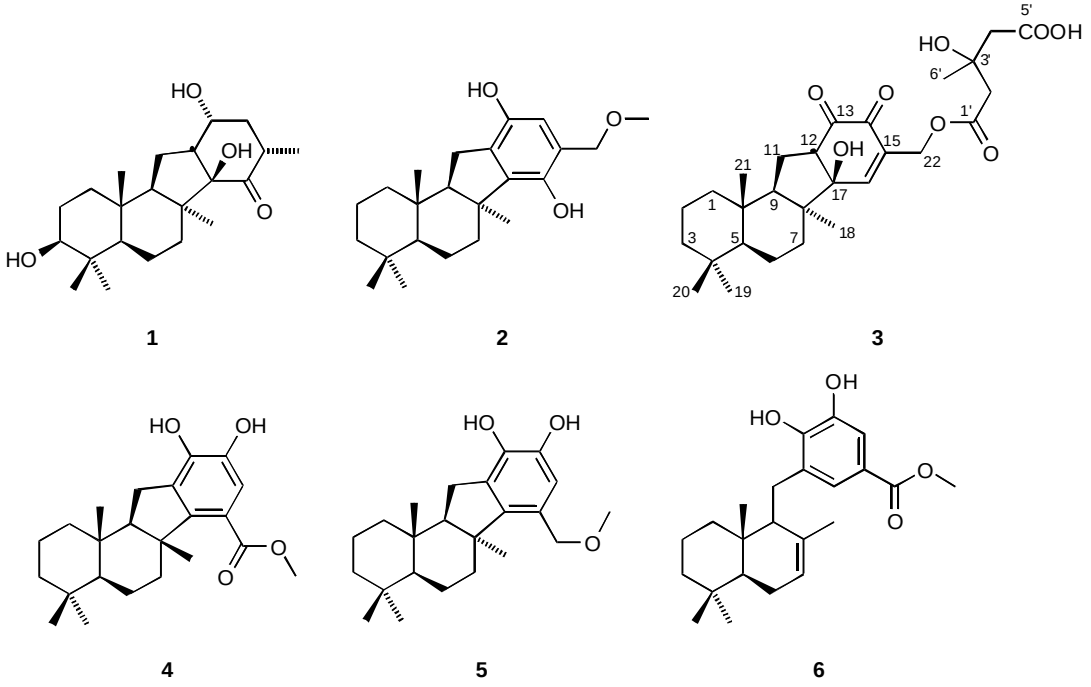


Figure 1.

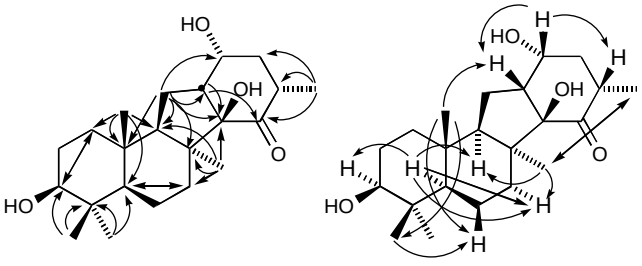


Figure 2. Pertinent HMBC (left) and NOESY (right) correlations observed with dasyscyphin A (**1**).

correlations were observed between 21-H_3 and 20-H_3 as well as 12-H, and both 21-H_3 and 20-H_3 gave NOESY correlations to 6-Hβ, which according to its ^1H–^1H coupling constants is axial. Also 5-H is axial but on the opposite side of the molecule compared to 6-Hβ, and this was confirmed by the NOESY correlation between 3-H and 5-H. 5-H also gives a NOESY correlation to 9-H determining the configuration of C-9, and the earlier mentioned correlation between 21-H_3 and 12-H therefore determines the configuration of C-12. 7-Hβ is equatorial and correlates to both 6-Hα and 6-Hβ, while 7-Hα is axial (according to its ^1H coupling constants) and correlates with 5-H. 18-H_3 correlate with 7-Hα, 9-H and 22-H_3, determining the configurations of C-8 and C-9 and showing that the C-17 hydroxyl group is on the same side as 12-H and that the C-22 methyl group is folded under the molecule. This was confirmed by the observation that 13-H only gives NOESY correlations to 12-H and 15-H, not to 11-H_2, and that there is no sign of a correlation between 15-H and 18-H_3. This configuration also explains the relative stability of the compound, if 12-H and 17-OH were trans an elimination of water to an aromatic compound would be facilitated but this was not observed even after many days in solution at room temperature.

Dasyscyphin B (**2**) contains an additional carbon compared to **1**, its composition according to high-resolution ESIMS experiments is $C_{23}H_{34}O_3$, and the UV spectrum indicated that it is aromatic. With an unsaturation index of 7 and three carbon–carbon double bonds (according to the ^{13}C shifts) **2** should be tetracyclic. The UV absorption maximum at 289 nm observed indicate that the three double bonds constitute a benzene ring. 33 of the 34 protons were visible in the ^1H NMR spectrum (see Tables 1 and 2 for 1D NMR data), and as the IR spectrum shows a strong band at 3420 cm^{-1} it is reasonable to assume that **2** has at least one hydroxyl group. The only proton attached to an unsaturated carbon, 14-H, gives HMBC correlations to C-12, C-13, C-16 and C-22. The presence of a methoxy group is suggested by the 1D NMR data, and the methoxy protons give a HMBC correlation to C-22. 22-H_2 give HMBC correlations to C-14, C-15 and C-16, 11-H_2 give HMBC correlations to C-12, C-13 and C-17, while a proton not attached to a carbon gives HMBC correlations to C-15, C-16 and C-17. This demonstrates that the compound contains a benzene ring, in fact a methyl benzyl ether. The presence of a hydroxyl group on C-16 is obvious, and a second on C-13 is reasonable according to the ^{13}C NMR data, however, the 13-OH proton was not observed in the ^1H NMR spectra. In the other direction, 11-H_2 also give HMBC correlations to C-8, C-9 and C-10, and together with the HMBC correlations from 18-H_3 to C-7, C-8, C-9 and C-17 a five-membered ring fused with the benzene ring can be closed. The HMBC correlations from 19-H_3 and 20-H_3 to C-3, C-4 and C-5, as well as from 21-H_3 to C-1, C-5, C-9 and C-10 suggest that **2** has a decalin system similar to that of **1**, although C-3 is not oxidised. This was confirmed by the COSY correlations from 1-H_2 via 2-H_2 to 3-H_2, and from 5-H via 6-H_2 to 7-H_2. The relative configuration of **2** was deduced from NOESY data. The two axial methyls 20-H_3 and 21-H_3 correlate to each other, as well as to the axial protons 2-Hβ and 6-Hβ. 20-H_3 in addition gives a NOESY

Table 1. ^{1}H (500 MHz) NMR data (δ; multiplicity; J) for dasyscyphins A (**1**), B (**2**) and C (**3**)

H	1	2	3
1α	0.94; m	0.93, ddd, 5.6, 12.8. 13.8	0.94; m
1β	1.69; ddd; 3.2, 3.8, 13.1	1.70; m	1.56; m
2α	1.54; m	1.38; m	1.38; m
2β	1.54; m	1.52; ddddd; 2.8, 3.2, 12.4, 12.8, 15.1	1.53; m
3α	3.15; dd; 5.9, 9.8	1.17; ddd; 4.2, 12.4, 14.8	1.10; m
3β	—	1.41; m	1.41; m
5	0.69; dd; 2.5, 11.7	1.00; dd; 4.5, 11.2	0.95; m
6α	1.41; dddd; 2.5, 3.0, 5.9, 13.3	1.64; dddd; 4.5, 5.8, 6.0, 13.6	1.54; m
6β	1.50; dddd; 4.4, 11.7, 12.2, 13.3	1.34; m	1.63; m
7α	1.11; ddd; 5.9, 12.2, 14.7	1.74; ddd; 6.0, 9.0, 14.0	1.05; ddd; 2.4, 7.6, 13.3
7β	1.94; ddd; 3.0, 4.4, 14.7	2.78; ddd; 5.8, 5.8, 14.0	2.05; ddd; 8.6, 10.3, 13.3
9	1.34; d; 8.1	1.70; m	1.34; dd; 8.6, 9.9
11α	1.72; dd; 8.8, 14.2	2.84; dd; 7.9, 16.4	2.44; ddd; 1.3, 8.6, 13.4
11β	1.82; ddd; 8.1, 12.4, 14.2	2.63; d; 16.4	1.91; ddd; 8.1, 9.9, 13.4
12	2.76; ddd; 6.4, 8.8, 12.4	—	3.12; dd; 1.3, 8.1
13	4.09; ddd; 6.4, 7.6, 8.2	—	—
14a	1.82; m	6.32; s	—
14b	1.82; m	—	—
15	2.37; qdd; 7.1, 8.7, 10.3	—	—
16	—	—	6.88; s
18	0.79; s	1.25; s	0.79; s
19	0.93; s	0.89; s	0.92; s
20	0.74; s	0.82; s	0.82; s
21	0.96; s	0.52; s	0.93; s
22a	1.10; d; 7.1	4.60; d; 11.9	5.03; d; 16.4
22b	—	4.52; d; 11.9	4.98; d; 16.4
2′a	—	—	2.78; d; 15.5
2′b	—	—	2.72; d; 15.5
4′a	—	—	2.75; d; 15.5
4′b	—	—	2.64; d; 15.5
6′	—	—	1.41; s
OCH_3	—	3.42; s	—

The spectra of **1** were recorded in $CDCl_3$ containing 5% CD_3OD while those of **2** and **3** were recorded in $CDCl_3$. The solvent signal of $CHCl_3$ (7.26 ppm) was used as reference. The coupling constants J are given in Hz.

correlation to 3-Hβ while 21-H_3 correlate to 1-Hβ as well as to 7-Hβ. 5-H, also axial but on the other side of the molecule, consequently gives NOESY correlations to 1-Hα and 3-Hα, as well as to 6-Hα, 7-Hα and 9-H. Additional NOESY correlations, from 18-H_3 to 7-Hα, 9-H and 11-Hα, from 1-Hβ to 11-Hβ, and from 9-H to 11-Hα, establish that the configuration of **2** is the same as that shown above for **1**, in relevant parts of the molecule.

Table 2. ^{13}C (125 MHz) NMR data (δ; multiplicity) for dasyscyphins A (**1**), B (**2**) and C (**3**)

C	1	2	3
1	40.6; t	41.5; t	42.9; t
2	27.1; t	18.5; t	18.6; t
3	79.1; d	42.2; t	42.3; t
4	38.5; s	33.2; s	33.5; s
5	51.8; d	51.9; d	49.0; d
6	20.5; t	19.6; t	18.1; t
7	34.7; t	33.1; t	24.6; t
8	48.6; s	48.4; s	50.6; s
9	61.9; d	62.2; d	60.9; d
10	36.5; s	37.2; s	36.7; s
11	24.5; t	28.2; t	24.9; t
12	51.8; d	130.3; s	59.1; d
13	67.1; d	144.1; s	197.0; s
14	34.7; t	112.9; d	200.8; s
15	42.0; d	121.3; s	146.4; s
16	219.3; s	146.5; s	138.8; d
17	87.2; s	139.2; s	87.3; s
18	30.2; q	30.6; q	30.3; q
19	28.4; q	33.3; q	21.1; q
20	15.6; q	21.8; q	32.7; q
21	15.8; q	15.5; q	15.9; q
22	15.2; q	74.3; t	59.7; t
1′	—	—	170.9; s
2′	—	—	44.6; t
3′	—	—	69.7; s
4′	—	—	44.8; t
5′	—	—	174.7; s
6′	—	—	27.4; q
OCH_3	—	58.0; q	—

The spectra of **1** were recorded in $CDCl_3$ containing 5% CD_3OD while those of **2** and **3** were recorded in $CDCl_3$. The solvent signal of $CDCl_3$ (77.0 ppm) was used as reference. The multiplicities of the carbon signals were determined indirectly from HMQC experiments.

LCMS analyses during the isolation procedure indicated that dasyscyphin C (**3**) has the molecular weight 504, although it was evident that the molecular ion easily loses one molecule of water. High-resolution ESIMS experiments confirmed this, and established that **3** has the elemental composition $C_{28}H_{40}O_8$, which is in agreement with the presence of 28 signals in the ^{13}C NMR spectrum and visible signals integrating for 37 protons in the ^{1}H NMR spectrum (see Tables 1 and 2 for 1D NMR data). That gives **3** the unsaturation index 9, and as the NMR data suggested the presence of four carbonyl groups (two keto functions and two acids/esters) and one carbon–carbon double bond, dasyscyphin C (**3**) is consequently tetracyclic. The decaline system was established based on the HMBC correlations from the methyl protons, as well as on the COSY correlations. HMBC correlations from both geminal methyls, 19-H_3 and 20-H_3, to C-3, C-4 and C-5, from 21-H_3 to C1, C-5, C-9 and C-10, as well as from 18-H_3 to C-7, C-8, C-9 and C-17 were observed, and the two rings could be closed by the COSY correlations from 1-H_2 via 2-H_2 to 3-H_2, and from 5-H via 6-H_2 and 7-H_2. An isolated ^{1}H spin system from 9-H via 11-H_2 to 12-H suggested by COSY correlations was confirmed by the HMBC correlations from 11-H to C-8, C-9 and C-10 as well as to C-12, C-13 and C-17. The latter closes the third ring, which is five-membered. Turning to the hydroxymethylglutaric acid ester moiety, this could be established by the HMBC correlations from 6′-H_3 to C-2′, C-3′ and C-4′ of which C-2′ and C-4′ are very similar methylene groups. 2′-H_2 give HMBC correlations to C-1′, C-3′, C-4′ and C-6′ while 4′-H_2 give

correlations to C-2′. C-3′. C-5′ and C-6′, and the chemical shifts of C-1′. C-3′ and C-5′ confirm that this is a hydroxymethylglutaric acid derivative. However, in the absence of signals for the exchangeable protons in the NMR spectra obtained here, it was at this point not clear whether the hydroxymethylglutaric acid moiety is part of the fourth and last ring. There were no HMBC correlations to C-5′, besides those from 4′-H_2, but 22-H_2 give a strong HMBC correlation to C-1′. This is consistent with the suggestion that C-22 is part of a hydroxymethylglutaric acid ester, and the ^{1}H as well as ^{13}C NMR data of 22-H_2/C-22 support this. 22-H_2 also give HMBC correlations to C-14, C-15 and C-16, making this methylene group part of an α,β-unsaturated ketone moiety as well. 16-H in turn correlates to C-14, C-15 and C-22, as expected, but also to C-12 and C-17. This establishes the connection between C-16 and C-17, and closes the fourth ring. Hydroxymethylglutaric acid is consequently present as the mono ester. The relative configuration of **3** was determined in the same way as described for **1** and **2** above. Important correlations observed in the NOESY spectrum were between 21-H_3 and 12-H as well as 20-H_3, and between 9-H and 5-H as well as 18-H_3, as well as a weak correlation between 18-H_3 and 22-H_2 supporting the suggested configuration of C-17.

3. Conclusion

The dasyscyphin terpenoids from *D. niveus* isolated and characterised in this investigation have a novel skeleton, although similar compounds have been reported. Examples are the bioactive pelorol (**4**) obtained from the Micronesian sponges *Dactylospongia elegans*[2] and *Petrosaspongia metachromia*,[3] and the quinol **5**, which actually is a structural isomer of dasyscyphin B (**2**), which was isolated from another Micronesian sponge.[4] In addition, several tricyclic metabolites of this type with the bond corresponding to C-8/C-17 opened, for example, smenodiol (**6**)[5] have been reported. Dasyscyphins B (**2**) and C (**3**) are strongly cytotoxic, with IC_{50} values towards several human cell lines between 0.5 and 3 μg per millilitre. In general it can be assumed that the biological activity of the terpenoid quinols, of which many of the compounds discussed here belong to, is due to the quinol moiety. This may well be the case for dasyscyphin B (**2**), while the α,β-unsaturated 1,2-dione moiety of dasyscyphin C (**3**) probably is important for its cytotoxicity.

4. Experimental

4.1. General

^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were recorded at room temperature with a Bruker DRX500 spectrometer with an inverse multinuclear 5 mm probehead equipped with a shielded gradient coil. The spectra were recorded in $CDCl_3$ and DMSO-d_6, and the solvent signals (7.26 and 77.0 ppm for $CDCl_3$, 2.50 and 39.51 ppm for DMSO-d_6) were used as reference. The chemical shifts (δ) are given in ppm, and the coupling constants (J) in Hz. COSY, HMQC and HMBC experiments were recorded with gradient enhancements using sine shaped gradient pulses. For the 2D heteronuclear correlation spectroscopy the refocusing delays were optimised for $^1J_{CH}=145$ Hz, $^nJ_{CH}=10$ Hz. The raw data were transformed and the spectra were evaluated with the standard Bruker XWIN-NMR software (rev. 010101). LCMS measurements were carried out with a HP 1100 with APCI ionisation, in both positive and negative modes). HRMS spectra were recorded with a JEOL SX102 spectrometer (FAB ionisation) and a Micromass Q-TOF MICRO instrument (ES ionisation). UV and the IR spectra were recorded with a Perkin Elmer λ 16 and a Bruker IFS 48 spectrometer, and the optical rotations were measured with a Perkin-Elmer 141 polarimeter at 22 °C.

The fermentation of the producing organism is described in Ref.1. The producing organism, the ascomycete *D. niveus* strain A01-01, was isolated from spore prints of fruiting bodies found on a rose twig collected in Mannheim, Germany, and is deposited in the culture collection of the LB Biotechnology, University of Kaiserslautern. The compounds were isolated by solid phase extraction of the culture medium, silica gel chromatography with different mixtures of EtOAC and cyclohexane as eluent followed by preparative HPLC on RP-18 material with water:methanol. The isolation of the active compounds was carried out by bioassay-guided fractionation.

4.1.1. Dasyscyphin A (1). The title compound was obtained as a colourless oil, with the yield 0.7 mg per litre of fermentation medium. $[\alpha]_D^{20}$ −6 (*c* 0.8, MeOH); λ_{max} (ε) in MeOH: 214 nm (5000); ν_{max} (liquid film) 3435, 2955, 1735, 1635, 1450, 1375, 1245, 1130, 1100, 1045, 1015, 960, 795 and 610 cm^{-1}; *m/z* HRMS (ESI, $M+Na^+$) found 387.2505, $C_{22}H_{36}O_4$ requires 387.2511 (mass error 1.7 ppm). See Table 1 for ^{1}H and ^{13}C NMR data. Strong COSY correlations were observed between 1- and 2-H_2, between 2-H_2 and 3-H, between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 11-H_2, between 11-H_2 and 12-H, between 12-H and 13-H, between 13-H and 14-H_2, between 14-H_2 and 15-H, and between 15-H and 22-H_3. Pertinent HMBC correlations were observed between 1-H_2 and C-3, between 3-H and C-1, between 19-H_3 and C-3, C-4, C-5 and C-20, between 20-H_3 and C-3, C-4, C-5 and C-19, between 5-H and C-7, between 7-H_2 and C-5, between 18-H_3 and C-7, C-8, C-9 and C-17, between 21-H_3 and C-1, C-5, C-9 and C-10, between 11-H_2 and C-8, C-9, C-10, C-12, C-13 and C-17, between 12-H and C-16 as well as C-17, and between 22-H_3 and C-14, C-15 and C-16.

4.1.2. Dasyscyphin B (2). The title compound was obtained as a colourless oil, with the yield 1.1 mg per litre of fermentation medium. $[\alpha]_D^{20}$ −19 (*c* 0.5, $CHCl_3$); λ_{max} (ε) in MeOH: 289 nm (1,550); ν_{max} (liquid film) 3425, 2925, 1650, 1465, 1385, 1305, 1240, 1105, 1070, 905 and 595 cm^{-1}; *m/z* HRMS (ESI, $M+Na^+$) found 381.2395, $C_{23}H_{34}O_3Na$ requires 381.2406 (mass error 2.9 ppm). See Table 1 for ^{1}H and ^{13}C NMR data. Strong COSY correlations were observed between 1- and 2-H_2, between 2-H_2 and 3-H_2, between 5-H and 6-H_2, between 6-H_2 and 7-H_2, and between 9-H_2 and 11-H_2. Pertinent HMBC correlations were observed between 19-H_3 and C-3, C-4, C-5 and C-20, between 20-H_3 and C-3, C-4, C-5 and C-19, between 18-H_3 and C-7, C-8, C-9 and C-17, between 21-H_3 and C-1, C-5, C-9 and C-10, between 11-H_2 and C-8, C-9, C-10, C-12, C-13 and C-17, between 14-H and C-12, C-13

and C-16, between 22-H_2 and C-14, C-15 and C-16, and between 22-OCH_3 and C-22.

4.1.3. Dasyscyphin C (3). The title compound was obtained as a colourless oil, with the yield 1.6 mg per litre of fermentation medium. $[\alpha]_D^{20}$ −25 (*c* 0.8, $CHCl_3$); λ_{max} (ε) in MeOH: 236 nm (11,400); ν_{max} (liquid film) 3450, 2925, 1735, 1675, 1390, 1205, 1000, 905 and 545 cm^{-1}; *m/z* HRMS (ESI, $M+Na^+$) found 527.2609, $C_{28}H_{40}O_8$ requires 527.2621 (mass error 2.3 ppm). See Table 1 for ^1H and ^{13}C NMR data. Strong COSY correlations were observed between 1- and 2-H_2, between 2-H_2 and 3-H_2, between 5-H and 6-H_2, between 6-H_2 and 7-H_2, between 9-H_2 and 11-H_2, and between 11-H_2 and 12-H. Pertinent HMBC correlations were observed between 19-H_3 and C-3, C-4, C-5 and C-20, between 20-H_3 and C-3, C-4, C-5 and C-19, between 18-H_3 and C-7, C-8, C-9 and C-17, between 21-H_3 and C-1, C-5, C-9 and C-10, between 11-H_2 and C-8, C-9, C-10, C-12, C-13 and C-17, between 12-H and C-16 and C-17, between 22-H_2 and C-1′, C-14, C-15 and C-16, between 2′-H_2 and C-1′, C-3′, C-4′ and C-6′, between 4′-H_2 and C-2′, C-3′, C-5′ and C-6′, and between 6′-CH_3 and C-2′, C-3′ and C-4′.

Acknowledgements

Financial support from the Swedish Foundation for International Cooperation in Research and Higher Education (STINT) and the Swedish Natural Science Council (V.R.) is gratefully acknowledged.

References and notes

1. Mierau, V.; Rojas de la Parra, V.; Anke, T.; Sterner, O., *J. Antibiot.*, in press.
2. Goclik, E.; Konig, G. M.; Wright, A. D.; Kaminsky, R. *J. Nat. Prod.* **2000**, *63*, 1150–1152.
3. Kwak, J. H.; Schmitz, F. J.; Kelly, M. *J. Nat. Prod.* **2000**, *63*, 1153–1156.
4. Mukku, V. J. R. V.; Edrada, R. A.; Schmitz, F. J.; Shanks, M. K.; Chaudhuri, B.; Fabbro, D. *J. Nat. Prod.* **2003**, *66*, 686–689.
5. Venkateswarlu, Y.; Faulkner, D. Y. *J. Org. Chem.* **1991**, *56*, 6271–6274.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1833–1844

Asymmetric alkylation of diarylmethane derivatives

James A. Wilkinson,[a,*] Steven B. Rossington,[a] Sylvie Ducki,[a] John Leonard[b] and Nigel Hussain[c]

[a]*Biosciences Research Institute, Centre for Drug Design, Cockcroft Building, University of Salford, Salford M5 4WT, UK*
[b]*AstraZeneca Process R&D, Silk Road, Macclesfield, Cheshire SK10 2NG, UK*
[c]*GlaxoSmithKline Chemical Development, Old Powder Mills, Tonbridge, Kent TN11 9AN, UK*

Received 9 September 2005; revised 2 November 2005; accepted 17 November 2005

Available online 19 December 2005

Abstract—Deprotonation–alkylation of prochiral diarylmethane substrates using *sec*-BuLi and (−)-sparteine has been carried out in excellent yields and up to 94% ee. A variety of enantioselective alkylations, silylations and stannylations have been performed on four different diarylmethanes. Surrogates for (+)-sparteine have also been applied in this study including a novel surrogate.

1. Introduction

A number of important cytotoxic compounds contain the diarylmethane structural motif and a few examples are shown in Figure 1.[1] Several of these diarylmethanes exert their activity by binding to the colchicine site on tubulin, thus preventing microtubule assembly and hence cell division.[2] Compounds of this type have considerable potential in anti-cancer drug design and for this reason we had an interest in developing a versatile, efficient, enantioslective route to this type of compound. We sought a route, which was short, high yielding, tolerant of functionality and which would give good selection for either enantiomeric product. Lateral lithiation of toluene derivatives equipped with a suitable directing group is a well-known protocol and high enantioselectivities have been obtained when prochiral substrates have been used with appropriate chiral base systems, particularly by Beak's group.[3] Here we report the application of a variety of chiral base systems to the alkylation of prochiral diarylmethanes.[4]

2. Results and discussion

2.1. Screening of oxygen stabilising groups

Compounds **5**–**7** were considered as potential substrates for asymmetric alkylation (Fig. 2). These substrates were chosen since the products of alkylation were either compounds of known optical rotation or could be converted into compounds of known optical rotation. Other removable oxygen substituents such as methoxymethyl and trimethylsilylethoxymethyl were thought likely to give poor results as they have multiple sites for deprotonation.[5] Initial experiments on the methoxy derivative **5**, using *sec*-BuLi/(−)-sparteine as the chiral base system (Table 1), produced poor

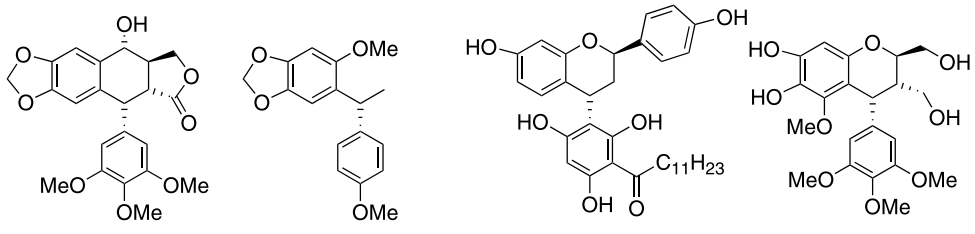
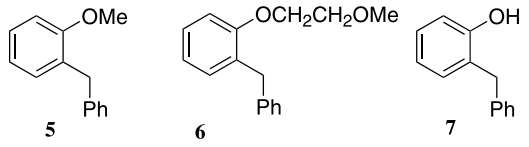


Figure 1.

Keywords: Asymmetric; Alkylation; Diarylmethane; Sparteine.
* Corresponding author. Tel.: +44 161 295 4046; fax: +44 161 295 5111; e-mail: j.a.wilkinson@salford.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.044



5 6 7

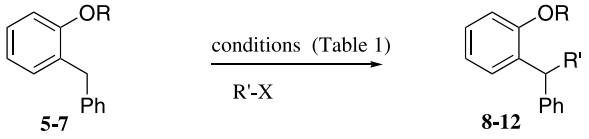
Figure 2.

results when alkylating with methyl iodide (entries 1 and 3) but a significant ee was obtained with allyl bromide (entries 2 and 4). The yields were high in both cases. The enantioselection was found to depend more on the electrophile than on the method of generating the anion, with a warm–cool cycle according to the method of Beak producing a lower ee than a procedure in which the anion was generated at −78 °C and kept at this temperature throughout.[6] The methoxyethoxy compound **6** behaved very differently, giving good enantioselectivity with a range of different alkylating agents (entries 6–8). The best allylation results were with allyl tosylate as the electrophile, giving a 94% ee (entry 8). While methyl iodide again proved poor, methyl tosylate gave a 58% ee (entry 6). Organolithium species derived from **5** failed to react with methyl or allyl tosylate. The optimum conditions for all reactions of **6** were found to involve a warm–cool cycle followed by addition of 0.5 equiv of electrophile, another warm–cool cycle and further addition of electrophile (vide infra). The dilithio species derived from **7** was more difficult to form and less versatile, failing to give any selectivity with most electrophiles. However, a 46% ee with allyl bromide was formed in favour of the opposite enantiomer to that obtained from **5** and **6**. Diethyl ether was the only solvent which gave a high ee in any of these reactions.

The absolute configurations of products **9–12** were determined by comparison of optical rotation with known compounds while that of product **8** was assigned as arising from the same sense of stereochemical induction as for the other reactions of **5** and **6**. Allyl compounds **9** and **11** were converted by oxidative cleavage into the carboxylic acid **13** and the lactone **14**, respectively, while the methyl compound **10** could be deprotected under fairly harsh conditions to give **15** (Schemes 1–3).

Compounds **13–15** all have known absolute configuration and optical rotation.[7] It was also possible to measure ees using ^{1}H NMR spectroscopy in the presence of a chiral shift

Table 1. Asymmetric alkylations of **1–3**

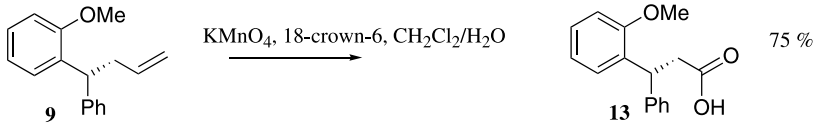


5-7 8-12

Entry	Substrate	R	Product	R′-X	Cond.	Yield	Config.	ee
1	**5**	Me	**8**	MeI	A	95	*R*[a]	7
2	**5**	Me	**9**	AllylBr	A	84	*R*	60
3	**5**	Me	**8**	MeI	B	95	*R*[a]	6
4	**5**	Me	**9**	AllylBr	B	84	*R*	48
5	**6**	CH_2CH_2OMe	**10**	MeI	C	86	*R*	12
6	**6**	CH_2CH_2OMe	**10**	MeOTs	C	95	*R*	58
7	**6**	CH_2CH_2OMe	**11**	AllylBr	C	96	*R*	71
8	**6**	CH_2CH_2OMe	**11**	AllylOTs	C	93	*R*	94
9	**7**	H	**12**	AllylBr	D	74	*S*	46

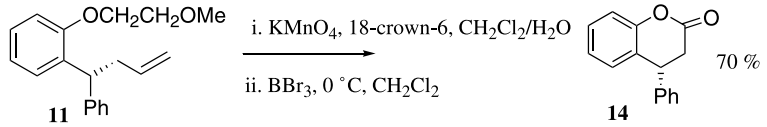
Conditions: A. Mixture of substrate, (−)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether stirred at −78 °C for 6 h followed by addition of alkylating agent (1.2 equiv) and warming to rt. B. Substrate, (−)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at −78 °C, then warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (1.2 equiv) and warming to rt. C. **6**, (−)-Sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at −78 °C, then warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (0.5 equiv). Mixture warmed to −20 °C for a further 1 h before recooling to −78 °C and addition of electrophile (0.5 equiv) and warming to rt. D. Mixture of **7**, (−)-sparteine (1.1 equiv) and *sec*-BuLi (2.2 equiv) in ether stirred at 0 °C for 5 h followed by cooling to −78 °C, addition of alkylating agent (1.2 equiv) and warming to rt. ee values were calculated using TFAE in the ^{1}H NMR and by comparison of optical rotations (see text).

[a] Denotes that the configuration of the major enantiomer was assigned by analogy with product **10**.



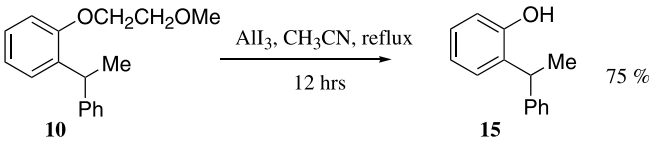
9 13

Scheme 1.



11 14

Scheme 2.



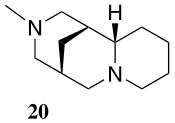
10 15

Scheme 3.

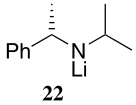
reagent, TFAE, which gave good agreement with the ee values obtained by optical rotation.

2.2. Asymmetric reactions of methoxyethoxy diarylmethane 6

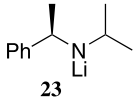
Having established that the methoxyethyl group was the best oxygen substituent, work was then carried out varying base, reaction conditions and electrophile in order to optimise the chemistry and probe its scope (Table 2). High chemical yields were obtained with most electrophiles, the only exception being ethyl iodide. Enantiomeric excesses were generally respectable for alkyl halides with the exception of iodomethane, which gave poor results (Table 1, entry 5). We observed a marked tendency for tosylate electrophiles to give a higher ee than their halide counterparts. Increased selectivities for the tosylates were not unexpected since similar effects have been observed by others and rationalised as being due to a slower reaction and possible coordination of the sulfonyl oxygen to lithium.[8] Changing the chiral base system to one using O'Brien's (+)-sparteine surrogate **20** resulted in comparable yield and ee of the *S*-enantiomer of compound **11** as would be expected from the work of O'Brien and others.[9] A variation on O'Brien's surrogate, compound **21** was also used for this reaction giving the same sense of selectivity but slightly poorer results. The extra coordinating site on the base seems to make little difference at least in these reactions. Chiral lithium amide bases **22**, **23** and **24** failed to produce any reaction presumably due to the pK_a of the benzyl protons being too high for their removal with these bases. In terms of conditions for reactions of **6** it was found that, regardless of the electrophile or chiral ligand, the method of generation of the organolithium species had a considerable impact on selectivity. When the organolithium species was generated at −78 °C and kept at this temperature until the electrophile was added selectivities were fairly low. Results were improved by the use of a warm–cool cycle with the lithium species (after generation in the presence of (−)-sparteine at −78 °C) being warmed to −20 °C for 1 h and then re-cooled to −78 °C before addition of electrophile. When the electrophile was added in two batches of 0.5 equiv with a warm–cool cycle between additions the ee rose again and all of the best results were obtained under these conditions.[6b]



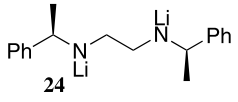
20



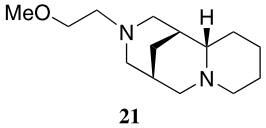
22



23



24



21

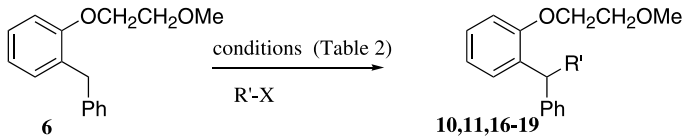
Compound **21** was synthesised, following O'Brien's approach, from the readily available natural product (−)-cytisine (Scheme 4). After attachment of the side-chain as an amide and hydrogenation the amides were reduced out to give **21**.

2.3. Asymmetric reactions of *N*-pivaloyl-*o*-benzylaniline (25)

Extension of this research to include nitrogen-based stabilising groups was realised in the preparation and reactions of **25** (Table 3).[10] This compound has already been laterally lithiated and the resulting dilithio species reacted with an electrophile but not in the presence of any chiral control element. The behaviour of the dilithium species derived from **25** was generally very different to that of the lithio-derivative of **6**. The sense of asymmetric induction was opposite to that previously observed in methylation reactions (whether with methyl tosylate or iodide) and was assumed to be opposite (i.e., to give *S*-products) in the other examples also. The levels of selectivity never approached the best results obtained with **6**. Chemical yields while generally high were a little lower than in reactions of **6** and the indole side-product **26** was generally isolated in 5–15% yield. In terms of optimal conditions for allylation reactions, allyl bromide was very much better than allyl tosylate and the method of generation of the dilithium species made little difference to the ee. To form the dilithio species required that the substrate be stirred with 2.2 equiv of base at 0 °C for 3 h before being cooled to −78 °C prior to addition of sparteine/**20**/**21** and stirring at this temperature for 2 h. The best selectivities were observed when the reaction was kept at −78 °C thereafter, which is in contrast to the results obtained by Beak using *N*-pivaloyl-*o*-ethylaniline wherein the use of a warm–cool cycle was highly beneficial.[6b] As with **6**, the use of (+)-sparteine surrogates **20** and **21** produced the opposite enantiomer of the product, in the case of **20** in slightly better ee. The use of chiral lithium amide bases was much more successful in this case (no products were obtained when **5** or **6** were treated with these bases). While yields were modest and selectivities poor it is interesting that the dilithio species could be formed at all with bases of this type particularly as it formed so reluctantly when *sec*-BuLi was used. It seems possible that these weaker bases form only an equilibrium amount of the dilithio species, which would help to explain the poor results.

The absolute configuration of the methyl product **28** was determined by removal of the pivaloyl group (Scheme 5), albeit in poor yield, to give the amine **31** whose absolute configuration is known.[11]

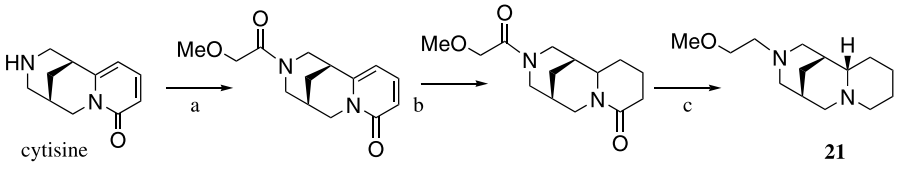
Table 2. Asymmetric alkylations of **6**



Entry	Base	Product	R′-X	Cond.	Yield	Config.	ee
1	*sec*-BuLi/sparteine	**11**	AllylBr	A	84	*R*	44
2	*sec*-BuLi/sparteine	**11**	AllylBr	B	85	*R*	50
3	*sec*-BuLi/sparteine	**11**	AllylBr	C	96	*R*	71
4	*sec*-BuLi/sparteine	**11**	AllylOTs	C	93	*R*	94
5	*sec*-BuLi/sparteine	**16**	EtI	C	65	*R*[a]	70
6	*sec*-BuLi/sparteine	**17**	PrI	C	78	*R*[a]	64
7	*sec*-BuLi/sparteine	**18**	BnBr	C	90	*R*[a]	68
8	*sec*-BuLi/sparteine	**19**	TMSCl	C	91	*R*[a]	82
9	*sec*-BuLi/**20**	**11**	AllylOTs	C	90	*S*	92
10	*sec*-BuLi/**21**	**11**	AllylOTs	C	83	*S*	68
11	**22** or **23** or **24**	**11**	AllylOTs	D	0	NA	

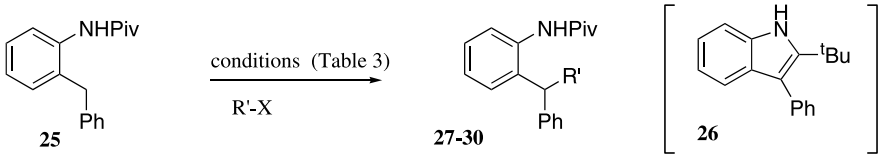
Conditions: A. Mixture of **6**, (−)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether stirred at −78 °C for 6 h followed by addition of alkylating agent (1.2 equiv) and warming to rt. B. **6**, C (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at −78 °C, then warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (1.2 equiv) and warming to rt. C. **6**, Chiral ligand (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at −78 °C, then warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (0.5 equiv). Mixture warmed to −20 °C for a further 1 h before recooling to −78 °C and addition of electrophile (0.5 equiv) and warming to rt. D. Lithium amide base added to **6** in ether and mixture stirred at −5 °C for 4 h before addition of electrophile. ee values were calculated using TFAE in the ^{1}H NMR.

[a] Denotes that the configuration of the major enantiomer was assigned by analogy with product **11**.



Scheme 4. Conditions: (a) Methoxyacetyl chloride, NEt_3, CH_2Cl_2, 0 °C to rt, 18 h, 97%; (b) H_2 (1 atm), PtO_2, EtOH, rt, 15 h 90%; (c) $LiAlH_4$, THF, reflux, 20 h, 73%.

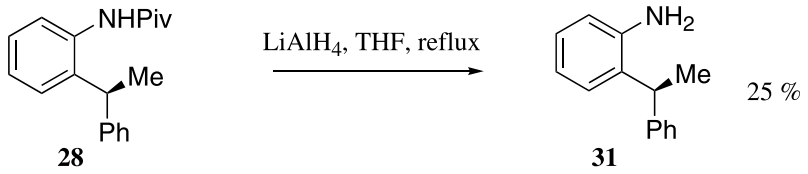
Table 3. Asymmetric alkylations of **25**



Entry	Base	Product	R′-X	Cond.	Yield	Config.	ee
1	*sec*-BuLi/sparteine	**27**	AllylBr	A	90	*S*[a]	76
2	*sec*-BuLi/sparteine	**27**	AllylBr	B	93	*S*[a]	71
3	*sec*-BuLi/sparteine	**27**	AllylBr	C	95	*S*[a]	70
4	*sec*-BuLi/sparteine	**27**	AllylOTs	A	65	*S*[a]	20
5	*sec*-BuLi/sparteine	**28**	MeI	A	0		NA
6	*sec*-BuLi/sparteine	**28**	MeOTs	A	41	*S*	56
7	*sec*-BuLi/sparteine	**29**	BnBr	A	80	*S*[a]	46
8	*sec*-BuLi/sparteine	**30**	EtI	A	60	*S*[a]	56
9	*sec*-BuLi/**20**	**27**	AllylBr	A	89	*R*[a]	80
10	*sec*-BuLi/**21**	**27**	AllylBr	A	92	*R*[a]	60
11	**22**	**27**	AllylBr	D	38	*S*[a]	16
12	**23**	**27**	AllylBr	D	55	*R*[a]	12
13	**24**	**27**	AllylBr	D	41	*S*[a]	40

Conditions: A. Mixture of **25** and *sec*-BuLi (2.4 equiv) in ether stirred at 0 °C for 3 h to form anion. Mixture cooled to −78 °C and chiral ligand (2.6 equiv) added dropwise. Mixture stirred at −78 °C for 2 h followed by addition of alkylating agent (1.2 equiv) and warming to rt. B. (−)-Sparteine (2.6 equiv) added to preformed dilithio in ether at −78 °C, mixture warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (1.2 equiv) and warming to rt. C. (−)-Sparteine (2.6 equiv) added to preformed dilithio in ether at −78 °C, mixture warmed to −20 °C for 1 h and recooled to −78 °C before addition of electrophile (0.5 equiv). Mixture warmed to −20 °C for a further 1 h before recooling to −78 °C and addition of electrophile (0.5 equiv) and warming to rt. D. Lithium amide base added to **25** in ether and mixture stirred at −5 °C for 4 h before addition of electrophile. ee values were calculated using TFAE in the ^{1}H NMR.

[a] Denotes that the configuration of the major enantiomer was assigned by analogy with product **28**.



Scheme 5.

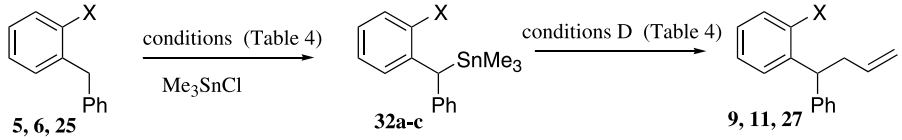
2.4. Gauging the configurational stability of lithio species derived from 5, 6 and 25

Results so far suggested to us that the organolithium derived from **6** was configurationally stable at −78 °C in the presence of (−)-sparteine while that derived from **5** and the dilithio species from **25** were rapidly interconverting at this temperature since a warm–cool had no positive effect on ee. Attempts were made to provide further evidence for these suppositions by making the trimethyltin derivatives of these compounds and regenerating the organolithiums according to the established procedure (Table 4).[12]

The three trimethyltin compounds were formed using *sec*-BuLi/(−)-sparteine as the chiral base system. In each case the conditions used were those, which had given the best results for other electrophiles but the ees obtained were moderate. Most surprising in this respect was the formation of **32b** from substrate **6**, which gave only a 29% ee. The reason for this is not clear. These compounds were subjected to treatment with *sec*-BuLi in ether at −78 °C in the presence of (−)-sparteine and the mixtures kept at that temperature for 2 h before quenching with allyl bromide. All of the products were found to have an ee close to the estimated ee of the starting tin compound (based on chiral shift reagent), in the case of **11** and **27** the ee was almost identical. Overall the opposite configuration was obtained, in each case, to that provided by simple deprotonation/allylation of **5**, **6**, and **25** suggesting that either reaction with trimethyltin chloride or regeneration of the organolithium compound proceeded with inversion. In the absence of (−)-sparteine an ee of 0–3% was obtained from each of the three substrates after regenerating the organolithum and stirring for 2 h. The behaviour of the organolithium derived from **6** was much as we had expected since the optimum conditions for reaction suggested that it was configurationally stable at −78 °C in the presence of (−)-sparteine and that we were observing a thermodynamic resolution. The organolithium derived from **5** seemed to be much less configurationally mobile than we had anticipated; the lack of improvement in ee when a warm–cool cycle was employed[3a] and the high sensitivity to electrophile had led us to believe that this lithium species was configurationally unstable at −78 °C in the presence of (−)-sparteine and that dynamic kinetic resolution was occurring.[13] The very slight loss of stereochemical integrity when the organolithium was regenerated from **32a** contradicts this. Finally, the dilithio species derived from **25** was puzzling, with apparently very high configurational stability at −78 °C in the presence of (−)-sparteine. This species gave similar stereoselectivities regardless of the method by which it was generated (see Table 3) and hence was originally considered to be configurationally labile even though Beak had demonstrated configurational stability in organolithium derived from *N*-pivaloyl-*o*-ethylaniline. More work needs to be done on this system to establish at what point the stereoselectivity occurs.

In conclusion, a methodology has been demonstrated, which allows high chemical yield and ee to be achieved in alkylations of prochiral diarylmethane substrates. The method is highly versatile with regard to which enantiomer is obtained and to the nature of the directing group.

Table 4. Asymmetric stannylation and organolithium regeneration of **9**, **11**, and **27**



Entry	Substrate	X	Sn product	Cond.	Yield	ee	Final product	Config.	ee
1	**5**	OMe	**32a**	A	75	34	**9**	*S*	15
2	**6**	OCH_2CH_2OMe	**32b**	B	92	29	**11**	*S*	27
3	**25**	NHPiv	**32c**	C	73	54	**27**	*R*[a]	52

A. Mixture of **5**, (−)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether stirred at −78 °C for 6 h followed by addition of trimethyltin chloride (1.2 equiv) and warming to rt. B. **6**, (−)-Sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether mixed at −78 °C, then warmed to −20 °C for 1 h and recooled to −78 °C before addition of trimethyltin chloride (0.5 equiv). Mixture warmed to −20 °C for a further 1 h before recooling to −78 °C and addition of trimethyltin chloride (0.5 equiv) and warming to rt. C. Mixture of **25** and *sec*-BuLi (2.4 equiv) in ether stirred at 0 °C for 3 h to form anion. Mixture cooled to −78 °C and (−)-sparteine (2.6 equiv) added dropwise. Mixture stirred at −78 °C for 2 h followed by addition of trimethyltin chloride (1.2 equiv) and warming to rt. D. Mixture of **32**, (−)-sparteine (1.1 equiv) and *sec*-BuLi (1.1 equiv) in ether stirred at −78 °C for 2 h followed by addition of allyl bromide, stirring at −78 °C for 3 h and warming to rt. ee values were calculated using TFAE in the ^{1}H NMR.

[a] Denotes that the configuration of the major enantiomer was assigned by analogy with 28.

3. Experimental

3.1. General

Proton and carbon NMR were recorded on a 400 MHz Bruker AC-400 instrument. Spectra were recorded as solutions in $CDCl_3$ unless otherwise stated and resonances are quoted in ppm relative to trimethylsilane. Mass spectra were recorded on a Finnegan 4500 instrument under chemical ionisation with ammonia. High resolution spectra were recorded on a Kratos Concept 1-S instrument. Percentage figures refer to the relative intensity as a proportion of the base peak. Infra-red spectra were recorded on a Perkin 1710 FT-IR instrument with melting points (uncorrected) determined by a Gallenkamp melting point apparatus and optical activities recorded on an Optical Activity Ltd. instrument. All new compounds were determined to be >95% pure by ^{13}C NMR. Flash chromatography was carried out over Merck silica gel 60 (40–60 (m). All dried solvents were prepared according to the recommended methods. Compounds **20**,[9a] **22–24**[14] and **25**[10] were prepared according to literature procedures.

3.1.1. 2-Benzyl anisole (5). 2-Benzylphenol **7** (2.99 g, 0.016 mol, 0.89 equiv) in THF (6 ml) was added dropwise, under an argon atmosphere, to sodium hydride (60% dispersion in mineral oils) (0.71 g, 0.018 mol, 1.0 equiv) in THF (35 ml) at 0 °C. The mixture was then heated 1 h at reflux followed by cooling to rt and the addition of methyl iodide (2.72 g, 0.019 mol, 1.05 equiv) in THF (5 ml). The mixture was stirred at rt for 15 h. Quenching with satd aq ammonium chloride (20 ml) was followed by dilution with water (30 ml) and extraction into ether (3×40 ml). The combined organics were then washed with 1 M sodium hydroxide (2×20 ml) and brine (2×20 ml), dried ($MgSO_4$) and concentrated in vacuo to yield an oil. Column chromatography (90:10 petroleum ether/ethyl acetate) yielded the title compound as a clear, colourless oil (2.88 g, 90%). Spectral data were in accordance with literature values.[15]

3.1.2. 2-Methoxyethoxyphenyl phenylmethane (6). 2-Benzylphenol **7** (2.99 g, 8.0 mmol, 1.0 equiv) in THF (4 ml) was added dropwise, under an argon atmosphere, to sodium hydride (60% dispersion in mineral oils) (0.32 g, 8.0 mmol, 1.0 equiv) in THF–DMF (20/7 ml) at 0 °C. The mixture was then heated for 1 h at reflux followed by cooling to rt and the addition of 2-bromoethyl methyl ether (1.12 g, 8.0 mmol, 1.0 equiv) in THF (4 ml). The mixture was stirred at rt for 16 h. The mixture was then quenched with water (20 ml) and extracted into ether (4×30 ml). The combined organics were washed with water (2×20 ml), brine (20 ml), dried ($MgSO_4$), and concentrated in vacuo to afford an oil. Column chromatography (90:10 petroleum ether/ethyl acetate) afforded the product as a clear, colourless oil (1.09 g, 80%). ν_{max} (cm^{-1}) (thin film) 3027, 2929, 1590 (–C=C–). δ ^1H NMR (400 MHz, $CDCl_3$) 3.45 (3H, s, OCH_3), 3.74 (2H, t, J=3.8 Hz, $OCH_2CH_2OCH_3$), 4.02 (2H, s, $ArCH_2Ph$), 4.12 (2H, t, J=3.8 Hz, $OCH_2CH_2OCH_3$), 6.87–6.93 (2H, m, 2×Ph-*H*), 7.10–7.29 (7H, m, 7×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 35.2 ($ArCH_2Ph$), 58.3 (OCH_3), 66.7 (CH_2OCH_3), 70.3 (OCH_2CH_2), 110.8, 119.9, 125.4, 126.5, 127.3, 127.8, 129.3, 129.5, 140.2, 155.7 (10×=C). *m/z* (EI) 242.1 (M^+, 48%). M=$C_{16}H_{18}O_2$ requiring 242, HRMS (EI) $C_{16}H_{18}O_2$ required 242.1307, found 242.1307.

3.2. General procedure 1 for asymmetric alkylations of 5 and 6 at −78 °C using (−)-sparteine (conditions A, Tables 1 and 2)

s-BuLi (1.4 M in cyclohexane) (8.00 ml, 0.011 mol, 1.08 equiv) was added dropwise, under an argon atmosphere, to (−)-sparteine (2.93 g, 0.013 mol, 1.23 equiv) in ether (80 ml) at −78 °C. Stirring for 10 min at −78 °C was followed by the addition of 2-alkoxyphenyl phenylmethane **5** or **6** (0.0102 mol, 1.0 equiv) in ether (10 ml). After 6 h at −78 °C alkylating agent (0.0264 mol, 2.59 equiv) in ether (5 ml) was added dropwise. The mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2×20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate). All reaction products of **5** and **6** with electrophiles gave a clean splitting of the methoxy singlet in the ^1H NMR when treated with 2–3 equiv of (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE).

3.3. General procedure 2 for asymmetric alkylations of 5 and 6 using (−)-sparteine with a warm–cool cycle (conditions B, Tables 1 and 2)

s-BuLi (1.4 M in cyclohexane) (8.00 ml, 0.011 mol, 1.08 equiv) was added dropwise, under an argon atmosphere, to (−)-sparteine (2.93 g, 0.013 mol, 1.23 equiv) in ether (80 ml) at −78 °C. Stirring for 10 min at −78 °C was followed by the addition of 2-alkoxyphenyl phenylmethane **5** or **6** (0.010 mol, 1.0 equiv) in ether (10 ml). The mixture was warmed with stirring from −78 to −20 °C for a period of 1 h and then re-cooled to −78 °C for 20 min before alkylating agent (0.026 mol, 2.60 equiv) in ether (5 ml) was added dropwise. The mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2×20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate).

3.4. General procedure 3 for asymmetric alkylations of 5 and 6 using (−)-sparteine with a warm–cool cycle and batch addition (conditions C, Tables 1 and 2)

s-BuLi (1.4 M in cyclohexane) (8.00 ml, 0.011 mol, 1.08 equiv) was added dropwise, under an argon atmosphere, to (−)-sparteine (2.93 g, 0.013 mol, 1.23 equiv) in ether (80 ml) at −78 °C. Stirring for 10 min at −78 °C was followed by the addition of 2-alkoxyphenyl phenylmethane **5** or **6** (0.010 mol, 1.0 equiv) in ether (10 ml). The mixture was warmed with stirring from −78 to −20 °C for a period of 1 h and then re-cooled to −78 °C for 20 min before the first portion of alkylating agent (0.5 mol equiv) in ether (5 ml) was added dropwise. The mixture was then warmed to −20 °C for 1 h before being recooled to −78 °C for 5 min. The second

portion of alkylating agent (0.5 mol equiv) in ether (5 ml) was added dropwise. The mixture was allowed to warm to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2×20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate).

3.4.1. 1-Methoxy-2-(1-phenylethyl)benzene (8). 1-Methoxy-2-(1-phenylethyl)-benzene was prepared using iodomethane as alkylating agent according to general procedure 1 as an oil (0.52 g, 95%). $[\alpha]_D$ +2.9 (*c* 0.2, $CHCl_3$), ee=6%. Lit. ref.; $[\alpha]_D$ +49.2 (*c* 1, $CHCl_3$).[16] ν_{max} (cm^{-1}) (thin film) 2964, 1599 (–C=C–). δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (3H, d, *J*=7.2 Hz, $CHCH_3$), 3.78 (3H, s, OCH_3), 4.61 (1H, q, *J*=7.2 Hz, $CHCH_3$), 6.85–6.95 (2H, m, 2×Ph-*H*), 7.16–7.31 (7H, m, 7×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 21.3 (CH_3), 37.8 ($CHCH_3$), 55.8 (OCH_3), 110.8, 120.9, 126.2, 127.5, 128.1, 128.2, 128.7, 135.3, 146.8, 157.3 (10×=C). *m/z* (EI) 212.1 (M^+, 100%). M=$C_{15}H_{16}O$ requiring 212.

3.4.2. 1-Methoxy-2-(1′-phenylbut-3′-enyl)-benzene (9). 1-Methoxy-2-(1′-phenylbut-3′-enyl)-benzene was prepared using allyl bromide as alkylating agent according to general procedure 1 as an oil (0.170 g, 95%), 60% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. $[\alpha]_D^{25}$ −1.9 (*c* 1.1, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 2928 (CH), 1640 (–C=C–, allyl), 1598 (–C=C–, aromatic), 1491, 1460. δ ^{1}H NMR (400 MHz, $CDCl_3$) 2.80–2.85 (2H, m, $CH_2CH=CH_2$), 3.80 (3H, s, OCH_3), 4.52 (1H, t, *J*=7.9 Hz, ArC*H*Ph), 4.93–4.96 (1H, m, one of $CH_2CH=CH_2$), 5.02–5.07 (1H, m, one of $CH_2CH=CH_2$), 5.71–5.79 (1H, m, $CH_2CH=CH_2$), 6.85–6.87 (1H, m, 1×Ph-*H*), 6.92–6.96 (1H, m, 1×Ph-*H*), 7.17–7.29 (7H, m, 7×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 39.5 (Ar*C*HPh), 43.7 ($CH_2CH=CH_2$), 55.9 (OCH_3), 111.1 (1×=*C*), 116.3 ($CH_2CH=CH_2$), 120.9, 126.2, 127.5, 128.3, 128.5, 128.6 133.4 (7×=*C*), 137.6 ($CH_2CH=CH_2$), 144.8, 157.4 (2×=*C*). *m/z* (CI, NH_3) 256 (MNH_4^+, 70%), HRMS (EI) $C_{17}H_{18}O$ required 238.1358, found 238.1361.

3.4.3. 1-(2′-Methoxyethoxy)-2-(1″-phenylethyl)-benzene (10). 1-(2′-Methoxyethoxy)-2-(1″-phenylethyl)-benzene was prepared using methyl tosylate as alkylating agent according to general procedure 3 as a clear yellow oil (0.305 g, 95%), 58% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +40.6 (*c* 1.2, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 3027, 2929, 1590. (–C=C–). δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.61 (3H, d, *J*=7.2 Hz, CH_3), 3.43 (3H, s, OCH_3), 3.66–3.69 (2H, t, *J*=5.0 Hz, $OCH_2CH_2OCH_3$), 3.98–4.03 (1H, m, $OCH_2CH_2OCH_3$), 4.09–4.14 (1H, m, $OCH_2CH_2OCH_3$), 4.61 (1H, q, *J*=7.2 Hz, $CHCH_3$), 6.85 (1H, d, *J*=8.1 Hz, 1×Ph-*H*), 6.89–6.97 (1H, m, 1×Ph-*H*), 7.12–7.30 (7H, m, 7×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 21.2 ($CHCH_3$), 38.1 ($CHCH_3$), 59.5 (OCH_3), 68.0 (CH_2OCH_3), 71.5 (OCH_2CH_2), 112.2, 121.2, 126.0, 127.4, 127.6, 128.1, 128.4, 145.5, 147.0, 156.5 (10×=C). *m/z* (CI, NH_3) 274 (MNH_4^+, 100%), HRMS (EI) M=$C_{17}H_{20}O_2$ required 256.1463, found 256.1466.

3.4.4. (*R*)-1-(2-Methoxyethoxy)-2-(1″-phenylbut-3″-enyl)-benzene (*R*-11). (*R*)-1-(2-Methoxyethoxy)-2-(1″-phenylbut-3-enyl)-benzene was prepared using allyl tosylate as alkylating agent according to general procedure 3 as a clear yellow oil (0.363 g, 93%), 94% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +11.7 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 2925, 1598, 1492, 1452. δ ^{1}H NMR (400 MHz, $CDCl_3$) 2.73–2.82 (2H, m, $CH_2CH=CH_2$), 3.41 (3H, s, OCH_3), 3.67 (2H, t, *J*=5.0 Hz, $OCH_2CH_2OCH_3$), 3.95–4.10 (2H, m, $OCH_2CH_2OCH_3$), 4.45 (1H, t, *J*=7.9 Hz, ArCHPh), 4.89–4.91 (1H, m, one of $CH_2CH=CH_2$), 4.98–5.02 (1H, m, one of $CH_2CH=CH_2$), 5.69–5.78 (1H, m, $CH=CH_2$), 6.68–6.78 (1H, m, 1×Ph-*H*), 6.80–6.88 (1H, m, 1×Ph-*H*), 7.03–7.11 (2H, m, 2×Ph-*H*), 7.14–7.27 (5H, m, 5×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 39.4 (Ar*C*HPh), 44.0 ($CH_2CH=CH_2$), 59.5 (OCH_3), 67.0 (CH_2OCH_3), 71.5 (OCH_2CH_2), 112.3 (1×=C), 115.1 ($CH_2CH=CH_2$), 126.7, 127.4, 128.3, 128.4, 128.8, 129.1, 131.4 (7×=*C*), 137.6 ($CH_2CH=CH_2$), 144.8, 156.7 (2×=*C*). *m/z* (EI) 292 (M^+, 90%), HRMS (EI) $C_{19}H_{22}O_2$ required 282.1620, found 282.1620.

3.4.5. (*S*)-1-(2-Methoxyethoxy)-2-(1″-phenylbut-3″-enyl)-benzene (*S*-11). (*S*)-1-(2-Methoxyethoxy)-2-(1″-phenylbut-3-enyl)-benzene was prepared using allyl tosylate as alkylating agent according to general procedure 3, except that compound **20** was substituted for (−)-sparteine, as a clear yellow oil (90%), 92% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ −11.5 (*c* 1, $CHCl_3$). Spectral data as above.

3.4.6. 2-(1′-Phenylbut-3′-enyl)-phenol (12). 2-Benzylphenol **7** (1.60 g, 8.7 mmol, 1.0 equiv) in ether (3 ml) was added dropwise, under argon to (−)-sparteine (2.16 g, 9.2 mmol, 1.06 equiv) and *s*-BuLi (1.4 M in cyclohexane) (13.00 ml, 18.2 mmol, 2.09 equiv) in ether (50 ml) at 0 °C. The mixture was warmed to rt and stirred for 5 h. The mixture was cooled to −78 °C and after 1 h at this temperature allyl bromide (5.16 g, 46.3 mmol, 5.32 equiv) was added dropwise. Warming to rt was followed by stirring for 15 h. Dilution with ether (110 ml) was followed by washing with 2 M hydrochloric acid (2×20 ml), water (20 ml), brine (2×20 ml), drying ($MgSO_4$) and concentration in vacuo to afford an orange oil (1.43 g, 74%). ν_{max} (cm^{-1}) (thin film) 3552 (OH), 3026 (CH), 1647 (–C=C–, allyl), 1587 (–C=C–, aromatic). δ ^{1}H NMR (400 MHz, $CDCl_3$) 2.77–2.88 (2H, m, $CH_2CH=CH_2$), 4.32 (1H, t, *J*=7.8 Hz, ArCHPh), 4.66 (1H, s, O*H*), 4.97 (1H, dd, *J*=17.1, 0.9 Hz, one of $CH=CH_2$), 4.89 (1H, dd, *J*=8.3, 0.9 Hz, one of $CH=CH_2$), 5.72–5.82 (1H, m, $CH=CH_2$), 6.73 (1H, d, *J*=8.0 Hz, 1×Ph-*H*), 6.78 (1H, d, *J*=7.5 Hz, 1×Ph-*H*), 6.81–6.96 (2H, m, 2×Ph-*H*), 7.08–7.32 (5H, m, 5×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 39.5 (Ar*C*HPh), 44.7 ($CH_2CH=CH_2$), 116.1 ($CH_2CH=CH_2$), 116.8, 121.3, 126.8, 127.4, 128.7, 129.0, 129.3, 130.9 (8×=*C*), 137.4 ($CH_2CH=CH_2$), 144.0, 153.7 (2×=*C*). *m/z* (CI, NH_3) 242 (MNH_4^+, 100%), HRMS (EI) $C_{16}H_{16}O$ required 224.1117, found 224.1121.

3.4.7. (2′-Methoxyphenyl)-3-phenylpropionic acid (13). 1-Methoxy-2-(1′-phenylbut-3′-enyl)benzene (34 mg, 0.144 mmol, 1.0 equiv, 60% ee by NMR) in dichloromethane (1 ml) was acidified with glacial acetic acid (0.125 ml),

diluted with water (1 ml) and 18-crown-6-ether (11 mg, 0.042 mmol, 0.29 equiv) in dichloromethane (0.2 ml) was added. Potassium permanganate (82 mg, 0.520 mmol, 3.61 equiv) was added in small portions over 1 h. Stirring at rt over 18 h followed. The solution was filtered followed by the addition of water (2.5 ml) and adjustment to pH=14 (KOH). The solution was filtered again and the layers separated. The aqueous layer was then washed with dichloromethane (3×2 ml), acidified to pH=3 with concentrated hydrochloric acid and extracted into ether (2× 3 ml). The combined organics were then washed with brine (1 ml), dried ($MgSO_4$) and concentrated in vacuo to afford the title compound as a yellow solid (28 mg, 75%). $[\alpha]_D^{23}$ +14.0 (*c* 0.7, $CHCl_3$). Lit. ref.; $[\alpha]_D$ −24.8, (*S*)-enantiomer.[7a] Spectral data were in accordance with literature values.

3.4.8. (*R*)-4-Phenylchroman-2-one (14). 1-(2-Methoxyethoxy)-2-(1″-phenylbut-3-enyl)benzene (0.150 g, 0.530 mmol, 1.0 equiv, 94% ee by NMR) in dichloromethane (2 ml) was acidified with glacial acetic acid (0.25 ml), diluted with water (1 ml) and 18-crown-6-ether (0.039 g, 0.148 mmol, 0.28 equiv) in dichloromethane (0.2 ml) was added. Potassium permanganate (0.280 g, 1.770 mmol, 3.33 equiv) was added portionwise over 1 h. Stirring at rt for 24 h followed. The solution was filtered followed by the addition of water (10 ml) and adjustment to pH=14 (KOH). The solution was filtered and separated. The aqueous layer was washed with dichloromethane (3× 3 ml), acidified to pH=3 with concentrated hydrochloric acid and extracted into ether (2×10 ml). The combined organics were then washed with brine (5 ml), dried ($MgSO_4$) and concentrated in vacuo to afford 3-(2′-methoxyethoxyphenyl)-3-phenyl propionic acid as a yellow solid (0.12 g, 75%). Mp 120–122 °C. $[\alpha]_D^{20}$ +110.1 (*c* 0.7, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 3383 (OH, w), 3067, 2923, 1705, 1494, 1445. δ ^{1}H NMR (400 MHz, $CDCl_3$) 3.04–3.18 (2H, m, C$H_2$$CO_2$H), 3.44 (3H, s, OCH_3), 3.71–3.74 (2H, m, $OCH_2CH_2OCH_3$), 4.04–4.10 (2H, m, $OCH_2CH_2OCH_3$), 4.91 (1H, t, *J*=8.0 Hz, ArC*H*Ph), 6.83 (1H, d, *J*=7.3 Hz, 1×Ph-*H*), 6.88–6.91 (1H, m, 1×Ph-*H*), 7.11–7.30 (7H, m, 7×Ph-*H*). δ ^{13}C NMR (400 MHz, $CDCl_3$) 39.2 (ArC*H*Ph), 41.0 (CH_2CO_2H), 59.0 (OCH_3), 67.4 (OCH_2CH_2), 71.0 (OCH_2CH_2), 118.8, 120.9, 126.3, 127.8, 128.0, 128.3, 129.4, 132.0, 142.9, 156.0 (10×=*C*), 176.0 (CO_2H). *m*/*z* (EI) 300 (M^+, 60%), HRMS (EI) $C_{18}H_{20}O_4$ required 300.1358, found 300.1362. Boron tribromide (1.0 M in dichloromethane) (0.700 ml, 0.700 mmol, 3.5 equiv) was added dropwise, over a period of 5–10 min, at −78 °C, to 3-(2′-methoxyethoxyphenyl)-3-phenyl propionic acid (0.060 g, 0.200 mmol, 1.0 equiv) in dichloromethane (2 ml). After the addition was complete, an ice/water bath was employed, and stirring at ca. 0 °C followed for 1 h. The reaction was quenched with sodium carbonate (0.4 g) in water (2 ml). Dilution with water (4 ml) was followed by extraction into dichloromethane (3×2 ml) and washing with brine (2 ml). The combined organics were dried ($MgSO_4$) and concentrated in vacuo to afford the title compound as a yellow solid (0.040 g, 89%). $[\alpha]_D^{25}$ −40.9 (*c* 1.0, C_6H_6). Lit. ref. $[\alpha]_D^{25}$ +43.7 (*c* 1.0, C_6H_6), (*S*)-enantiomer.[7a] Spectral data were in accordance with literature values.

3.4.9. 2-(1-Phenylethyl)-phenol (15). Under argon, aluminium (granular) (0.087 g, 3.20 mmol, 2.29 equiv) and iodine (0.580 g, 2.30 mmol, 1.64 equiv) in acetonitrile (5 ml) were heated at reflux for 1.5 h until a pale yellow solution formed. At this point 1-(2-methoxyethoxy)-2-(1-phenylethyl)benzene (**206**) (0.350 g, 1.40 mmol, 1.0 equiv, 12% ee by NMR) in acetontrile (2 ml) was added dropwise. TLC indicated consumption of starting material after 18 h at reflux. Cooling was followed by dilution with water (20 ml) and extraction into ether (3×25 ml), drying ($MgSO_4$) and concentration in vacuo to afford an oil. Column chromatography (75:25 petroleum ether/ethyl acetate) afforded the title compound as a golden oil (0.20 g, 74%). $[\alpha]_D$ +8.44 (*c* 1.0, $CHCl_3$). Lit. ref.; $[\alpha]_D$ −27.85 (*c* 1, $CHCl_3$) (*S*)-enantiomer.[11] Spectral data were in accordance with literature values.

3.4.10. 1-(2′-Methoxyethoxy)-2-(1″-phenylethyl)-benzene (16). 1-(2′-Methoxyethoxy)-2-(1″-phenylpropyl)-benzene was prepared using ethyl iodide as alkylating agent according to general procedure 3 to give a clear yellow oil (0.241 g, 65%), 70% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +8.4 (*c* 1.2, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 2934, 2866, 1599, 1495, 1450. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.90 (3H, t, *J*=9.3 Hz, CH_2CH_3), 2.02 (2H, app. dq, *J*=7.5, 1.7 Hz, C$H_2$$CH_3$), 3.44 (3H, s, OCH_3), 3.64–3.76 (2H, m, OCH_2-C$H_2$$OCH_3$), 3.95–4.01 (1H, m, $OCH_2CH_2OCH_3$), 4.05–4.11 (1H, m, $OCH_2CH_2OCH_3$), 4.28 (1H, t, *J*=7.3 Hz, ArC*H*Ph), 6.76–6.85 (1H, m, 1×Ph-*H*), 6.87–6.98 (1H, m, 1×Ph-*H*), 7.10–7.20 (2, m, 2×Ph-*H*), 7.20–7.36 (5H, m, 5×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 13.2 (CH_3), 28.4 (CH_2), 36.9 (ArCHPh), 59.5 (OCH_3), 68.2 (OCH_2CH_2), 71.6 (OCH_2CH_2), 112.2, 121.2, 126.0, 127.4, 127.6, 128.1, 128.4, 145.5, 146.9, 156.6 (10×=*C*). *m*/*z* 270 (M^+, 100%), HRMS (EI) $C_{18}H_{22}O_2$ required 270.1620, found 270.1617.

3.4.11. 1-(2′-Methoxyethoxy)-2-(1″-phenylbutyl)-benzene (17). 1-(2′-Methoxyethoxy)-2-(1″-phenylbutyl)-benzene was prepared using propyl iodide as alkylating agent according to general procedure 3 to give a clear oil (0.300 g, 78%), 64% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +10.98 (*c* 0.7, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 2932, 2863, 1599, 1495, 1449. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.95 (3H, t, *J*=7.7 Hz, $CH_2CH_2CH_3$), 1.23–1.35 (2H, m, $CH_2CH_2CH_3$), 1.98 (2H, app. dt, *J*=8.4, 6.3 Hz, C$H_2$$CH_2$-$CH_3$), 3.44 (3H, s, OCH_3), 3.70 (2H, t, *J*=5.2 Hz, $OCH_2CH_2OCH_3$), 3.96–4.02 (1H, m, $OCH_2CH_2OCH_3$), 4.05–4.11 (1H, m, $OCH_2CH_2OCH_3$), 4.41 (1H, t, *J*= 7.3 Hz, ArC*H*Ph), 6.81 (1H, d, *J*=8.0 Hz, 1×Ph-*H*), 6.89–6.95 (2H, m, 2×Ph-*H*), 7.10–7.16 (2, m, 2×Ph-*H*), 7.21–7.33 (3H, m, 3×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 14.5 (CH_3), 21.5 (CH_2CH_3), 37.5 ($CH_2CH_2CH_3$), 43.5 (ArCHPh), 59.5 (OCH_3), 68.0 (OCH_2CH_2), 71.6 (OCH_2CH_2), 112.3, 121.2, 126.0, 127.5, 127.6, 128.2, 128.4, 145.9, 146.8, 156.7 (10×=*C*). *m*/*z* 280 ($(M-4)^+$, 76%), 284 (M^+, 100%), HRMS (EI) $C_{19}H_{24}O_2$ required 284.1776, found 284.1780.

3.4.12. 1-(1′,2′-Diphenylethyl)-2-(2″-methoxyethoxy)-benzene (18). 1-(1′,2′-Diphenylethyl)-2-(2″-methoxyethoxy)-benzene was prepared using benzyl bromide as

alkylating agent according to general procedure 3 to give a clear oil (0.382 g, 90%), 68% ee by ^{1}H NMR in the presence of 4 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +4.9 (*c* 0.8, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 3027, 2925, 1600, 1494, 1453. δ ^{1}H NMR (400 MHz, $CDCl_3$) 3.37 (2H, dd, *J*=16.0, 8.0 Hz, CH_2Ph), 3.39 (3H, s, OCH_3), 3.67 (2H, t, *J*=5.1 Hz, $OCH_2CH_2OCH_3$), 3.95–4.02 (2H, m, $OCH_2CH_2OCH_3$), 4.77 (1H, t, *J*=8.0 Hz, ArCHPh), 6.74 (1H, d, *J*=8.5 Hz, 1×Ph-*H*), 6.80–6.85 (1H, m, 1×Ph-*H*), 7.04–7.47 (12H, m, 12×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 37.4 (Ar*C*HPh), 43.5 (CH_2Ph), 59.5 (OCH_3), 67.9 (OCH_2CH_2), 71.6 (OCH_2CH_2), 112.3, 121.2, 126.0, 127.4, 127.6, 128.2, 128.3, 128.4, 128.9, 129.5, 144.9, 145.8, 156.7 (14×Ar *C*). *m*/*z* 332 (M^+, 85%), HRMS (EI) $C_{23}H_{24}O_2$ required 332.1776, found 332.1772.

3.4.13. 1-(2-Methoxyethoxy)-2-(1″-trimethylsilyl-phenylmethyl)-benzene (19). 1-(2-Methoxyethoxy)-2-(1″-phenylbut-3″-enyl)-benzene was prepared using trimethylsilyl chloride as electrophile according to general procedure 3 as an oil (0.399 g, 91%), 82% ee by ^{1}H NMR in the presence of 2 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{25}$ +4.29 (*c* 1.0, $CHCl_3$). ν_{max} (cm^{-1}) 3026, 2955, 1598, 1489, 1450. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.04 (9H, s, $Si(CH_3)_3$), 3.43 (3H, s, OCH_3), 3.68 (2H, t, *J*=4.9 Hz, $OCH_2CH_2OCH_3$), 3.92–4.01 (1H, m, one of $OCH_2CH_2OCH_3$), 4.06–4.11 (1H, m, one of $OCH_2CH_2OCH_3$), 4.12 (1H, s, ArC*H*Ph), 6.85 (1H, d, *J*=9.3 Hz, 1×Ph-*H*), 6.89–6.95 (1H, m, 1×Ph-*H*), 7.06–7.15 (2H, m, 2×Ph-*H*), 7.16–7.39 (5H, m, 5×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) −1.48 ($Si(CH_3)_3$), 36.8 (Ar*C*HPh), 59.1 (OCH_3), 67.8 (OCH_2CH_2O), 71.1 (OCH_2CH_2O), 112.3, 120.6, 126.2, 127.2, 127.9, 128.9, 130.1, 130.8, 143.4, 156.3 (10×=*C*). *m*/*z* 314 (M^+, 51%), HRMS (EI) $C_{19}H_{26}SiO_2$ required 314.1702, found 314.1703.

3.4.14. (1*R*, 5*S*)-3-(2′-Methoxyethyl)-decahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocine (21). To (−)-cytisine (0.366 g, 19.2 mmol, 1.0 equiv) in dichloromethane (11 ml) was added at 0 °C triethylamine (2.700 ml, 192.0 mmol, 10.0 equiv) and methoxyacetyl chloride (0.242 g, 22.3 mmol, 1.16 equiv). The mixture was stirred at rt for 18 h. Concentration in vacuo afforded a pasty solid. Ethyl acetate (7 ml) was added and the remaining solids removed by filtration. The filtrate was concentrated in vacuo to an oil. Column chromatography (90:10 dichloromethane/methanol) afforded (1*R*, 5*S*)-*N*-(2-Methoxyacetyl)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido-[1,2-*a*]diazocin-8-one as an oil (0.490 g, 97%). $[\alpha]_D^{28}$ −202.3 (*c* 1.0, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 3451, 2935, 1650, 1546, 1448. δ ^{1}H NMR (400 MHz, $CDCl_3$) (restricted rotation apparent) 2.00–2.06 (2H, m, C(13)H_2), 2.48–2.59 (1H, m, C(5)*H*), 2.88 (1H, t, *J*=13.8 Hz, C(1)*H*), 3.04–3.09 (2H, m, C(2)H_2), 3.23 (3H, s, OCH_3), 3.30 (1H, m, one of C(6)H_2), 3.78–3.92 (2H, m, one of C(4)H_2), one of C(6)H_2), 4.01–4.29 (2H, m, one of C(4)H_2), one of CH_2O), 4.59 and 4.71 (1H, 2×d, *J*=12.7 Hz, CH_2O). δ ^{13}C NMR (100 MHz, $CDCl_3$) 26.1 (*C*-13), 27.3 (*C*-5), 34.5 (*C*-1), 45.4 (*C*-6), 48.5 (*C*-2), 51.3 (*C*-4), 58.7 (OCH_3), 71.7 (OCH_2), 105.3 (*C*-11), 117.3 (*C*-9), 138.8 (*C*-10), 148.2 (*C*-12), 163.2 (*C*-8), 168.6 (*C*O). *m*/*z* 263 (M^++1, 100%), HRMS (CI) $C_{14}H_{19}N_2O_3$ required 263.1325, found 263.1344. A suspension of (1*R*, 5*S*)-*N*-(2-methoxyacetyl)-1,2,3,4,5,6-hexahydro-1,5-methanopyrido-[1,2-*a*]diazocin-8-one (0.440 g, 1.68 mmol, 1.0 equiv) and platinum(IV) oxide (0.034 g, 0.15 mmol, 0.089 equiv) in ethanol (7 ml) was stirred at rt under hydrogen (1 atm) for 15 h. The mixture was then filtered through a Celite plug, washing with 9:1 dichloromethane/methanol (30 ml), and concentrated in vacuo to afford a clear yellow oil (0.441 g). Column chromatography (9:1 dichloromethane/methanol; iodine stain) afforded (1*R*, 5*S*)-3-(2-methoxyacetyl)decahydro-1,5-methanopyrido[1,2-*a*][1,5]diazocin-8-one as a clear yellow oil (0.401 g, 90%). R_f 0.44 (90:10 dichloromethane/methanol). $[\alpha]_D^{21}$ −206.7(*c* 0.7, $CHCl_3$). ν_{max} (cm^{-1}) (thin film) 3441, 2958, 2935, 1649. δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.51–1.64 (1H, m, 1×ring proton (rp)), 1.69–1.75 (1H, m, 1×rp), 1.78–2.12 (6H, m, 6×rp), 2.30–2.36 (2H, m, 2×rp), 2.69 (1H, d, *J*=14.8 Hz, 2×rp), 2.81 (1H, d, *J*=14.8 Hz, 2×rp), 3.36 (3H s, OCH_3), 3.45–3.51 (1H, m, 1×rp), 3.87 (1H, d, *J*=17.6 Hz, 1×rp), 3.95–3.99 (1H, d, *J*=17.6 Hz, 1×rp), 4.16 (1H, d, *J*=13.7 Hz, 1×rp), 4.86 (1H, d, *J*=13.8 Hz, one of $OCH_2C(O)$), 5.04 (1H, d, *J*=13.8 Hz, $OCH_2C(O)$). δ ^{13}C NMR (100 MHz, $CDCl_3$) 19.8 (*C*-8), 27.6 (*C*-1), 27.8 (*C*-5), 32.6 (*C*-13), 32.8 (*C*-11), 33.5 (*C*-9), 42.0 (*C*-2), 45.8 (*C*-6), 49.7 (*C*-4), 59.0 (*C*-12), 59.3 (OCH_3), 71.2 ($OCH_2C(O)$), 168.1 (*C*O), 170.2 (N*C*O). *m*/*z* 267 (M^++1, 100%), HRMS (CI) $C_{14}H_{23}N_2O_3$ required 267.1703, found 267.1709. (1*R*, 5*S*)-3-(2-Methoxyacetyl)-decahydro -1,5-methanopyrido[1,2-*a*][1,5]diazocine (3.30 g, 12.4 mmol, 1.0 equiv) in THF (35 ml) was added dropwise under argon to a suspension of lithium aluminium hydride (3.01 g, 79.2 mmol, 6.39 equiv) in THF (60 ml) heated at reflux. The mixture was heated at reflux for 20 h and cooled to 0 °C, diluted with ether (110 ml) and quenched by the dropwise addition of satd aq sodium sulphate (25 ml). The mixture was passed through a Celite plug, washing with 9:1 dichloromethane/methanol (300 ml), dried ($MgS0_4$) and concentrated in vacuo to afford a tan intermediate oil (2.60 g). Kugelrohr distillation (pot temperature 180 °C/3 mmHg) afforded the title compound **17** as a golden oil (2.15 g, 73%), 95% ee by ^{1}H NMR in the presence of 1 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. ν_{max} (cm^{-1}) (thin film) 3390, 2931, 2808. δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.18–1.33 (2H, m, 2×ring proton (rp)), 1.40–1.66 (6H, m, 6×rp), 1.68–1.83 (2H, m, 2×rp), 1.85–1.93 (1H, m, 1×rp), 2.03 (1H, dd, *J*=10.9, 3.8 Hz, 1×rp), 2.16–2.35 (3H, m, 3×rp), 2.62 (1H, app. td, *J*=12.7, 5.9 Hz, C(12)*H*), 2.76–2.91 (3H, m, 2×rp, 1×OCH_2), 3.02 (1H, d, *J*=11.5 Hz, 1×OCH_2), 3.31 (3H, s, OCH_3), 3.44–3.55 (2H, m, NCH_2). δ ^{13}C NMR (100 MHz, $CDCl_3$) 25.0, 25.4, 30.4, 30.5, 33.7, 34.7, 53.6, 56.3, 57.3, 58.6, 58.7 (OCH_3), 60.4, 66.1 (NCH_2), 70.4 (OCH_2). *m*/*z* 239 (M^++1, 88%), HRMS (CI) $C_{14}H_{27}N_2O$ required 239.2118, found 239.2117.

3.5. General procedure 4 for asymmetric alkylations of 25 at −78 °C using (−)-sparteine (conditions A, Table 3)

Under an argon atmosphere to *N*-pivaloyl-*o*-benzylaniline **25** (0.01 mol, 1.0 equiv) at 0 °C in ether (100 ml) was added dropwise *s*-BuLi (2.4 equiv). The mixture was stirred at 0 °C for 3.5 h, cooled to −78 °C and (−)-

sparteine (2.6 equiv) in ether was added dropwise. The mixture was then stirred at −78 °C for 2 h. Alkylating agent (1.2 equiv) in ether was added dropwise, the reaction mixture warmed to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2×20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate). All reaction products of **25** with electrophiles gave a clean splitting of the *tert*-butyl singlet in the ^{1}H NMR when treated with 2–3 equiv of (−)-2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE).

3.6. General procedure 5 for asymmetric alkylations of 25 using (−)-sparteine with a warm–cool cycle (conditions B, Table 3)

Under an argon atmosphere to *N*-pivaloyl-*o*-benzylaniline **25** (0.01 mol, 1.0 equiv) at 0 °C in ether (100 ml) was added dropwise *s*-BuLi (2.4 equiv). The mixture was stirred at 0 °C for 3.5 h, cooled to −78 °C and (−)-sparteine (2.6 equiv) in ether (5 ml) was added dropwise. The mixture was kept at −78 °C for 1 h. The mixture was then warmed to −20 °C for 1 h before being recooled to −78 °C. The mixture was stirred at this temperature for a further 30 min. Alkylating agent (1.2 equiv) in ether (5 ml) was added dropwise, the reaction mixture warmed to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2× 20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate).

3.7. General procedure 6 for asymmetric alkylations of 25 using (−)-sparteine with a warm–cool cycle and batch addition (conditions C, Table 3)

Under an argon atmosphere to *N*-pivaloyl-*o*-benzylaniline **25** (0.01 mol, 1.0 equiv) at 0 °C in ether (100 ml) was added dropwise *s*-BuLi (2.4 equiv). The mixture was stirred at 0 °C for 3.5 h, cooled to −78 °C and (−)-sparteine (2.6 equiv) in ether (5 ml) was added dropwise. The mixture was kept at −78 °C for 1 h. The mixture was then warmed to −20 °C and stirred at this temperature for 1 h and then recooled to −78 °C for a further 5 min. The first portion of alkylating agent (0.5 mol equiv) in ether (5 ml) was added dropwise. The mixture was then warmed to −20 °C for a further 1 h before being recooled to −78 °C for 5 min. The second portion of allyl bromide (0.5 mol equiv) in ether (5 ml) was added dropwise, the reaction mixture warmed to rt and stirred for 16 h. The reaction mixture was diluted with ether (100 ml) and washed with 2 M hydrochloric acid (2× 20 ml), water (30 ml), and brine (30 ml). Drying ($MgSO_4$) and concentration in vacuo gave the crude product, which was purified by column chromatography (9:1 petroleum ether/ethyl acetate).

3.7.1. 2,2-Dimethyl-*N*-[2′-(1″-phenylbut-3″-enyl)-phenyl]-propionamide (27).

2,2-Dimethyl-*N*-[2′-(1″-phenylbut-3″-enyl)phenyl]propionamide was prepared using allyl bromide as alkylating agent according to general procedure 4 as a clear yellow oil (0.144 g, 90%), 76% ee by ^{1}H NMR in the presence of 3.5 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{22}$ −24.3 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 3422, 3323, 2963, 1669, 1584, 1507, 1447. δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.14 (9H, s, $C(CH_3)_3$), 2.71–2.89 (2H, m, $CH_2CH{=}CH_2$), 4.03 (1H, t, *J*=7.4 Hz, ArCHPh), 4.99–5.08 (2H, m, $CH_2CH{=}CH_2$), 5.70–5.82 (1H, m, $CH_2CH{=}CH_2$), 6.95–7.00 (1H, d, *J*=7.3 Hz, 1×Ph-*H*), 7.17 (1H, d, *J*=7.3 Hz, 1×Ph-*H*), 7.22–7.37 (5H, m, 5×Ph-*H*), 7.43 (1H, app. dd, *J*=8.0, 1.9 Hz, 1×Ph-*H*), 7.84 (1H, app. dd, *J*=8.2, 1.4 Hz, 1×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.7 ($C(CH_3)_3$), 39.0 ($C(CH_3)_3$), 46.5 ($CH_2CH{=}CH_2$), 117.4 ($CH_2CH{=}CH_2$), 123.8, 125.4, 127.4, 128.1, 128.7, 129.3, 129.4, 131.5, 136.7 (9×=*C*), 137.9 ($CH_2CH{=}CH_2$), 139.1 (1×=*C*), 176.9 (*C*O). *m*/*z* 307 (M^+, 100%), HRMS (EI) $C_{21}H_{25}NO$ required 307.1936, found 307.1934.

3.7.2. 2,2-Dimethyl-*N*-[2′-(1″-phenylethyl)-phenyl]-propionamide (28).

2,2-Dimethyl-*N*-[2′-(1″-phenylethyl)phenyl]propionamide was prepared, using methyl tosylate as alkylating agent, according to general procedure 4 as a clear yellow oil (0.073 g, 41%), 56% ee by ^{1}H NMR in the presence of 4.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. $[\alpha]_D^{22}$ +4.8 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 3445, 3336, 2977, 1672, 1584, 1525, 1448. δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.04 (9H, s, $(CH_3)_3$), 1.64 (3H, d, *J*=7.3 Hz, CH_3), 4.15 (1H, q, *J*=7.3 Hz, ArCHPh), 7.08–7.34 (8H, m, 8×Ph-*H*), 7.42 (1H, d, *J*=8.4 Hz, 1×Ph-*H*), 7.88 (1H, d, *J*=7.8 Hz, 1×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 22.4 (CH_3), 27.6 ($C(CH_3)_3$), 39.9 ($C(CH_3)_3$), 41.1 (ArCHPh), 123.8, 125.3, 127.3, 128.1, 128.6, 129.4, 131.5, 136.0, 139.0, 145.3 (10×=*C*), 176.9 (*C*O). *m*/*z* 281 (M^+, 36%), HRMS (EI) $C_{19}H_{23}NO$ required 281.1780, found 281.1782.

3.7.3. *N*-[2′-(1″,2″-Diphenylethyl)-phenyl]-2,2-dimethyl-propionamide (29).

N-[2′-(1″,2″-Diphenylethyl)phenyl]-2,2-dimethylpropionamide was prepared, using benzyl bromide as alkylating agent, according to general procedure 4 as a clear oil (0.117 g, 80%), 46% ee by ^{1}H NMR in the presence of 3.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{22}$ −12.4 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 3444, 3220, 1672, 1578, 1496, 1450. δ ^{1}H NMR (400 MHz, $CDCl_3$) 1.09 (9H, s, $C(CH_3)_3$), 3.27–3.38 (2H, m, CH_2Ph), 4.23 (1H, t, *J*=8.0 Hz, ArCHPh), 6.55–6.59 (1H, m, 1×Ph-*H*), 6.88–6.92 (1H, m, 1×Ph-*H*), 7.02–7.07 (1H, m, 1×Ph-*H*), 7.17–7.28 (9H, m, 9×Ph-*H*), 7.37 (1H, dd, *J*=7.9, 1.8 Hz, 1×Ph-*H*), 7.62 (1H, dd, *J*=8.3, 1.9 Hz, 1×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 27.7 ($C(CH_3)_3$), 39.8 ($C(CH_3)_3$), 42.3 (CH_2Ph), 48.2 (ArCHPh), 123.8, 125.1, 127.4, 128.1, 128.3, 128.6, 129.0, 129.4, 129.6, 131.5, 135.8, 139.1, 140.1, 140.3 (14×=*C*), 176.9 (*C*O). *m*/*z* 327 (M^+, 100%), HRMS (EI) $C_{25}H_{27}NO$ required 357.2093, found 357.2092.

3.7.4. 2,2-Dimethyl-*N*-[2′-(1″-phenylpropyl)-phenyl-]-propionamide (30).

2,2-Dimethyl-*N*-[2′-(1″-phenylpropyl)-phenyl]propionamide was prepared using ethyl iodide as alkylating agent, according to general procedure 4 as a clear yellow oil (0.075 g, 60%), 56% ee by ^{1}H NMR in the presence of 4.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{22}$ −21.4 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 3423, 3316, 2964, 1658, 1585, 1514, 1450. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.94 (3H, t,

$J=7.3$ H_2, CH_3), 1.04 (9H, S, $(CH_3)_3$), 2.06 (2H, dq, $J=7.5$, 7.3 H_2, CH_2), 3.79 (1H, t, $J=7.5$ H_2, A C*H* Ph) 7.08–7.34 (8H, m, 8×Ph-*H*), 7.42 (1H, d, $J=8.4$ Hz, 1×Ph-*H*), 7.88 (1H, d, $J=7.8$ Hz, 1×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) 13.2 (CH_3), 27.9 (C(CH_3)$_3$), 28.9 (CH_2), 39.8 ($C(CH_3)_3$), 48.5 (Ar*C*HPh), 123.8, 125.3, 127.4, 128.1, 128.5, 129.4, 131.5, 136.1, 139.1, 143.9 (10×=*C*), 176.9 (*C*O). *m/z* 295 (M^+, 38%), HRMS (EI) $C_{20}H_{25}NO$ required 295.1936, found 295.1936.

3.7.5. 2-(1-Phenylethyl)-phenylamine (31). 2,2-Dimethyl-*N*-[2′-(1″-phenylethyl)phenyl]propionamide (31 mg, 0.107 mmol, 1.0 equiv) in THF (0.5 cm^3) was added dropwise, under an argon atmosphere, at 0 °C to a suspension of lithium aluminium hydride (24 mg, 0.621 mmol, 5.80 equiv) in THF (2 cm^3). The mixture was heated at reflux for 12 h. The mixture was cooled, diluted with ether (1 cm^3) and washed with satd aq sodium sulphate (1 cm^3). Filtering through a Celite plug was followed by washing with 9:1 dichloromethane/methanol (10 cm^3), drying ($MgSO_4$) and concentration in vacuo to afford a yellow oil (14 mg). Column chromatography (90:10 petroleum ether/ethyl acetate) afforded the title compound as a pale yellow oil (5.4 mg, 25%). $[\alpha]_D$ +2.45 (*c* 1.0, $CHCl_3$). Lit. ref.; $[\alpha]_D$ +4.4 (*c* 1, $CHCl_3$) (*S*)-enantiomer.[11] Spectral data in accordance with literature values.

3.7.6. [(2-Methoxyphenyl)-phenylmethyl]-trimethyl stannane (32a). (*R*)-[(2-Methoxyphenyl)-phenylmethyl]-trimethyl stannane was prepared using trimethyltin chloride as electrophile according to general procedure 1 as a clear colourless oil (0.221 g, 75%), 34% ee by ^{1}H NMR in the presence of 3.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. $[\alpha]_D^{22}$ −12.4 (*c* 1, $CHCl_3$). R_f 0.16 (90:10 petroleum ether/ethyl acetate). ν_{max} (cm^{-1}) 2938, 1656, 1597, 1487, 1457, 1403. δ ^{1}H NMR (400 MHz, $CDCl_3$) −0.04 (9H, s, Sn(CH_3)$_3$), 3.81 (3H, s, OCH_3), 3.98 (1H, s, ArC*H*Ph), 6.84–6.90 (2H, m, 2×Ph-*H*), 6.99–7.06 (3H, m, 3×Ph-*H*), 7.11–7.18 (1H, m, 1×Ph-*H*), 7.19–7.26 (3H, m, 3×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) −7.7 (Sn(CH_3)$_3$), 38.8 (Ar*C*HPh), 55.1 (OCH_3), 110.0, 121.2, 124.3, 126.4, 127.8, 128.5, 129.5, 132.6, 144.6, 156.4 (10×=*C*). *m/z* 362 (M^+, 5%), HRMS (EI) $C_{17}H_{22}O_2$ Sn^{120} required 326.0693, found 362.0705.

3.7.7. [(2-(2′-Methoxyethoxy)-phenyl)-phenylmethyl]-trimethyl stannane (32b). [(2-(2′-Methoxyethoxy)-phenyl)-phenylmethyl]-trimethyl stannane was prepared using trimethyltin chloride as electrophile according to general procedure 3 as a golden oil (0.461 g, 92%). 29% ee by ^{1}H NMR in the presence of 2.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{22}$ +0.99 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 2926, 1599, 1486, 1447, 1233. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.00 (9H, s, Sn(CH_3)$_3$), 3.40 (3H, s, OCH_3), 3.70 (2H, t, $J=5.1$ Hz, OCH_2CH_2OCH$_3$), 4.08–4.18 (2H, m, OCH$_2$CH_2OCH$_3$), 4.18 (1H, s, ArC*H*Ph), 6.87–6.91 (2H, m, 2×Ph-H), 7.03–7.13 (1H, m, 1×Ph-*H*), 7.16–7.19 (3H, m, 3×Ph-*H*), 7.20–7.26 (3H, m, 3×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) −8.2 (Sn(CH_3)$_3$), 37.5 (Ar*C*HPh), 58.9 (OCH_3), 67.1 (OCH$_2$$CH_2$O), 70.8 (O$CH_2$-$CH_2$O), 111.6, 121.3, 124.4, 126.2, 128.5, 129.3, 129.6, 132.7, 144.5, 155.7 (10×=*C*). *m/z* 406 (M^+, 8%), HRMS (EI) $C_{19}H_{26}O_2S_n^{120}$ required 406.0955, found 406.0945.

3.7.8. 2,2-Dimethyl-*N*-[2-(phenyltrimethylstannyl-methyl)-phenyl]-propionamide (32c). 2,2-Dimethyl-*N*-[2-(phenyltrimethylstannylmethyl)-phenyl]-propionamide was prepared using trimethyltin chloride as electrophile according to general procedure 4 as a clear yellow oil (0.365 g, 73%), 54% ee by ^{1}H NMR in the presence of 2.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol. $[\alpha]_D^{22}$ +20.8 (*c* 1, $CHCl_3$). ν_{max} (cm^{-1}) 3420, 3335, 2963, 1670, 1596, 1577, 1513, 1487, 1440. δ ^{1}H NMR (400 MHz, $CDCl_3$) 0.14 (9H, s, Sn(CH_3)$_3$), 1.10 (9H, s, C(CH_3)$_3$), 3.90 (1H, s, ArC*H*Ph), 6.98 (1H, d, $J=3.1$ Hz, Ph-*H*), 7.04–7.28 (7H, m, 7×Ph-*H*), 7.97 (1H, d, $J=8.5$ Hz, 1×Ph-*H*). δ ^{13}C NMR (100 MHz, $CDCl_3$) −9.3 (Sn(CH_3)$_3$), 27.4 (C(CH_3)$_3$), 38.0 ($C(CH_3)_3$), 39.4 (Ar*C*HPh), 123.8, 124.3, 124.7, 126.0, 126.8, 128.2, 128.8, 132.0, 136.7, 143.5 (10×=*C*), 176.4 (*C*O). *m/z* 429 (M(Sn^{118})$^+$, 18%), 431 (M(Sn^{120})$^+$, 23%), HRMS (EI) $C_{21}H_{29}NOSn^{120}$ required 431.1271, found 431.1273.

3.8. General procedure for regeneration and quenching of organolithiums from 32a–b

Under argon, stannane **32** (0.263 mmol, 1.0 equiv) in ether (2 ml) was cooled to −78 °C. In a separate flask, (−)-sparteine (0.103 g, 0.439 mmol, 1.67 equiv) in ether (3 ml) was cooled to −78 °C and *s*-BuLi (1.4 M in cyclohexane) (0.30 ml, 0.420 mmol, 1.60 equiv) was added dropwise. This complex was transferred at −78 °C (via cannula) to the flask containing stannane and the reaction stirred at −78 °C for 2 h. At this point, pre-cooled allyl bromide (0.101 g, 0.835 mmol, 3.17 equiv) in ether (1 ml) was added dropwise. Stirring at −78 °C followed for 3 h and at this point the reaction was quenched by the dropwise addition of methanol (1 ml). The mixture was diluted with ether (10 ml) and washed with 2 M hydrochloric acid (2×1 ml), brine (2 ml), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (90:10 petroleum ether/ethyl acetate) afforded product.

3.8.1. 1-Methoxy-2-(1′-phenylbut-3′-enyl)-benzene (8). The title compound was obtained as a golden oil (0.045 g, 72%), 15% ee by ^{1}H NMR in the presence of 2.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol with optical rotation indicating a *S*-configuration. Spectral data as previously recorded.

3.8.2. 1-(2-Methoxyethoxy)-2-(1″-phenylbut-3″-enyl)-benzene (11). The title compound was obtained as a golden oil (0.0518 g, 86%), 27% ee by ^{1}H NMR in the presence of 2.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol with optical rotation indicating a *S*-configuration. Spectral data as previously recorded.

3.9. Procedure for regeneration and quenching of organolithium from 32c

Under argon, (*S*)-2,2-dimethyl-*N*-[2-(phenyltrimethylstannyl-methyl)phenyl] propionamide **32c** (0.056 g, 0.131 mmol, 1.0 equiv) (54% ee) in ether (2 ml) was cooled to −78 °C. In a separate flask, (−)-sparteine (0.103 g, 0.439 mmol, 3.35 equiv) in ether (3 ml) was cooled to −78 °C and *s*-BuLi (1.4 M in cyclohexane) (0.280 ml, 0.392 mmol, 2.99 equiv) was added dropwise. The resulting complex was transferred at

−78 °C (via cannula) to the flask containing stannane and the reaction stirred at −78 °C for 2 h. Pre-cooled allyl bromide (0.062 g, 0.512 mmol, 3.91 equiv) in ether (1 ml) was added dropwise. Stirring at −78 °C followed for 3 h and at this point the reaction was quenched by the dropwise addition of methanol (1 ml). The mixture was diluted with ether (10 ml) and washed with 2 M hydrochloric acid (2×1 ml), brine (2 ml), dried ($MgSO_4$) and concentrated in vacuo. Column chromatography (90:10 petroleum ether/ethyl acetate) afforded 2,2-dimethyl-*N*-[2′-(1″-phenylbut-3″-enyl)-phenyl]-propionamide **27** as a golden oil (0.0309 g, 77%), 52% ee by ^{1}H NMR in the presence of 2.0 equiv of (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol with optical rotation indicating *R*-configuration. Spectra as previously recorded.

Acknowledgements

The authors wish to acknowledge EPSRC/GSK for a CASE award (S.B.R.), GSK for mass spectrometry and Dr. Peter O'Brien (University of York) for helpful conversations.

References and notes

1. Podophyllotoxin **1**: VanVliet, D. S.; Tachibana, Y.; Bastow, K. F.; Huang, E.-S.; Lee, K.-H. *J. Med. Chem.* **2001**, *44*, 1422–1428 and references therein. Dioxolanes **2**: Getahun, Z.; Jurd, L.; Chu, P. S.; Lin, C. M.; Hamel, E. *J. Med. Chem.* **1992**, *35*, 1058–1067. Myristinin B **3**: Sawdjoon, S.; Kittakoop, P.; Kirtikara, K.; Vichai, V.; Tanticharoen, M.; Thebtharanonth, Y. *J. Org. Chem.* **2002**, *67*, 5470–5475. Unnamed natural product **4**: Chang, F.-R.; Hsieh, T.-J.; Huang, T.-L.; Chen, C.-Y.; Kuo, R.-Y.; Chan, Y.-C.; Chiu, H.-F.; Wu, Y.-C. *J. Nat. Prod.* **2002**, *65*, 255–258.
2. Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259–296.
3. (a) Clayden, J. *Organolithiums: Stereoselectivity for Synthesis*; Pergamon: Oxford, 2002; Chapter 2. (b) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed.* **2002**, *41*, 717–738 and references cited therein. (c) Nakamura, S.; Nakawaga, R.; Watanabe, Y.; Toru, T. *J. Am. Chem. Soc.* **2000**, *122*, 11340–11347. (d) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552–560 and references cited therein.
4. Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussain, N. *Tetrahedron Lett.* **2004**, *45*, 1191–1193. Wilkinson, J. A.; Rossington, S. B.; Leonard, J.; Hussain, N. *Tetrahedron Lett.* **2004**, *45*, 5481–5483. Wilkinson, J. A.; Rossington, S. B.; Ducki, S.; Leonard, J.; Hussain, N. *Tetrahedron: Asymmetry* **2004**, *15*, 3011–3013.
5. The methoxymethyl group is also known to promote *ortho*-lithiation more efficiently than lateral lithiation. See: Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101–2108.
6. (a) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575–1576. (b) Basu, A.; Gallagher, D. J.; Beak, P. *J. Org. Chem.* **1996**, *61*, 5718–5719.
7. (a) Meyers, A. I.; Smith, R. K.; Whitten, C. E. *J. Org. Chem.* **1979**, *44*, 2250–2256. (b) Bhatt, M. V.; Babu, J. R. *Tetrahedron Lett.* **1985**, *25*, 3497–3500.
8. Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209–8216.
9. (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P.R.; O'Brien, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871. (b) Hermet, J.-P.R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, S.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977–3988. (c) Dearden, M. J.; McGrath, M. J.; O'Brien, P. *J. Org. Chem.* **2004**, *69*, 5789–5792. (d) Strohmann, C.; Strohfeldt, K.; Schidbach, D.; McGrath, M. J. *Organometallics* **2004**, *23*, 5389–5391. (e) Johansson, M. J.; Schwartz, L. O.; Amedjkouh, M.; Kann, N. C. *Eur. J. Org. Chem.* **2004**, 1894–1896.
10. Schwartz, D. A.; Yates, P. *Can. J. Chem.* **1983**, *61*, 1126–1131.
11. Kinoshita, T.; Ueno, T.; Ikai, K.; Fujiwara, M.; Okamoto, K. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3273–3282.
12. Thayumanavan, S.; Lee, S.; Liu, C.; Beak, P. *J. Am. Chem. Soc.* **1994**, *116*, 9755–9756.
13. An elegant discussion of asymmetric deprotonation, dynamic thermodynamic and kinetic resolution is presented in Ref. 3d.
14. **22** and **23**: Cain, C. M.; Cousins, R. P. C.; Coumbarides, G.; Simpkins, N. S. *Tetrahedron* **1989**, *46*, 523–544. **24**: Mimoun, H.; de Saint Laumer, J. Y.; Giannini, L.; Scopelliti, R.; Floriani, C. *J. Am. Chem. Soc.* **1999**, *121*, 6158–6166.
15. Akiyama, T.; Hirfuji, H.; Ozaki, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1932–1938.
16. Hesse, G.; Hagel, R. *Liebigs Ann. Chem.* **1976**, 996–1008. The absolute stereochemistry was not assigned by the authors.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1845–1848

Reaction between alkyl isocyanides and dialkyl acetylenedicarboxylates in the presence of benzoyl cyanides: one-pot synthesis of highly functionalized iminolactones

Mohammad Bagher Teimouri,[a,*] Ahmad Shaabani[b] and Reihaneh Bazhrang[c]

[a]*Petrochemical Department, Iran Polymer and Petrochemical Institute, PO Box 14965-115, Tehran Iran*
[b]*Department of Chemistry, Shahid Beheshti University, PO Box 19396-4716, Tehran, Iran*
[c]*Biomaterial Department, Iran Polymer and Petrochemical Institute, PO Box 14965-115, Tehran, Iran*

Received 6 September 2005; revised 29 October 2005; accepted 17 November 2005

Available online 15 December 2005

Abstract—The highly reactive 1:1 adduct, produced from the reaction between dialkyl acetylenedicarboxylates and alkyl isocyanides, was trapped by benzoyl cyanide derivatives to afford dialkyl 5-alkylimino-2-cyano-2-aryl-2,5-dihydro-3,4-furandicarboxylates in fairly good yields.

1. Introduction

The development of a simple, efficient and general synthetic method for widely used organic compounds from readily available reagents is one of the major challenges in organic synthesis. Meanwhile, the increasing environmental awareness of the chemical community has led to the search for more efficient methods for chemical synthesis.[1] Among them, the multi-component reactions (MCRs), by virtue of their convergence, productivity, facile execution and generally high yields of products, have attracted much attention from the vantage point of synthetic chemistry.[2]

So far, many synthetic protocols for the synthesis of iminolactones have been reported.[3–9] The most widely used approach to iminolactones synthesis is the isocyanide-based reactions.[3–7] As early as 1982, Saegusa and his co-workers reported on the Et_2AlCl-mediated reaction of α,β-unsaturated carbonyl compounds with methyl isocyanide leading to unsaturated *N*-substituted iminolactones, which can be easily converted to γ-butyrolactone.[3] Recently, Chatani et al. reexamined a catalytic [1+4] cycloaddition reaction of isocyanides and α,β-unsaturated carbonyl compounds in the presence of a catalytic amount of $GaCl_3$ leading to the formation of unsaturated iminolactone derivatives.[6] Moreover, gallium(III) chloride-catalyzed double insertion of aryl isocyanides into terminal and disubstituted epoxides leads to α,β-unsaturated α-amino iminolactones was reported.[7] Furthermore, the reaction of 4,4-disubstituted 2,3-allenamides and organic iodides in toluene afforded iminolactones.[8] Finally, the haloiminolactonization of 4,4-disubstituted 2,3-alkadienamides with copper(II) halide (chloride or bromide) or I_2 in THF also proceeded to produce unsaturated iminolactones.[9]

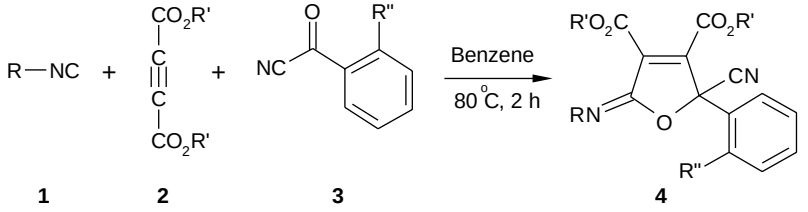
As part of an ongoing development of efficient protocols for the preparation of biologically active heterocycles from common intermediates using isocyanide-based reactions,[10] and electron deficient acetylenic esters,[11] we herein report an efficient one-pot condensation reaction of alkyl isocyanides, dialkyl acetylenedicarboxylates and benzoyl cyanide derivatives in refluxing benzene, which afforded a diverse array of dialkyl 5-alkylimino-2-cyano-2-aryl-2,5-dihydro-3,4-furandicarboxylates in good isolated yields in the absence of any added catalyst (Scheme 1).

2. Results and discussion

The one-pot three-component condensation reactions of alkyl isocyanides **1** with dialkyl acetylenedicarboxylates **2** in the presence of benzoyl cyanide derivatives **3** proceeded spontaneously at 80 °C in benzene and were complete after 2 h to afford 5-alkylimino-2-cyano-2-aryl-2,5-dihydro-3,4-furandicarboxylates **4**, in good yields. ^1H and ^{13}C NMR spectra of the crude products clearly indicated the formation of

Keywords: Acetylenic ester; Iminolactones; Isocyanide; One-pot three-component reaction.
* Corresponding author. Tel.: +98 21 44580000; fax: +98 21 44580032; e-mail: m.teimouri@ippi.ac.ir

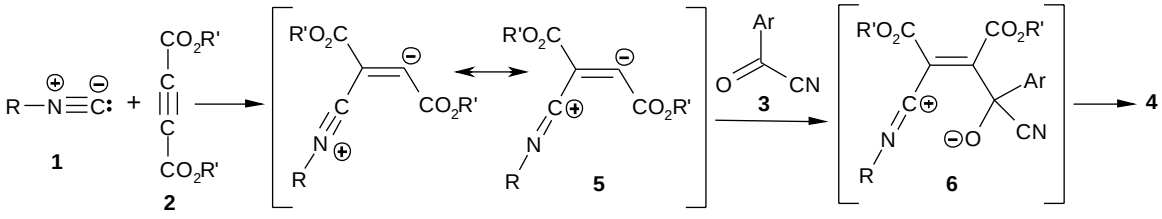
0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.043



1 2 3 4

4	R	R'	R"	Yield (%)
a	*tert*-Butyl	Methyl	H	74
b	Cyclohexyl	Methyl	H	91
c	*tert*-Butyl	Ethyl	H	65
d	Cyclohexyl	Ethyl	H	71
e	*tert*-Butyl	Methyl	Cl	75
f	Cyclohexyl	Methyl	Cl	88
g	*tert*-Butyl	Ethyl	Cl	62
h	Cyclohexyl	Ethyl	Cl	65

Scheme 1.



Scheme 2.

iminolactones **4**. Any product other than **4** could not be detected by NMR spectroscopy. The structures of the products **4a**–**4h** were deduced from their elemental analyses and IR, ^{1}H and ^{13}C NMR spectra. The mass spectra of these compounds displayed molecular ion peaks at the appropriate *m*/*z* values.

The ^{1}H NMR spectrum of **4a** exhibited three single sharp lines readily recognized as arising from *tert*-butyl (δ 1.31 ppm) and methoxy (δ 3.74 and 3.98 ppm) protons. The aromatic hydrogens gave rise to characteristic multiplet signals in the aromatic region of the spectrum (δ 7.43–7.54 ppm).

The ^{1}H decoupled ^{13}C NMR spectrum of **4a** showed 15 distinct resonances in agreement with the suggested structure. The characteristic signal due to the cyano group carbon was discernible at δ 114.54 ppm. Carbons of imino and two carbonyl groups were resonated at δ 149.96, 159.27 and 161.28 ppm, respectively. Partial assignment of these resonances is given in Section 3.

The structural assignments made on the basis of the ^{1}H and ^{13}C NMR spectra of compounds **4a** was supported by measurement of its IR spectra. The IR spectrum of **4a** showed strong absorptions at 1730 and 1757 cm^{-1} due to the ester carbonyls and the cyano group at 2345 cm^{-1} as a weak sharp band.

The ^{1}H and ^{13}C NMR spectra of **4b**–**4h** are similar to those of **4a** and the results are summarized in Section 3.

Although the mechanism of this reaction has not been established the formation of these heterocycles can be rationalized by initial formation of a highly reactive 1:1 zwitterionic intermediate **5** by the Michael-type addition reaction[12,13] of the alkyl isocyanide **1** with the dialkyl acetylenedicarboxylate **2**, which adds to the carbonyl group of benzoyl cyanide derivarives **3** leading to a dipolar species **6**. Cyclization of the latter leads to the iminolactones **4** (Scheme 2).

In conclusion, we have found that the one-pot three-component reaction of isocyanides, with dialkyl acetylenedicarboxylate in the presence of benzoyl cyanides leads to a facile synthesis of highly functionalized 5-alkylimino-2-cyano-2-aryl-2,5-dihydro-3,4-furandicarboxylates **4**, in good yields. The present method carries the advantages that, not only is the reaction performed under neutral conditions, but the substances can be mixed without any activation or modification.

3. Experimental

3.1. General

Melting points were measured on a Büchi 535 apparatus and are uncorrected. Elemental analyses were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were recorded on a Finnigan-Mat 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 Avance spectrometer at 400.13 and 100.77 MHz, respectively. All reagents and solvents used in this work are

commercial materials and were purchased from Merck or Sigma-Aldrich chemical company and used without further purification.

3.1.1. Typical procedure for preparation of dimethyl 5-(*tert*-butylimino)-2-cyano-2-phenyl-2,5-dihydro-3,4-furandicarboxylate (4a)

To a magnetically stirred solution of benzoyl cyanide (0.146 g, 1.1 mmol) and dimethyl acetylenedicarboxylate (0.143 g, 1.0 mmol) in dry benzene (30 mL) was added *tert*-butyl isocyanide (0.084 g, 1 mmol) via a syringe and refluxing was continued for 2 h. The solvent was removed under vacuum and the residue was washed with diethyl ether to give white crystals (0.264 g, 74%). Mp 97–99 °C. IR (KBr) (ν_{max}, cm^{-1}): 2345 (C≡N), 1757, 1730 (2C=O), 1693 (C=N), 1657 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.31 (9H, s, CMe_3), 3.74 and 3.98 (6H, 2s, $2OCH_3$), 7.43–7.54 (5H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 29.65 (CMe_3), 53.06 and 53.27 ($2OCH_3$), 55.91 (N–CMe_3), 83.29 (N≡C–*C*–O), 114.54 (C≡N), 125.91, 128.77, 129.26, 130.62, 132.95 and 138.92 (arom. and C=C), 149.96 (C=N), 159.27 and 161.28 (2C=O). MS (*m*/*z*, %) 356 (M^+, 10), 341 (100), 309 (47), 265 (19), 140 (17), 84 (25), 57 (60). Anal. Calcd for $C_{19}H_{20}N_2O_5$ (356.37): C, 64.04; H, 5.66; N, 7.86%. Found: C, 64.16; H, 5.59; N, 7.93%.

3.1.2. Dimethyl 5-(cyclohexylimino)-2-cyano-2-phenyl-2,5-dihydro-3,4-furandicarboxylate (4b)

White crystals (0.348 g, 91%). Mp 133–135 °C. IR (KBr) (ν_{max}, cm^{-1}): 2350 (C≡N), 1755, 1728 (2C=O), 1686 (C=N), 1645 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.20–1.81 (10H, m, $5CH_2$), 3.66 (1H, m, N–CH), 3.74 and 3.96 (6H, 2s, $2OCH_3$), 7.44–7.55 (5H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.54, 25.26, 25.68, 33.19 and 33.30 ($5CH_2$ of cyclohexyl), 53.23 and 53.53 ($2OCH_3$), 57.25 (N–CH), 82.99 (N≡C–*C*–O), 114.48 (C≡N), 126.03, 129.22, 130.70, 132.87, 137.98 and 139.79 (arom. and C=C), 151.97 (C=N), 159.19 and 161.01 (2C=O). MS (*m*/*z*, %) 382 (M^+, 7), 225 (63), 140 (34), 96 (56), 77 (33), 41 (100). Anal. Calcd for $C_{21}H_{22}N_2O_5$ (382.41): C, 65.96; H, 5.80; N, 7.33%. Found: C, 66.05; H, 5.78; N, 7.25%.

3.1.3. Diethyl 5-(*tert*-butylimino)-2-cyano-2-phenyl-2,5-dihydro-3,4-furandicarboxylate (4c)

White crystals (0.250 g, 65%). Mp 100–102 °C. IR (KBr) (ν_{max}, cm^{-1}): 2350 (C≡N), 1755, 1731 (2C=O), 1688 (C=N), 1646 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.16 and 1.38 (6H, 2t, $^3J_{HH}=7.1$ Hz, $2CH_3$), 1.30 (9H, s, CMe_3), 4.13 and 4.43 (4H, 2q, $^3J_{HH}=7.1$ Hz, $2OCH_2$), 7.45–7.53 (5H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.51 and 14.06 ($2CH_3$), 29.59 (CMe_3), 56.30 ($NCMe_3$), 62.46 and 62.68 ($2OCH_2$), 82.30 (N≡C–C–O), 114.79 (C≡N), 126.29, 129.89, 130.38, 133.29, 137.92 and 139.36 (arom. and C=C), 151.60 (C=N), 158.04 and 160.11 (2C=O). MS (*m*/*z*, %) 384 (M^+, 10), 327 (7), 225 (65), 96 (52), 57 (100), 41 (83). Anal. Calcd for $C_{21}H_{24}N_2O_5$ (384.42): C, 65.61; H, 6.29; N, 7.29%. Found: C, 65.70; H, 6.37; N, 7.20%.

3.1.4. Diethyl 5-(cyclohexylimino)-2-cyano-2-phenyl-2,5-dihydro-3,4-furandicarboxylate (4d)

White crystals (0.292 g, 71%). Mp 92–94 °C. IR (KBr) (ν_{max}, cm^{-1}): IR (KBr) (ν_{max}, cm^{-1}): 2350 (C≡N), 1746, 1730 (2C=O), 1686 (C=N), 1643 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.18 and 1.39 (6H, 2t, $^3J_{HH}=7.1$ Hz, $2CH_3$), 1.16–1.80 (10H, m, $5CH_2$), 3.65 (1H, m, N–CH), 4.18 (2H, ABX_3 system, $^2J_{HH}=10.2$ Hz, $^3J_{HH}=7.1$ Hz, OCH_2), 4.43 (2H, q, $^3J_{HH}=7.1$ Hz, $2OCH_2$), 7.45–7.53 (5H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.66 and 14.02 ($2CH_3$), 24.44, 24.49, 25.61, 33.09 and 33.29 ($5CH_2$ of cyclohexyl), 57.00 (N–CH), 62.53 and 62.82 (OCH_2), 82.87 (N≡C–*C*–O), 114.56 (C≡N), 126.04, 129.14, 130.58, 133.00, 137.86 and 139.63 (arom. and C=C), 151.97 (C=N), 158.65 and 160.60 (2C=O). MS (*m*/*z*, %) 410 (M^+, 6), 364 (8), 313 (10), 239 (47), 167 (30), 140 (19), 97 (23), 69 (75), 41 (100). Anal. Calcd for $C_{23}H_{26}N_2O_5$ (410.46): C, 67.30; H, 6.38; N, 6.82%. Found: C, 67.39; H, 6.25; N, 6.80%.

3.1.5. Dimethyl 5-(*tert*-butylimino)-2-(2-chlorophenyl)-2-cyano-2,5-dihydro-3,4-furandicarboxylate (4e)

White crystals (0.294 g, 75%). Mp 121–123 °C. IR (KBr) (ν_{max}, cm^{-1}): 2350 (C≡N), 1751, 1732 (2C=O), 1687 (C=N), 1648 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.31 (9H, s, CMe_3), 3.75 and 3.97 (6H, 2s, $2OCH_3$), 7.47–8.28 (4H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 29.71 (CMe_3), 53.05 and 53.30 ($2OCH_3$), 56.11 (N–CMe_3), 84.21 (N≡C–*C*–O), 113.61 (C≡N), 127.54, 128.84, 129.89, 131.45, 132.25, 132.36, 137.77 and 139.12 (arom. and C=C), 150.24 (C=N), 159.31 and 161.03 (2C=O). MS (*m*/*z*, %) 390 (M^+, 8), 375 (68), 339 (31), 278 (44), 223 (17), 57 (100), 41 (47). Anal. Calcd for $C_{19}H_{19}ClN_2O_5$ (390.82): C, 58.39; H, 4.90; N, 7.17%. Found: C, 58.44; H, 4.87; N, 7.23%.

3.1.6. Dimethyl 5-(cyclohexylimino)-2-(2-chlorophenyl)-2-cyano-2,5-dihydro-3,4-furandicarboxylate (4f)

White crystals (0.367 g, 88%). Mp 146–148 °C. IR (KBr) (ν_{max}, cm^{-1}): 2347 (C≡N), 1758, 1731 (2C=O), 1685 (C=N), 1641 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.19–1.80 (10H, m, $5CH_2$), 3.67 (1H, m, N–CH), 3.75 and 3.96 (6H, 2s, $2OCH_3$), 7.45–8.25 (4H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 24.53, 25.26, 25.67, 33.20 and 33.30 ($5CH_2$ of cyclohexyl), 53.25 and 53.56 ($2OCH_3$), 57.24 (N–CH), 83.04 (N≡C–*C*–O), 113.98 (C≡N), 127.46, 128.75, 129.91, 131.51, 132.24, 132.36, 137.75 and 139.20 (arom. and C=C), 151.90 (C=N), 159.23 and 161.14 (2C=O). MS (*m*/*z*, %) 416 (M^+, 12), 401 (68), 366 (25), 291 (17), 83 (86), 77 (42), 41 (100). Anal. Calcd for $C_{21}H_{21}ClN_2O_5$ (416.85): C, 60.51; H, 5.08; N, 6.72%. Found: C, 60.59; H, 5.00; N, 6.75%.

3.1.7. Diethyl 5-(*tert*-butylimino)-2-(2-chlorophenyl)-2-cyano-2,5-dihydro-3,4-furandicarboxylate (4g)

White crystals (0.260 g, 62%). Mp 108–110 °C. IR (KBr) (ν_{max}, cm^{-1}): 2348 (C≡N), 1756, 1731 (2C=O), 1686 (C=N), 1643 (C=C). ^1H NMR ($CDCl_3$, Me_4Si): δ_H 1.17 and 1.38 (6H, 2t, $^3J_{HH}=7.1$ Hz, $2CH_3$), 1.31 (9H, s, CMe_3), 4.12 and 4.43 (4H, 2q, $^3J_{HH}=7.1$ Hz, $2OCH_2$), 7.38–8.31

(4H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.56 and 14.10 ($2CH_3$), 29.64 (CMe_3), 56.28 ($NCMe_3$), 62.50 and 62.67 ($2OCH_2$), 83.29 (N≡C–*C*–O), 114.11 (C≡N), 128.11, 128.96, 129.14, 131.43, 132.20, 132.41, 138.04 and 138.74 (arom. and C=C), 149.88 (C=N), 158.21 and 160.03 (2C=O). MS (*m*/*z*, %) 418 (M^+, 5), 391 (88), 336 (25), 262 (18), 125 (23), 57 (100), 41 (46). Anal. Calcd for $C_{21}H_{23}ClN_2O_5$ (418.87): C, 60.22; H, 5.53; N, 6.69%. Found: C, 60.30; H, 5.49; N, 6.65%.

3.1.8. Diethyl 5-(cyclohexylimino)-2-(2-chlorophenyl)-2-cyano-2,5-dihydro-3,4-furandicarboxylate (4h)

White crystals (0.290 g, 65%). Mp 97–99 °C. IR (KBr) (ν_{max}, cm^{-1}): 2354 (C≡N), 1751, 1727 (2C=O), 1682 (C=N), 1643 (C=C). ^{1}H NMR ($CDCl_3$, Me_4Si): δ_H 1.20 and 1.39 (6H, 2t, $^3J_{HH}$=7.1 Hz, $2CH_3$), 1.18–1.81 (10H, m, $5CH_2$), 3.70 (1H, m, N–CH), 3.73 and 3.97 (6H, 2s, $2OCH_3$), 7.39–8.26 (4H, m, arom.). ^{13}C NMR ($CDCl_3$, Me_4Si): δ_C 13.68 and 14.00 ($2CH_3$), 24.54, 25.26, 25.68, 33.19 and 33.29 ($5CH_2$ of cyclohexyl), 53.27 and 53.58 ($2OCH_3$), 57.26 (N–CH), 83.51 (N≡C–*C*–O), 114.08 (C≡N), 127.51, 128.68, 129.90, 131.48, 132.28, 132.37, 137.77 and 139.25 (arom. and C=C), 150.83 (C=N), 159.49 and 161.25 (2C=O). MS (*m*/*z*, %) 444 (M^+, 5), 418 (100), 309 (22), 295 (34), 83 (39), 77 (22), 41 (75). Anal. Calcd for $C_{21}H_{21}ClN_2O_5$ (444.91): C, 62.09; H, 5.66; N, 6.30%. Found: C, 62.02; H, 5.70; N, 6.28%.

References and notes

1. (a) Sheldon, R. A. *Pure Appl. Chem.* **2000**, *72*, 1233–1246. (b) Trost, B. M. *Angew. Chem., Int. Engl. Ed.* **1995**, *34*, 259–281. (c) Trost, B. M. *Science* **1991**, *254*, 1471–1477.
2. (a) Orru, R. V. A.; Greef, M. *Synthesis* **2003**, 1471–1499. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168–3210. (c) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmidt, P. *Chem. Eur. J.* **2000**, *6*, 3321–3329.
3. Ito, Y.; Kato, H.; Saegusa, T. *J. Org. Chem.* **1982**, *47*, 741–743.
4. Winterfeldt, E.; Schumann, D.; Dillinger, H. J. *Chem. Ber.* **1969**, *102*, 1656–1664.
5. Nair, V.; Vinod, A. U.; Abhilash, N.; Menon, R. S.; Santhi, V.; Varma, R. L.; Viji, S.; Mathewa, S.; Srinivas, R. *Tetrahedron* **2003**, *59*, 10279–10286.
6. Chatani, N.; Oshita, M.; Tobisu, M.; Ishii, Y.; Murai, S. *J. Am. Chem. Soc.* **2003**, *125*, 7812–7813.
7. Bez, B.; Zhao, C.-G. *Org. Lett.* **2003**, *5*, 4991–4993.
8. Ma, S.; Xie, H. *J. Org. Chem.* **2002**, *67*, 6575–6578.
9. Ma, S.; Xie, H. *Tetrahedron* **2005**, *61*, 251–258.
10. (a) Teimouri, M. B. *Synth. Commun.* **2005**, *35*, 675–682. (b) Shaabani, A.; Teimouri, M. B.; Samadi, S.; Soleimani, K. *Synth. Commun.* **2005**, *35*, 535–541. (c) Shaabani, A.; Teimouri, M. B.; Arab-Ameri, S. *Tetrahedron Lett.* **2004**, *45*, 8409–8413. (d) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Monatsh. Chem.* **2004**, *135*, 441–446. (e) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Monatsh. Chem.* **2004**, *135*, 589–593. (f) Shaabani, A.; Teimouri, M. B. *J. Chem. Res. (S)* **2003**, 732–733. (g) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *J. Chem. Res. (S)* **2003**, 578–579. (h) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Tetrahedron Lett.* **2002**, *43*, 9151–9154. (i) Shaabani, A.; Teimouri, M. B.; Bijanzadeh, H. R. *J. Chem. Res. (S)* **2002**, 381–383.
11. (a) Teimouri, M. B.; Bazhrang, R. *J. Chem. Res. (S)* **2005**, 50–53. (b) Shaabani, A.; Teimouri, M. B.; Mirzaei, P.; Bijanzadeh, H. R. *J. Chem. Res. (S)* **2003**, 82–83. (c) Shaabani, A.; Bazgir, A.; Teimouri, M. B.; Bijanzadeh, H. R. *Phosphorus Sulfur Silicon* **2002**, *177*, 833–837.
12. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
13. Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033–8061.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1849–1863

Microwave-assisted synthesis and transformations of sterically hindered 3-(5-tetrazolyl)pyridines

Sergey M. Lukyanov,[a,*] Igor V. Bliznets,[b] Sergey V. Shorshnev,[a] Grigory G. Aleksandrov,[a] Aleksandr E. Stepanov[b] and Andrei A. Vasil'ev[c]

[a]*ChemBridge Corporation, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[b]*M.V. Lomonosov Moscow State Academy of Fine Chemical Technology, Malaya Pirogovskaya 1, 119435 Moscow, Russian Federation*
[c]*N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky pr. 47, 119991 Moscow, Russian Federation*

Received 3 August 2005; revised 31 October 2005; accepted 17 November 2005

Available online 13 December 2005

Abstract—Sterically hindered 2,4-disubstituted 3-(5-tetrazolyl)pyridines were synthesized from corresponding nicotinonitriles using microwave technology. 2-Methylnicotinonitriles were converted into the 2-azidomethyl-3-cyanopyridines via 2-hydroxymethyl and 2-chloromethyl derivatives. Intramolecular [3+2] cycloaddition of an heteroaromatic cyano group to side azido group was carried out to form a novel heterocyclic system containing a (tetrazolo)azaisoindole unit. Condensation of the 2-methylnicotinonitriles and aldehydes gave rise to the corresponding 2-vinyl derivatives, which were then transformed into novel heterocyclic system (5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine) by intramolecular N-alkylation reaction of tetrazole ring with olefinic fragment. The 3-(5-tetrazolyl)pyridines obtained were alkylated to give the various *N*- and *C*-benzyl derivatives as well as acylated to afford the 3-(1,3,4-oxadiazol-2-yl)pyridines in good yields. A majority of above-mentioned reactions was carried out under microwave irradiation.

1. Introduction

For a long time 3-(5-tetrazolyl)pyridine **1** and its derivatives have been of particular interest to the chemists because of the interesting pharmacological activity of these compounds[1–5] (Scheme 1). For example, some 3-(5-tetrazolyl)pyridines, substituted in the pyridine moiety, were described as potential lipolysis inhibitors similar to nicotinic acid, but of greater metabolic stability.[2,3,6] Indeed, tetrazole ring is well known as a bioisosteric substitute for the carboxylic group in many biologically active molecules,[7] since they both possess comparable acidity and size[2,3,8] (see also review[9]). On the other hand, related biphenyl derivatives **2** bearing a sterically hindered *ortho*-tetrazole group have been described recently as novel angiotensin II receptor antagonists.[10–12]

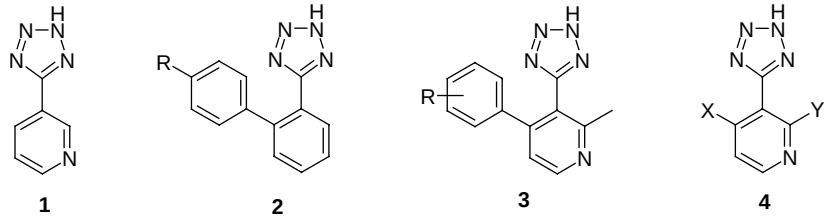
In this context, it would be interesting to synthesize a series of 3-(5-tetrazolyl)pyridines with substituents at both positions adjacent to the tetrazole unit such as 2-alkyl-4-aryl-3-(5-tetrazolyl)pyridines **3** as well as other similar compounds **4** where X is bulk aliphatic group, and Y is alkyl or (FG)–CH_2 (FG=functional group) (Scheme 1). These compounds **3**, **4** could be core structures for some combinatorial libraries based on the nicotinic acid derivatives such as nicotinonitriles.

We reported in our preliminary communication[13] that the corresponding nicotinonitriles **5a–c** (Scheme 2) prepared by the literature method[14] were used as starting materials for syntheses under three different conditions: (a) NaN_3, AcOH, *n*-BuOH;[1] (b) NaN_3, $ZnBr_2$, H_2O;[4,15] (c) Me_3SiN_3, Bu_2SnO, toluene.[11,16] However, only compound **3** (R=H) was obtained from nitrile **5a** in moderate yield using trimethylsilyl azide and dibutyltin oxide (conditions c, 100 °C, 72 h). All attempts to obtain the desired tetrazoles from nitriles **5b**,**c** were ineffective under above-named conditions. It should be noted that these results turned out not surprising for us since many reactions of nitrile group are very susceptible to sterical hindrances (e.g., Pinner reaction). Poor yields of tetrazoles from *ortho*-substituted benzonitriles were also reported.[10,11]

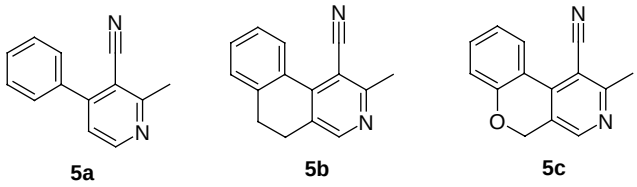
We have found[13] that the sterically hindered 3-(5-tetrazolyl)pyridines **3**, **4** can be successfully synthesized using microwave technology (MW) (see footnote below in Section 4.3.5.3). At that time a synthesis of tetrazoles from some simplest model nitriles under microwave irradiation was described in only one paper.[17] Another investigation on

Keywords: Nicotinic acid; Nicotinonitriles; Tetrazolyl derivatives; 1,3,4-Oxadiazoles; Intramolecular cycloaddition; Fused tetrazoles; Microwave irradiation.
* Corresponding author. Tel.: +7 95 775 06 54; fax: +7 95 956 49 48; e-mail: semiluk@chembridge.ru

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.039



Scheme 1.

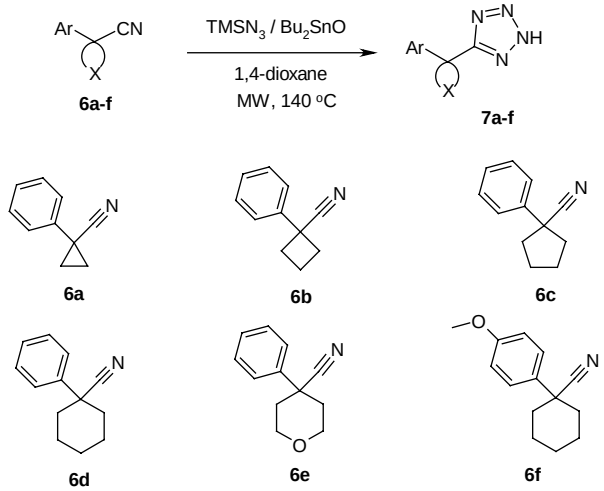


Scheme 2.

the same subject was reported[18] concurrently and independently of our preliminary communication.[13] Now, we describe in more detail not only the synthesis but also transformations of 2,4-disubstituted 3-(5-tetrazolyl)pyridines carried out under microwave irradiation.

2. Results and discussion

Initially, we investigated the reactions of nicotinonitriles **5a–c** as well as a series of model sterically hindered aliphatic nitriles **6a–f** (Scheme 3) under above-mentioned conditions (a–c) using Milestone Ethos SYNTH and CEM Discover microwave labstations. We quickly discovered that an application of NaN_3 was unsuitable for microwave-assisted reactions because of both toxic and explosion risk (conditions a, acid promoted HN_3 liberation) as well as a considerable hydrolysis of the starting nitriles to amides in the presence of water (conditions b). At the same time the reagent system $TMSN_3/Bu_2SnO$ (conditions c) was found to be best with respect to the reproducibility and ease of handling. It should be noted that 1,4-dioxane was used instead of toluene for this reagent system as the solvent more suitable for microwave conditions.



Scheme 3. Synthesis of model tetrazoles **7a–f**.

The optimal reaction conditions were initially determined using the model nitriles **6a–f**. We found that the yields of target products **7a–f** depended considerably on the ratio of reactants, and the optimal molar ratio being 'nitrile/Bu_2SnO/$TMSN_3$ = 1:0.3:4'. The results of the model experiments are presented in Table 1. It is seen that the yields of tetrazoles **7a–f** decreased gradually along with the growth of the carbocycle size. The unreacted nitriles **6a–f** can be isolated from the reaction mixtures; therefore, the yields coincided practically with the conversion of the starting reactants. The yields can be also improved upon by a prolongation of microwave irradiation as well as by an increasing of Bu_2SnO content (entries 5, 8).

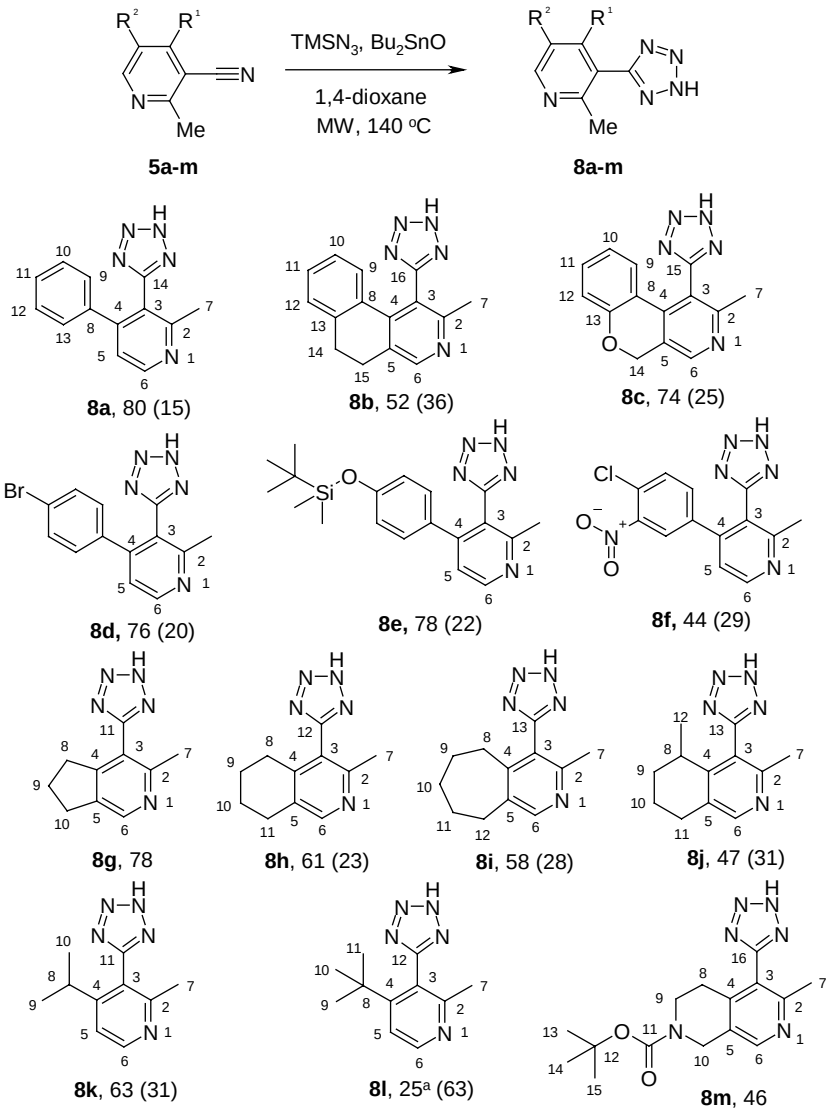
Table 1. Conditions and yields of model tetrazoles **7a–f**

Entry	**6**,**7**	Ar	X	Time (h)	Yield **7** (%)
1	**a**	Ph	$-(CH_2)_2-$	3	100
2	**b**	Ph	$-(CH_2)_3-$	3	90
3	**c**	Ph	$-(CH_2)_4-$	5	84
4	**d**	Ph	$-(CH_2)_5-$	7	38
5	**d**	Ph	$-(CH_2)_5-$	8	89[a]
6	**e**	Ph	$-(CH_2)_2O(CH_2)_2-$	5	83
7	**f**	*p*-$CH_3OC_6H_4$	$-(CH_2)_5-$	9	63
8	**f**	*p*-$CH_3OC_6H_4$	$-(CH_2)_5-$	8	85[a]

[a] Bu_2SnO (1 equiv) used.

These reaction conditions were applied in the preparation of the 2,4-disubstituted 3-(5-tetrazolyl)pyridines **8a–m** from the corresponding nicotinonitriles **5a–m** (Schemes 4 and 5). All the experiments were carried out at 140 °C for 8 h (but only for 4 h at 120 °C for **8m** because of partial thermal deprotection as well as at 110 °C for **8f** owing to resinification).

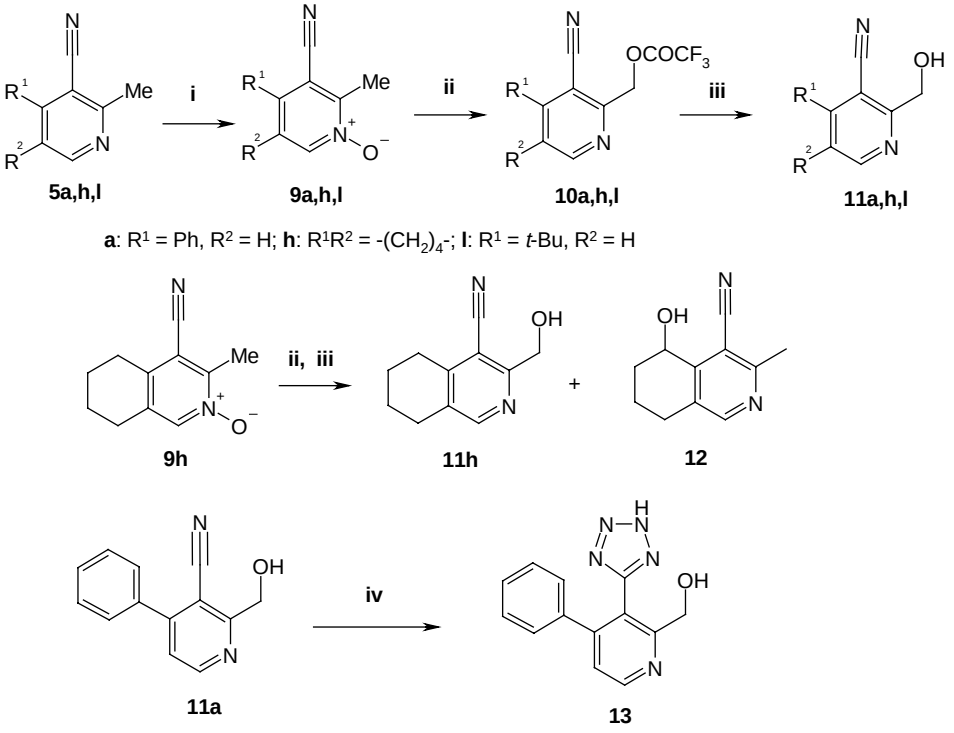
That the 3-(5-tetrazolyl)pyridines **8a–m** obtained may serve as core structures for combinatorial libraries, they should contain two or more functional groups as derivatization points. These groups can be positioned in 4-aryl substituent (e.g., structures **8d–f**) and/or in alkyl (cycloalkyl) group (e.g., structure **8m**). To achieve more diversity and enhance the synthetical potential of the system, it could be of interest to introduce an aliphatic functional group into the core structures. One of these possibilities was a functionalization of the 2-methyl group at pyridine nucleus. It seemed promising to transform the 2-methyl group prior to constructing a tetrazole ring. Therefore, we have chosen a pathway for the functionalization of nicotinonitriles **5**. As we reported in our preliminary communication[19] this functionalisation involved the well-known rearrangement[20] of pyridine *N*-oxides **9a**,**h**,**l** under acylation conditions as a key step. The use of hydrogen peroxide followed by trifluoroacetic anhydride gave rise to labile trifluoroacetates **10a**,**h**,**l** that were converted very



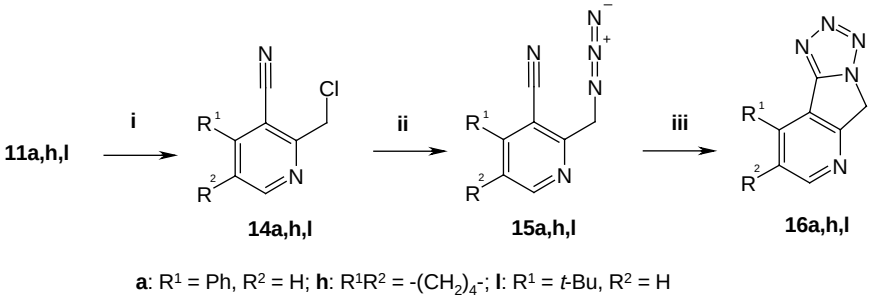
Scheme 4. 3-(5-Tetrazolyl)pyridines **8a**–**m**, yields (%) and recovered starting nitriles (%, in brackets). [a] 1 equiv of Bu_2SnO used.

smoothly into alcohols **11a**,**h**,**l** by treatment with methanol. It should be noted that two isomeric alcohols **11h** and **12** were obtained from the pyridine *N*-oxide **9h** in yields of 23 and 31%, respectively (Scheme 5). Such introduction of a hydroxy group into a 4-alkyl substituent at a pyridine ring has been reported previously.[21] At last, this pathway was successfully accomplished by straightforward conversion of the alcohol **11a** into 2-hydroxymethyl-3-(5-tetrazolyl)pyridine **13** under microwave irradiation (Scheme 5). It is of note that no protection of hydroxyl group was required for this transformation.

Further to this result we carried out an intramolecular reaction between aromatic cyano and side azido groups (Scheme 6). The corresponding 2-azidomethyl-3-cyanopyridines **15a**,**h**,**l** were prepared in two steps from the 2-hydroxymethyl derivatives **11a**,**h**,**l**. Treatment of alcohols **11a**,**h**,**l** with mesyl chloride gave rather the desired 2-chloromethylated intermediates **14a**,**h**,**l** than mesylates. Then 2-azidomethyl-3-cyanopyridines **15a**,**h**,**l** obtained from chlorides were cyclized on heating in the toluene solution at 130–140 °C. It is significant to note that a flexibility of the azidomethyl group is very important for this intramolecular cycloaddition. Therefore, only the azidomethylated intermediate **15h** obtained from compound **11h** underwent smooth cyclization to give the tetracyclic product **16h**. However, no reaction between the fixed cyano and azido groups in azidomethylated isomer prepared from the intermediate **12** occurred under various conditions (heating in sealed tube for several days in toluene at 160 °C or microwave irradiation for 4 h at 150 °C). This result is in accordance with literature data concerning a significance of positional relationship of a nitrile and an azido group for the thermal intramolecular [3+2] cycloaddition. It was reported that the tetrazoles formed under these conditions can be fused only to five- or six-membered ring systems but not to seven-membered cycles.[22] Very few examples of the similar intramolecular tetrazole formation were described in literature. In the most of cases aliphatic[23] and heteroatom-substituted nitriles (cyanates, thiocyanates, cyanamides)[15,22] were used in such cycloaddition while only one example with aromatic nitrile was reported.[24] To the best of our knowledge, such intramolecular cycloaddition in a heterocyclic series was unprecedented.



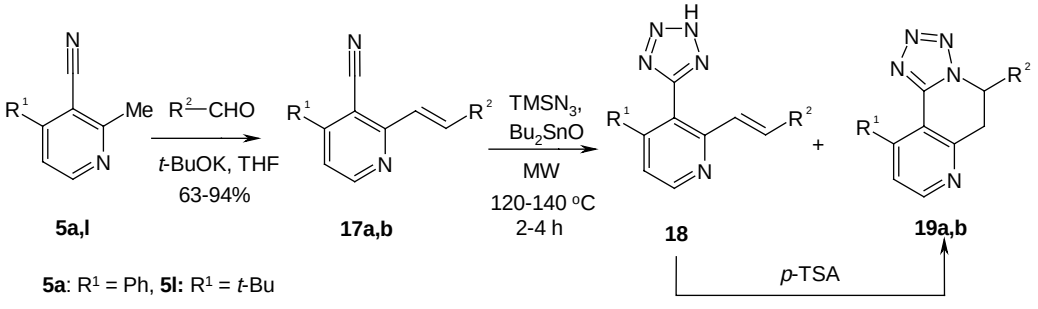
Scheme 5. Functionalization of methyl group in 2-methyl-3-cyanopyridines **5a**,**h**,**l**. Reagents and conditions: (i) H_2O_2, AcOH, 70 °C; (ii) $(CF_3CO)_2O$, CH_2Cl_2, 40 °C; (iii) MeOH, rt; (iv) Me_3SiN_3, Bu_2SnO, dioxane, MW, 140 °C.



Scheme 6. Reaction pathway to tricyclic tetrazolylpyridine system **16a**,**h**,**l**. Reagents and conditions: (i) MsCl, TEA, CH_2Cl_2, rt; (ii) NaN_3, DMSO, rt; (iii) PhMe, MW, 120–140 °C.

It should be noted that the compounds **16a**,**h**,**l** are the first representatives of novel heterocyclic (tetrazolo)azaisoindole system that were initially obtained in our laboratory by refluxing of intermediates **15a**,**h**,**l** in toluene for 90–120 h.[19] More recently we have found that this intramolecular [3+2] cycloaddition can be carried out under microwave irradiation, and the reaction occurred at the same temperature (130–140 °C) for 2–4 h to afford the products **16a**,**l** in yields 80–99%.

The reaction of nicotinonitriles **5** with aldehydes in the presence of potassium *tert*-butoxide was found as another possibility to functionalize the 2-methyl substituent (Scheme 7). The interaction resulted in 2-vinyl derivatives



Scheme 7. Reaction pathway to tricyclic tetrahydro(tetrazolo)naphthyridine system **19a**,**b**.

17a,**b** that were then subjected to tetrazole ring formation from 3-cyano group. The reaction of intermediate **17a** (R^1 = Ph, R^2 = *t*-Bu) under microwave irradiation (140 °C, 2 h) afforded a mixture of two products **18** and **19a** in yields 22 and 52%, respectively. The structure of the tricyclic product **19a** was unequivocally confirmed by X-ray crystallographic analysis (Fig. 1) and manifested an intramolecular N-alkylation of tetrazole moiety with olefinic fragment. There are some reports in literature about similar intermolecular N-alkylation in the presence of strong acids (to convert the olefins into carbocations).[25] Indeed, we succeeded to convert the 2-(3,3-dimethylbut-1-enyl)-3-(5-tetrazolyl)-4-phenylpyridine **18** into the product **19a** using *para*-toluenesulfonic acid. The analogous reaction of the isomeric 2-styryl derivative **17b** (R^1 = *t*-Bu, R^2 = Ph; MW, 140 °C, 4 h) gave the tricyclic product **19b** directly in yield 68%. Therefore, we are inclined to believe that we found a first example of an intramolecular N-alkylation of tetrazoles with olefins under neutral conditions. Further, the obtained 5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridines **19a**,**b** are the representatives of another novel heterocyclic system that could serve not only as a core structure for combinatorial libraries but also as an interesting subject for further investigation.

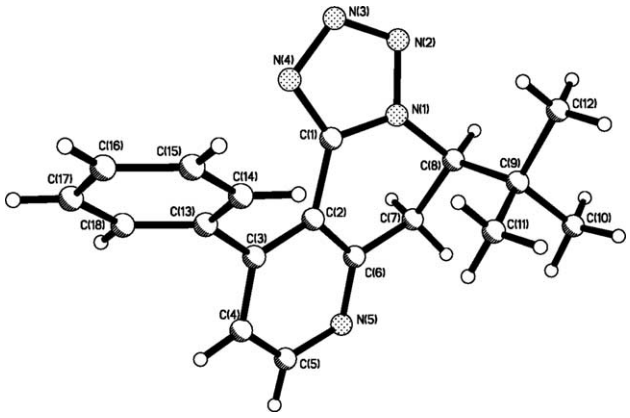


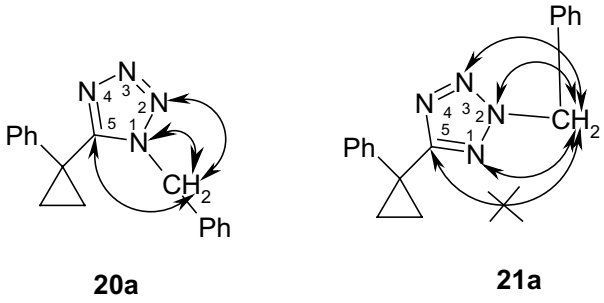
Figure 1. X-ray crystal structure of compound **19a**.

A diversity of above-mentioned potential combinatorial libraries can be extended also by a modification of the tetrazole fragment as such, for example, an alkylation in the presence of bases. This alkylation can yield both 1-alkyl and 2-alkyl substituted tetrazoles.[26] To determine a behavior of sterically hindered tetrazoles in this process, we carried out N-alkylation of the model tetrazoles **7a**–**e** using benzyl bromide as test alkylating reagent (Scheme 8). The yields of isomeric products **20**, **21** are presented in Table 2.

Table 2. Yields of alkylation products **20**, **21**

Entry	**7**, **20**, **21**	X	Yield **20** (%)	Yield **21** (%)
1	**a**	$-(CH_2)_2-$	37	47
2	**b**	$-(CH_2)_3-$	33	58
3	**c**	$-(CH_2)_4-$	23	72
4	**d**	$-(CH_2)_5-$	20	79
5	**e**	$-(CH_2)_2O(CH_2)_2-$	11	79

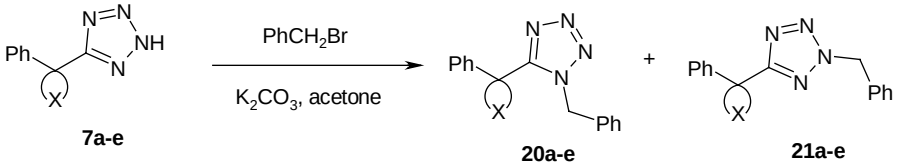
The structures of the isomers **20a** and **21a** were determined by the assignment of the ^1H and ^{13}C NMR spectra involving ^1H ^{13}C HSQC, HMBC and ^1H ^{15}N HMBC experiments. The position of benzyl group at N(1) atom in compound **20a** was established by the cross-peak in the proton-carbon 2D-HMBC spectrum between *N*-methylene protons and C(5) atom of tetrazole ring (Scheme 9). Such cross-peak resulted from a coupling ^3J of these atoms through three bonds. Besides, two cross-peaks were found in the proton-nitrogen 2D-HMBC spectrum resulted from the coupling constants ^2J and ^3J of *N*-methylene protons and the nitrogen nuclei N(1) and N(2) (Scheme 9).



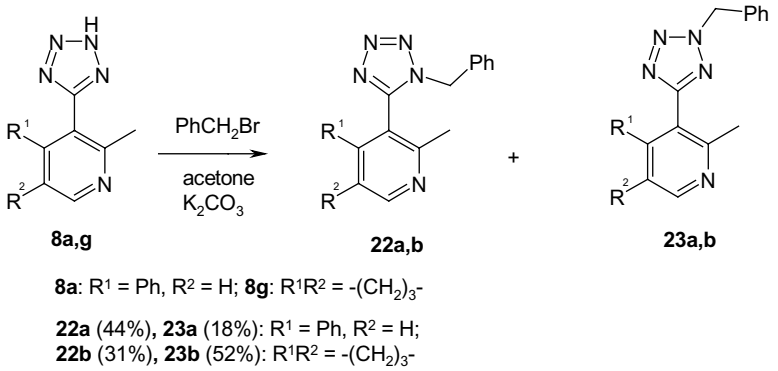
Scheme 9. The proton-carbon and proton-nitrogen couplings in structures **20a** and **21a**.

As regards the compound **21a**, no cross-peak between *N*-methylene protons and C(5) atom of tetrazole ring through four bonds was observed in the ^1H ^{13}C 2D-HMBC spectrum. At the same time three cross-peaks were registered in the ^1H ^{15}N 2D-HMBC spectrum resulted from a coupling of *N*-methylene protons with three nitrogen nuclei N(1), N(2), and N(3) (Scheme 9). These facts indicate the position of benzyl group at N(2) atom of tetrazole moiety.

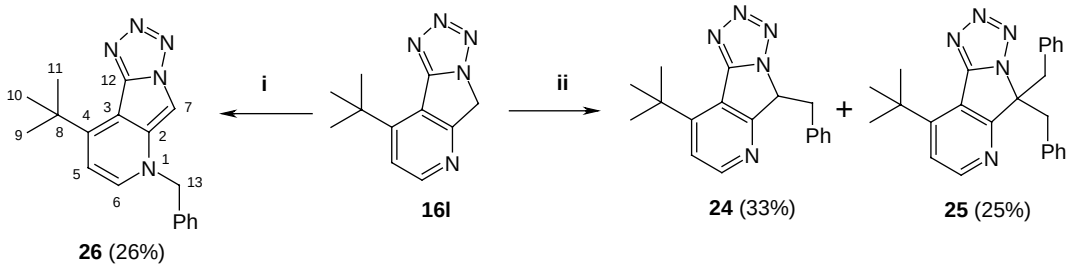
Besides, it should be noted that the signal of the *N*-methylene (i.e., benzylic) protons in ^1H NMR spectrum of compound **21a** was characterized by a low-field chemical shift (δ 5.83 ppm) in comparison with that for compound



Scheme 8. N-Alkylation of model tetrazoles **7a**–**e**.



Scheme 10. N-Alkylation of 3-(5-tetrazolyl)pyridines **8a**,**g**.



Scheme 11. Alkylation of tricyclic compound **16l**. Reagents and conditions: (i) $PhCH_2Br$, acetone, 65 °C, 80 h, then aqueous $NaHCO_3$; (ii) *t*-BuOK, THF, then $PhCH_2Br$.

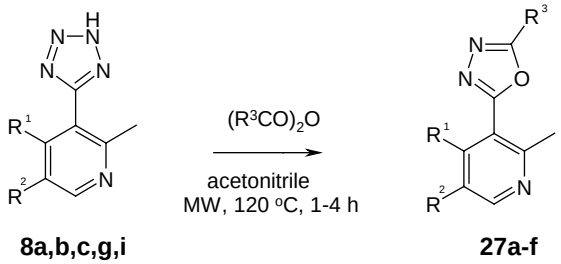
20a (δ 5.38 ppm). Therefore, we distinguished other pairs of isomers **20b**–**e** and **21b**–**e** using this feature of the corresponding ^{1}H NMR spectra.

It is obvious from Table 2 that the N-alkylation of tetrazoles occurred with good yields of products but a fraction of 2-alkylated derivatives **21a**–**e** increased as a carbocycle enlarged. An analogous N-alkylation of the 3-(5-tetrazolyl)pyridines **8a**,**g** gave rise also to mixtures of isomeric products **22a**,**b** and **23a**,**b** (Scheme 10). The structures of the isomers **22a** and **23a** were also determined by the assignment of the ^{1}H and ^{13}C NMR spectra involving ^{1}H ^{13}C HSQC, HMBC and ^{1}H ^{15}N HMBC experiments. The same proton-carbon and proton-nitrogen couplings were registered in the corresponding spectra. It is noteworthy that the signals of benzylic protons in ^{1}H NMR spectra of 2-benzylated isomers **23a**,**b** appeared again as the low-field singlets while the same protons in 1-benzylated compounds **22a**,**b** gave the pairs of high-field doublet signals.

The isomeric *N*-alkylated tetrazoles **20**, **21** as well as **22**, **23** can be effectively separated by column chromatography, with the 2-alkyl derivatives migrating quicker than their 1-isomers.

We have found that the tricyclic compound **16l** can be also subjected to alkylation (Scheme 11). A treatment with benzyl bromide in the presence of potassium *tert*-butoxide in THF resulted in a separable mixture of *C*-benzyl **24** and *C*,*C*-dibenzyl derivative **25**. Alternatively, refluxing of tricyclic compound **16l** with benzyl bromide in acetone followed by treatment with aqueous $NaHCO_3$ afforded a bright red N-alkylation product **26**. The structure **26** was established with the help of ^{1}H and ^{13}C NMR spectra involving HSQC and HMBC experiments.

Finally, tetrazoles can be recyclized into 1,3,4-oxadiazoles by action of acylating reagents.[27] We carried out an acylation of 3-(5-tetrazolyl)pyridines **8a**,**b**,**c**,**g**,**i** with a series of carboxylic anhydrides and obtained the corresponding 3-(1,3,4-oxadiazol-2-yl)pyridines **27a**–**f** in good to excellent yields (Scheme 12) (Table 3). It should be emphasized that this rearrangement under conventional conditions (refluxing in toluene) turned out extremely slow (more than 100 h) and resulted in complicated mixtures of products, and the target 3-(1,3,4-oxadiazol-2-yl)pyridines were isolated from these mixtures in poor yields. However, an application of microwave irradiation and acetonitrile as solvent allowed reduction of the reaction time up to 1–4 h and dramatically increase the yields. To our knowledge, it is a first example of such recyclization under microwave irradiation.



Scheme 12. Recyclization of 3-(5-tetrazolyl)pyridines **8** upon acylation.

Table 3. Yields of 3-(1,3,4-oxadiazol-2-yl)pyridines **27a–f**

8	27	R^1	R^2	R^3	Yield (%)
a	**a**	Ph	H	Me	95
a	**b**	Ph	H	CF_3	100
b	**c**	-*o*-C_6H_4–$(CH_2)_2$–		*t*-Bu	96
c	**d**	*o*-C_6H_4–OCH_2–		$MeO(CH_2)_2$	80
g	**e**	–$(CH_2)_3$–		*i*-Pr	99
i	**f**	–$(CH_2)_5$–		4-Cl–C_6H_4	68

3. Conclusion

In summary, we revealed some possibilities to convert a series of readily available sterically hindered nitriles into the corresponding tetrazole derivatives, including the fused polycyclic systems, using microwave technology. Besides, it was found that the 3-(5-tetrazolyl)pyridines can be derivatized by alkylation and acylation reactions to give a wide variety of nicotinic acid analogs that could constitute a basis for a potential combinatorial library. This library containing 222 compounds was tested by the computer software PASS (prediction of activity spectra for substances).[28] This program illustrates the predicted activity spectrum of a compound as probability of activity (P_a) and probability of inactivity (P_i). For example, it was predicted by the PASS that the tricyclic system **16** can possess an antineurotoxic activity for in all the tested examples with P_a more than 80% as well as all the 3-(5-tetrazolyl)pyridines **8** can be a 5-hydroxytriptamine release inhibitors with P_a more than 70%. Our further investigations will be directed to the synthesis of the compounds with the potential activity predicted, and then to a pharmacological evaluation of the latter.

4. Experimental

4.1. General

Milestone Ethos SYNTH (reactors MPR 600/12S and PRO-24) and CEM Discover microwave labstations (both operating at 2450 MHz under continuous internal temperature control) were used for the experimental and scale-up reactions. Melting points were determined by open glass capillary method and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance DRX 400 (400 MHz) spectrometer equipped with a 5 mm inverse multinuclear gradient probehead in DMSO-d_6 or $CDCl_3$. ^{13}C NMR spectra were recorded on the same instrument at 100 MHz using DMSO-d_6 as solvent. The assignments of signals in ^{1}H and ^{13}C NMR spectra were performed using HSQC and HMBC experiments. Mass spectra were run by electron impact at 70 eV on a Kratos MS-30 spectrometer or by chemical ionization (LCMS) on an 1100 LCMSD (Agilent Technologies) instrument with ELSD (PL-ELS-1000) detector. IR spectra were measured on an EQUINOX 55 Bruker spectrometer. Elemental analyses were carried out in CARLO-ERBA 1106 and 1500 automatic elemental analyzers. Single-crystal X-ray diffraction data were measured using an Enraf-Nonius Cad-4 diffractometer (graphite-monochromated λMo Kα radiation, λ= 0.71073 Å) and processed using the SHELX97 package.[29] The reactions were monitored by TLC (aluminium sheets, silica gel 60 F_{254}, Merck). Merck Kieselgel 60 (230–400 mesh) was used for a column chromatography.

Materials. Starting nicotinonitriles **5** for 3-(5-tetrazolyl)-pyridines **8a–c**, **g–l** have already been described.[14] Nitriles **6a**,**b**,**d**,**f** are commercially available, and compounds **6c** and **6e** were prepared according to literature procedures.[30] 3-Methoxypropanoic, 2-methylpropanoic, and 4-chlorobenzoic anhydrides were synthesized using known procedures.[31]

4.2. General procedure for the preparation of model (1-aryl-cycloalkyl)tetrazoles 7a–f

Dibutyltin oxide (0.75 g, 3 mmol) and trimethylsilyl azide (4.61 g, 5.31 mL, 40 mmol) were added to a solution of nitrile **6** (10 mmol) in anhydrous 1,4-dioxane (10 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed Teflon vessel (70 mL) for 3–8 h at 140 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (80 °C/20 Torr). The residue was dissolved in diethyl ether (30 mL). The product was extracted with 2 N aqueous solution of NaOH (3× 10 mL). The aqueous layer was acidified with 4 N HCl to pH 1 and treated with ethyl acetate (4×10 mL). The organic extract was washed with brine (20 mL), dried over $MgSO_4$, and evaporated under reduced pressure (60 °C/20 Torr) to give the target tetrazole **7a–f** that was recrystallized from ethyl acetate.

4.2.1. 5-(1-Phenylcyclopropyl)-2*H*-tetrazole (7a). Reaction time: 3 h. Yield 100%; colorless needles, mp 176–178 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.43–1.50 (m, 2H, CH_2), 1.50–1.57 (m, 2H, CH_2), 7.26–7.39 (m, 5H, Ph), 15.0–17.0 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.3 (CH_2), 20.4 (CH_2), 127.3, 128.7, 140.2 (Ph), 160.1 (br s, CN_4H). IR $_{max}$ (KBr) 3127, 2996, 2858, 2705, 2599, 2469, 1875, 1566, 1429, 1267, 1044, 935, 701. Analysis found: C, 64.25; H, 5.48; N, 30.05%. Calcd for $C_{10}H_{10}N_4$ (186.22): C, 64.50; H, 5.41; N, 30.09%.

4.2.2. 5-(1-Phenylcyclobutyl)-2*H*-tetrazole (7b). Reaction time: 3 h; yield 90%; white needles, mp 105–108 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.87–2.05 (m, 2H, CH_2), 2.69–2.80 (m, 2H, CH_2), 2.81–2.91 (m, 2H, CH_2), 7.20–7.39 (m, 5H, Ph), 15.3–17.0 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 16.6 (CH_2), 33.6 (CH_2), 43.6 (Ph*C*), 125.8, 126.8, 128.6, 144.8 (Ph), 162.3 (br s, CN_4H). IR ν_{max} (KBr) 3103, 2978, 2859, 2702, 2603, 2486, 1870, 1551, 1411, 1257, 1149, 1038, 745. Analysis found: C, 66.07; H, 6.01; N, 27.94%. Calcd for $C_{11}H_{12}N_4$ (200.25): C, 65.98; H, 6.04; N, 27.98%.

4.2.3. 5-(1-Phenylcyclopentyl)-2*H*-tetrazole (7c). Reaction time: 5 h; yield 84%; colorless needles, mp 151–153 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47–1.61 (m, 2H, CH_2), 1.69–1.82 (m, 2H, CH_2), 2.14–2.26 (m, 2H, CH_2), 2.64–2.75 (m, 2H, CH_2), 7.18–7.35 (m, 5H, Ph), 15.5–16.6 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.8 (CH_2), 37.6 (CH_2), 49.6 (Ph*C*), 126.4, 126.8, 128.6, 144.2 (Ph), 161.4 (br s, CN_4H). IR ν_{max} (KBr) 3097, 2974, 2876, 2699, 2602, 2490, 1876, 1551, 1493, 1412, 1259, 1039, 749.

Analysis found: C, 67.24; H, 6.57; N, 26.09%. Calcd for $C_{12}H_{14}N_4$ (214.27): C, 67.27; H, 6.59; N, 26.15%.

4.2.4. 5-(1-Phenylcyclohexyl)-2*H*-tetrazole (7d). Reaction time: 8 h; yield 38% (89% with 1 equiv of Bu_2SnO); white crystals, mp 156–157 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.20–1.40 (m, 3H, CH_2, 4-H), 1.49–1.58 (m, 1H, 4-H), 1.59–1.70 (m, 2H, CH_2), 2.01–2.13 (m, 2H, CH_2), 2.53–2.63 (m, 2H, CH_2), 7.17–7.24 (m, 3H, Ph), 7.27–7.35 (m, 2H, Ph), 15.5–16.5 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (CH_2), 24.8 (CH_2), 35.4 (CH_2), 41.9 (Ph*C*), 125.7, 126.7, 128.6, 145.5 (Ph), 160.3 (br s, CN_4H). IR ν_{max} (KBr) 3094, 2944, 2857, 2738, 2600, 1812, 1544, 1496, 1448, 1257, 1155, 1040, 893, 747, 700. Analysis found: C, 68.54; H, 7.01; N, 24.68%. Calcd for $C_{13}H_{16}N_4$ (228.30): C, 68.39; H, 7.06; N, 24.54%.

4.2.5. 5-(4-Phenyltetrahydro-2*H*-pyran-4-yl)-2*H*-tetrazole (7e). Reaction time: 5 h; yield 83%; white crystals, mp 141–142 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.21–2.33 (m, 2H, CH_2), 2.58–2.68 (m, 2H, CH_2), 3.26–3.37 (m, 2H, CH_2), 3.79–3.88 (m, 2H, CH_2), 7.21–7.29 (m, 3H, Ph), 7.30–7.38 (m, 2H, Ph), 15.5–16.8 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 35.2 (CH_2), 39.7 (Ph*C*), 63.9 (OCH_2), 125.6, 127.1, 128.8, 144.5 (Ph), 160.3 (br s, CN_4H). IR ν_{max} (KBr) 3106, 2980, 2962, 2865, 2788, 2608, 1545, 1499, 1463, 1397, 1245, 1147, 1106, 1040, 1032, 838, 739, 691. Analysis found: C, 62.65; H, 6.18; N, 24.11%. Calcd for $C_{12}H_{14}N_4O$ (230.27): C, 62.59; H, 6.13; N, 24.33%.

4.2.6. 5-[1-(4-Methoxyphenyl)cyclohexyl]-2*H*-tetrazole (7f). Reaction time: 8 h; yield 63% (85% with 1 equiv of Bu_2SnO); white crystals, mp 188–190 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.18–1.39 (m, 3H, CH_2, 4-H), 1.47–1.56 (m, 1H, 4-H), 1.57–1.68 (m, 2H, CH_2), 1.97–2.10 (m, 2H, CH_2), 2.49–2.60 (m, 2H, CH_2), 3.70 (s, 3H, OCH_3), 6.86 (d, 2H$_{arom}$, J=9 Hz, 3′-H, 5′-H), 7.12 (d, 2H$_{arom}$, J=9 Hz, 2′-H, 6′-H), 15.5–16.5 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (CH_2), 24.9 (CH_2), 35.5 (CH_2), 41.1 (Ph*C*), 55.1 (OCH_3), 113.9, 126.9, 137.4, 157.9 (Ph), 160.8 (br s, CN_4H). IR ν_{max} (KBr) 3100, 2959, 2858, 2606, 1517, 1302, 1265, 1038, 807. Analysis found: C, 65.15; H, 7.04; N, 21.55%. Calcd for $C_{14}H_{18}N_4O$ (258.33): C, 65.09; H, 7.02; N, 21.69%.

4.3. Preparation of the 3-(5-tetrazolyl)pyridines 8a–m

Starting nicotinonitriles **5d–f,m** for 3-(5-tetrazolyl)pyridines **8d–f,m** were prepared according to literature procedure.[14]

4.3.1. 4-(4-Bromophenyl)-2-methylnicotinonitrile (5d). Obtained from 4-bromoacetophenone; yield 79%; creamy crystals, mp 138–140 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.76 (s, 3H, Me), 7.50 (d, 1H, J=5.1 Hz, 5-H), 7.61 (d, 2H$_{arom}$, J=8.6 Hz, 2′-H, 6′-H, Ar), 7.79 (d, 2H$_{arom}$, J=8.6 Hz, 3′-H, 5′-H, Ar), 8.75 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2216 (C≡N).

4.3.2. 4-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methylnicotinonitrile (5e). Obtained from 1-(4{[*tert*-butyl(dimethyl)silyl]oxy}phenyl)ethanone; yield 32%; amber crystals, mp 68–69 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.25 (s, 6H, $Si(CH_3)_2$), 0.98 (s, 9H, $SiC(CH_3)_3$), 2.74 (s, 3H, Me), 7.04 (d, 2H$_{arom}$, J=8.8 Hz, Ar), 7.46 (d, 1H, J=5.1 Hz, 5-H), 7.59 (d, 2H$_{arom}$, J=8.8 Hz, Ar), 8.68 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2224 (C≡N).

4.3.3. 4-(4-Chloro-3-nitrophenyl)-2-methylnicotinonitrile (5f). Obtained from 1-(4-chloro-3-nitrophenyl)ethanone; yield 46%; dark yellow crystals, mp 188–190 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.77 (s, 3H, Me), 7.60 (d, 1H, J=5.1 Hz, 5-H), 8.00–8.04 (m, 2H$_{arom}$, Ar), 8.39–8.42 (m, 1H$_{arom}$, Ar), 8.81 (d, 1H, J=5.1 Hz, 6-H). IR ν_{max} (film) 2223 (C≡N).

4.3.4. *tert*-Butyl 5-cyano-6-methyl-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (5m). Obtained from *tert*-butyl 4-oxopiperidine-1-carboxylate; yield 66%; pale yellow crystals, mp 133–134 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.43 (s, 9H, *t*-Bu), 2.63 (s, 3H, Me), 2.88 (t, 2H, J=5.9 Hz, 5-CH_2), 3.62 (t, 2H, J=5.9 Hz, 6-CH_2), 4.55 (s, 2H, 8-CH_2), 8.54 (s, 1H, 1-H). ^{13}C NMR (DMSO-d_6, δ ppm): 23.1, 26.9, 28.0, 40.2, 42.3, 79.5, 108.2, 115.7, 127.8, 147.4, 150.2, 153.9, 158.7. IR ν_{max} (KBr) 2975, 2870, 2230 (C≡N), 1695 (C=O), 1470, 1420, 1250, 1170, 1120, 920, 765. Mass (*m/z*): 273 (2) $[M]^+$, 216 (16) $[M-C_4H_9]^+$, 200 (13) $[M-C_4H_9O]^+$, 172 (24) $[M-C_4H_9OCO]^+$, 144 (21), 56 (100) $[C_4H_8]^+$, 55 (37). Analysis found: C, 65.98; H, 6.94; N, 15.31%. Calcd for $C_{15}H_{19}N_3O_2$ (273.34): C, 65.91; H, 7.01; N, 15.37%.

4.3.5. General procedure for the preparation of 3-(5-tetrazolyl)pyridines 8a–m. Dibutyltin oxide (0.75 g, 3 mmol) and trimethylsilyl azide (4.61 g, 5.31 mL, 40 mmol) were added to a solution of nitrile **5** (10 mmol) in anhydrous 1,4-dioxane (10 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed Teflon vessel (70 mL) for 8 h at 140 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (60 °C/15 Torr). The residue was dissolved in methanol (20 mL). Silica gel (5 g) was added to the solution, which was then evaporated to dryness. The solid residue was loaded on a top of a chromatography column packed with silica gel, and then eluted with chloroform and later with a gradient system with methanol in chloroform (0→30% v/v). The fractions obtained were concentrated under reduced pressure to give the target products, which were recrystallized from ethyl acetate.

Atom numbering for ^{1}H and ^{13}C NMR spectra below see in Scheme 4.

4.3.5.1. 2-Methyl-4-phenyl-3-(2*H*-tetrazol-5-yl)-pyridine, monohydrate (8a). Yield 80%; white crystals, mp 94–95 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.30 (s, 3H, Me), 7.06–7.13 (m, 2H, Ph), 7.28–7.35 (m, 3H, Ph), 7.44 (d, 1H, J=5.1 Hz, 5-H), 8.72 (d, 1H, J=5.1 Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.9 (CH_3), 119.0 (3-C), 122.2 (5-C), 128.3 (9-C, 13-C), 128.5 (10-C, 12-C), 128.6 (11-C), 137.1 (8-C), 149.9 (4-C), 151.0 (6-C), 152.8 (CN_4H), 157.6 (2-C). IR ν_{max} (film) 3070, 2460, 1940, 1595, 1440, 1240, 1160, 1100, 1060, 1010, 985, 855, 760, 710. Mass (*m/z*): 237 (29) $[M]^+$, 236 (76) $[M-H]^+$, 208 (38) $[M-HN_2]^+$, 194 (100) $[M-HN_3]^+$, 181 (64), 180 (45), 166 (32), 152 (35), 139 (31), 127 (33), 115 (20), 77 (41), 51 (38). Analysis

found: C, 61.11; H, 4.97; N, 27.46%. Calcd for $C_{13}H_{11}N_5$ + H_2O (255.29): C, 61.17; H, 5.13; N, 27.43%.

4.3.5.2. 2-Methyl-1-(2*H*-tetrazol-5-yl)-5,6-dihydrobenzo[*f*]isoquinoline (8b). Yield 52%; creamy crystals, mp 269–270 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.26 (s, 3H, Me), 2.82 (br s, 4H, CH_2–CH_2), 6.20–6.31 (m, 1H, Ph), 6.93–7.04 (m, 1H, Ph), 7.20–7.31 (m, 1H, Ph), 7.33–7.42 (m, 1H, Ph), 8.61 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (CH_3), 25.3 (15-C), 28.4 (14-C), 116.0 (3-C), 126.2 (10-C), 126.6 (12-C), 128.6 (11-C), 129.5 (9-C), 130.5 (8-C), 131.4 (5-C), 140.4 (13-C), 141.9 (4-C), 149.7 (6-C), 153.8 (CN_4H), 156.4 (2-C). IR ν_{max} (film) 2940, 2360, 1960, 1590, 1430, 1390, 1230, 1195, 1105, 1095, 1005, 890, 850, 750. Mass (*m*/*z*): 263 (14) $[M]^+$, 234 (13) $[M-HN_2]^+$, 220 (100) $[M-HN_3]^+$, 207 (18), 190 (14), 165 (19), 77 (10). Analysis found: C, 68.49; H, 4.94; N, 26.61%. Calcd for $C_{15}H_{13}N_5$ (263.30): C, 68.43; H, 4.98; N, 26.60%.

4.3.5.3. 2-Methyl-1-(2*H*-tetrazol-5-yl)-5*H*-chromeno[3,4-*c*]pyridine (8c). The title compound was described[†] in preliminary communication.[13]

4.3.5.4. 4-(4-Bromophenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8d). Yield 76%; pale grey crystals, mp 212–215 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 2.31 (s, 3H, Me), 7.01 (d, 2H, J=8.4 Hz, 2′-H, 6′-H, Ar), 7.45 (d, 1H, J=5.1 Hz, 5-H), 7.52 (d, 2H, J=8.3 Hz, 3′-H, 5′-H, Ar), 8.72 (d, 1H, J=5.1 Hz, 6-H), 15.5–17.3 (br s, 1H, NH). Analysis found: C, 49.19; H, 3.11; Br, 25.25; N, 22.11%. Calcd for $C_{13}H_{10}BrN_5$ (316.16): C, 49.39; H, 3.19; Br, 25.27; N, 22.15%.

4.3.5.5. 4-(4-{[*tert*-Butyl(dimethyl)silyl]oxy}phenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8e). $CHCl_3$/THF system was used for purification; yield 78%; pale yellow crystals, mp 207–210 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 0.16 (s, 6H, $Si(CH_3)_2$), 0.92 (s, 9H, $SiC(CH_3)_3$), 2.28 (s, 3H, Me), 6.77 (d, 2H, J=8.8 Hz, 3′-H, 5′-H, Ar), 6.97 (d, 2H, J=8.8 Hz, 2′-H, 6′-H, Ar), 7.42 (d, 1H, J=5.1 Hz, 5-H), 8.67 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 62.42; H, 7.01; N, 18.69%. Calcd for $C_{19}H_{25}N_5OSi$ (367.53): C, 62.09; H, 6.86; N, 19.06%.

4.3.5.6. 4-(4-Chloro-3-nitrophenyl)-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8f). Yield 44%; pale yellow crystals, mp 107–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.36 (s, 3H, Me), 7.31 (dd, 1H, J=8.4, 2.2 Hz, 6′-H, Ar), 7.53 (d, 1H, J=5.1 Hz, 5-H), 7.71 (d, 1H, J=8.4 Hz, 5′-H, Ar), 7.86 (d, 1H, J=2.2 Hz, 2′-H, Ar), 8.76 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 49.49; H, 3.02; N, 26.93%. Calcd for $C_{13}H_9ClN_6O_2$ (316.71): C, 49.30; H, 2.86; N, 26.54%.

4.3.5.7. 3-Methyl-4-(2*H*-tetrazol-5-yl)-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (8g). Yield 78%; pale brown crystals, mp 225–227 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.97–2.08 (m, 2H, 9-CH_2), 2.44 (s, 3H, Me), 2.84 (t, 2H, J=7.6 Hz, 8-CH_2), 2.95 (t, 2H, J=7.5 Hz, 10-CH_2), 8.48 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.3 (CH_3), 24.6 (9-CH_2), 29.8 (8-CH_2), 32.2 (10-CH_2), 118.2 (3-C), 138.3 (5-C), 144.8 (6-C), 153.4 (2-C), 153.5 (CN_4H), 155.1 (4-C). Mass (*m*/*z*): 201 (37) $[M]^+$, 173 (48) $[M-N_2]^+$, 172 (44) $[M-HN_2]^+$, 158 (62) $[M-HN_3]^+$, 157 (63) $[M-HN_3-H]^+$, 128 (58), 116 (22), 103 (18), 89 (15), 53 (37), 51 (46), 50 (100), 43 (48). Analysis found: C, 59.61; H, 5.68; N, 34.68%. Calcd for $C_{10}H_{11}N_5$ (201.23): C, 59.69; H, 5.51; N, 34.80%.

4.3.5.8. 3-Methyl-4-(2*H*-tetrazol-5-yl)-5,6,7,8-tetrahydroisoquinoline (8h). Yield 61%; pale yellow crystals, mp 220–222 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.59–1.75 (m, 4H, 9-CH_2, 10-CH_2), 2.15 (s, 3H, CH_3), 2.26–2.34 (m, 2H, 8-CH_2), 2.71–2.78 (m, 2H, 11-CH_2), 8.45 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 21.6 (10-CH_2), 21.7 (9-CH_2), 22.2 (CH_3), 25.6 (8-CH_2), 26.3 (11-CH_2), 120.2 (3-C), 130.6 (5-C), 146.0 (4-C), 150.9 (6-C), 152.5 (CN_4H), 153.4 (2-C). Mass (*m*/*z*): 215 (65) $[M]^+$, 187 (52) $[M-N_2]^+$, 186 (42) $[M-HN_2]^+$, 172 (100) $[M-HN_3]^+$, 171 (94) $[M-HN_3-H]^+$, 159 (71), 158 (34), 157 (47), 144 (73), 131 (17), 115 (30), 104 (24), 91 (41), 77 (62), 65 (38), 63 (54), 59 (51), 51 (58). Analysis found: C, 61.37; H, 6.09; N, 32.54%. Calcd for $C_{11}H_{13}N_5$ (215.26): C, 61.38; H, 6.09; N, 32.53%.

4.3.5.9. 3-Methyl-4-(2*H*-tetrazol-5-yl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (8i). Yield 58%; brown crystals, mp 224–226 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.35–1.45 (m, 2H, 9-CH_2), 1.53–1.62 (m, 2H, 11-CH_2), 1.69–1.79 (m, 2H, 10-CH_2), 2.05 (s, 3H, CH_3), 2.27–2.35 (m, 2H, 8-CH_2), 2.75–2.82 (m, 2H, 12-CH_2), 8.26 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (CH_3), 26.5 (9-CH_2), 27.7 (11-CH_2), 31.0 (10-CH_2), 31.6 (8-CH_2), 31.8 (12-CH_2), 122.6 (3-C), 136.0 (5-C), 148.6 (6-C), 151.6 (4-C), 154.7 (2-C), 154.8 (CN_4H). Mass (*m*/*z*): 229 (41) $[M]^+$, 200 (28) $[M-HN_2]^+$, 186 (100) $[M-HN_3]^+$, 172 (79), 159 (33), 145 (37), 144 (75), 132 (18), 115 (20), 101 (15), 91 (38), 77 (32), 59 (41), 57 (38), 43 (31). Analysis found: C, 62.88; H, 6.56; N, 30.45%. Calcd for $C_{12}H_{15}N_5$ (229.29): C, 62.86; H, 6.59; N, 30.54%.

4.3.5.10. 3,5-Dimethyl-4-(2*H*-tetrazol-5-yl)-5,6,7,8-tetrahydroisoquinoline (8j). Yield 47%; white powder, mp 172–174 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.77 (d, 3H, J=7.3 Hz, 12-CH_3), 1.55–1.85 (m, 4H, 9-CH_2, 10-CH_2), 2.10 (s, 3H, 7-CH_3), 2.63–2.89 (m, 3H, 8-H, 11-CH_2), 8.36 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 16.6 (10-CH_2), 21.2 (12-CH_3), 22.2 (7-CH_3), 25.4 (11-CH_2), 28.7 (9-CH_2), 28.8 (8-CH), 119.9 (3-C), 129.7 (5-C), 150.9 (4-C), 151.3 (6-C), 152.7 (CN_4H), 153.8 (2-C). Mass (*m*/*z*): 229 (39) $[M]^+$, 200 (12) $[M-HN_2]^+$, 186 (100) $[M-HN_3]^+$, 185 (38) $[M-HN_3-H]^+$, 172 (38), 156 (24), 144 (34), 130 (16), 114 (16), 102 (16), 91 (25), 76 (21), 59 (84), 57 (64), 43 (42), 42 (35). Analysis found: C, 62.99; H, 6.53; N, 30.46%. Calcd for $C_{12}H_{15}N_5$ (229.29): C, 62.86; H, 6.59; N, 30.54%.

4.3.5.11. 4-Isopropyl-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8k). Yield 63%; light brown crystals, mp 160–163 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.08 (d, 6H, J=6.8 Hz, 9-CH_3, 10-CH_3), 2.15 (s, 3H, 7-CH_3), 2.38 (m, 1H, J=6.8 Hz, 8-CH), 7.40 (d, 1H, J=5.2 Hz,

[†] The authors apologise for inaccuracy in structure **6c** in the communication[13] where oxygen atom was depicted as connected with pyridine ring. This oxygen atom has to be connected with phenyl ring; the correct structure is **8c** in this paper (Scheme 4).

5-H), 8.57 (d, 1H, $J=5.2$ Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.7 (9-CH_3, 10-CH_3), 22.8 (7-CH_3), 30.2 (8-CH), 118.5 (5-C), 119.7 (3-C), 150.8 (6-C), 152.6 (CN_4H), 156.7 (2-C), 157.6 (4-C). Mass (*m*/*z*): 203 (34) $[M]^+$, 174 (17) $[M-HN_2]^+$, 160 (100) $[M-HN_3]^+$, 159 (51) $[M-HN_3-H]^+$, 145 (78), 131 (29), 118 (34), 91 (32), 77 (53), 65 (56), 63 (31), 59 (50), 57 (35), 51 (58). Analysis found: C, 59.11; H, 6.41; N, 34.41%. Calcd for $C_{10}H_{13}N_5$ (203.25): C, 59.10; H, 6.45; N, 34.46%.

4.3.5.12. 4-*tert*-Butyl-2-methyl-3-(2*H*-tetrazol-5-yl)pyridine (8l). Yield 25%; pale yellow crystals, mp 165–167 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.05 (s, 9H, *t*-Bu), 1.98 (s, 3H, CH_3), 7.47 (d, 1H, $J=5.4$ Hz, 5-H), 8.55 (d, 1H, $J=5.4$ Hz, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.8 (7-CH_3), 30.6 (9-CH_3, 10-CH_3, 11-CH_3), 36.1 (8-C), 119.3 (3-C), 119.6 (5-C), 150.8 (6-C), 154.2 (CN_4H), 157.8 (2-C), 159.0 (4-C). Mass (*m*/*z*): 217 (43) $[M]^+$, 202 (14) $[M-NH]^+$, 189 (17) $[M-N_2]^+$, 174 (55) $[M-HN_3]^+$, 160 (61) $[M-t\text{-Bu}]^+$, 159 (100), 145 (43), 132 (29), 118 (14), 91 (21), 77 (36), 57 (31). Analysis found: C, 61.19; H, 7.03; N, 32.58%. Calcd for $C_{11}H_{15}N_5$ (217.28): C, 60.81; H, 6.96; N, 32.23%.

4.3.5.13. *tert*-Butyl-6-methyl-5-(2*H*-tetrazol-5-yl)-3,4-dihydro-2,7-naphthyridine-2(1*H*)-carboxylate (8m). Reaction time 4 h at 120 °C; yield 46%; pale yellow crystals, mp 187–190 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.42 (s, 9H, *t*-Bu), 2.24 (s, 3H, Me), 2.45 (t, 2H, $J=5.7$ Hz, 8-CH_2), 3.49 (t, 2H, $J=5.7$ Hz, 9-CH_2), 4.60 (s, 2H, 10-CH_2), 8.49 (s, 1H, 6-H). ^{13}C NMR (DMSO-d_6, δ ppm): 22.5 (7-CH_3), 26.1 (13-CH_3, 14-CH_3, 15-CH_3), 28.1 (8-C), 40.7 (10-C), 42.7 (9-C), 79.4 (12-C), 120.0 (3-C), 127.7 (5-C), 143.9 (4-C), 148.7 (6-C), 152.3 (CN_4H), 153.9 (11-C), 154.6 (2-C). IR ν_{max} (film) 2970, 2925, 2340, 1920, 1680 (C=O), 1600, 1455, 1420, 1285, 1250, 1165, 1105, 1045, 980, 910, 780. Mass (*m*/*z*): 316 (2) $[M]^+$, 259 (24) $[M-C_4H_9]^+$, 243 (10) $[M-C_4H_9O]^+$, 216 (24) $[M-C_4H_9-HN_3]^+$, 200 (12), 187 (27), 172 (45), 142 (28), 55 (100). Analysis found: C, 56.98; H, 6.41; N, 26.51%. Calcd for $C_{15}H_{20}N_6O_2$ (316.37): C, 56.95; H, 6.37; N, 26.56%.

4.4. Preparation of the 5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridines 15a,h,l

4.4.1. Functionalization of 2-methyl group. General procedure for a conversion **5a**,**h**,**l**→**9a**,**h**,**l**→**10a**,**h**,**l**→**11a**,**h**,**l** was described in preliminary communication (for compound **5a**).[19]

4.4.1.1. 3-Methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile 2-oxide (9h). Yield 94%; pale yellow crystals, mp 135–138 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.62–2.96 (m, 4H, 6-CH_2, 7-CH_2), 2.49 (s, 3H, CH_3), 2.62–2.69 (m, 2H, 5-CH_2), 2.74–2.80 (m, 2H, 8-CH_2), 8.35 (s, 1H, 1-H). IR ν_{max} (film) 2229 (C≡N).

4.4.1.2. 4-*tert*-Butyl-2-methylnicotinonitrile 1-oxide (9l). Yield 50%; pale yellow crystals, mp 147–149 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.44 (s, 9H, $(CH_3)_3$), 2.58 (s, 3H, CH_3), 7.39 (d, 1H, $J=7.1$ Hz, 5-H), 8.44 (d, 1H, $J=7.1$ Hz, 6-H). IR ν_{max} (film) 2227 (C≡N).

4.4.1.3. 3-(Hydroxymethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (11h). Yield 23%; pale yellow crystals, mp 69–72 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.84 (m, 4H, 6-CH_2, 7-CH_2), 2.72–2.77 (m, 2H, 5-CH_2), 2.83–2.88 (m, 2H, 8-CH_2), 4.61 (d, 2H, $J=5.8$ Hz, CH_2OH), 5.50 (t, 1H, $J=5.8$ Hz, OH), 8.46 (s, 1H, 1-H). IR ν_{max} (film) 3217 (OH), 2224 (C≡N).

4.4.1.4. 5-Hydroxy-3-methyl-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (12). Yield 31%; pale yellow crystals, mp 138–140 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.65–1.93 (m, 4H, CH_2), 2.53–2.62 (m, 1H, CH_2), 2.63 (s, 3H, CH_3), 2.72–2.83 (m, 1H, CH_2), 4.72–4.77 (m, 1H, CHOH), 5.56 (d, 1H, $J=5.9$ Hz, OH), 8.46 (s, 1H, 1-H). IR ν_{max} (film) 3187 (OH), 2228 (C≡N).

4.4.1.5. 4-*tert*-Butyl-2-(hydroxymethyl)nicotinonitrile (11l). yield 86%; pale yellow crystals, mp 66–68 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 4.71 (d, 2H, $J=5.6$ Hz, CH_2), 5.46 (t, 1H, $J=5.6$ Hz, OH), 7.49 (d, 1H, $J=5.4$ Hz, 5-H), 8.69 (d, 1H, $J=5.4$ Hz, 6-H). IR ν_{max} (film) 3226 (OH), 2221 (C≡N).

4.4.1.6. [4-Phenyl-3-(2*H*-tetrazol-5-yl)pyridine-2-yl]methanol (13). Dibutyltin oxide (0.046 g, 0.18 mmol) and trimethylsilyl azide (0.33 mL, 2.5 mmol) were added to a solution of nitrile **11a** (0.20 g, 0.95 mmol) in anhydrous 1,4-dioxane (5 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 2 h at 120 °C with stirring then cooled to room temperature. The solvent was removed under reduced pressure (80 °C/20 Torr). The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was mixed with acetonitrile (10 mL). The precipitate was filtered off and recrystallized from methanol to give the titled product **13** (0.13 g, 51%) as white powder, mp 240–242 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 3.01–3.60 (br s, 1H, OH), 4.44 (s, 2H, CH_2), 7.05–7.12 (m, 2H, Ph), 7.28–7.36 (m, 3H, Ph), 7.53 (d, 1H, $J=5.1$ Hz, 5-H), 8.78 (d, 1H, $J=5.1$ Hz, 6-H). Analysis found: C, 60.80; H, 4.50; N, 27.35%. Calcd for $C_{13}H_{11}N_5O+0.2H_2O$ (256.87): C, 60.79; H, 4.47; N, 27.26%.

4.4.1.7. 3-(Chloromethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (14h). Yield 55%; pale yellow glassy mass; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.85 (m, 4H, 2CH_2), 2.74–2.80 (m, 2H, CH_2), 2.85–2.92 (m, 2H, CH_2), 4.84 (s, 2H, CH_2Cl), 8.53 (s, 1H, 6-H).

4.4.1.8. 4-*tert*-Butyl-2-(chloromethyl)nicotinonitrile (14l). Yield 100%; pale yellow glassy mass; ^{1}H NMR (DMSO-d_6, δ ppm): 1.48 (s, 9H, $(CH_3)_3$), 5.74 (s, 2H, CH_2), 7.64 (d, 1H, $J=5.5$ Hz, 5-H), 8.79 (d, 1H, $J=5.5$ Hz, 6-H).

4.4.1.9. 3-(Azidomethyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (15h). Yield 91%; pale yellow crystals, mp 88–90 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.71–1.85 (m, 4H, 2CH_2), 2.74–2.80 (m, 2H, CH_2), 2.85–2.91 (m, 2H, CH_2), 4.63 (s, 2H, CH_2N_3), 8.55 (s, 1H, 6-H). IR ν_{max} (film) 2102 (N_3), 2224 (C≡N).

4.4.1.10. 2-(Azidomethyl)-4-*tert*-butylnicotinonitrile (15l). Yield 65%; pale yellow crystals, mp 65–67 °C; ^{1}H

NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 4.74 (s, 2H, CH_2), 7.57 (d, 1H, $J=5.5$ Hz, 5-H), 8.77 (d, 1H, $J=5.5$ Hz, 6-H). IR ν_{max} (film) 2111 (N_3), 2220 (C≡N).

4.4.2. Intramolecular [3+2] cycloaddition. All the compounds **16a**,**h**,**l** were described in preliminary communication.[19]

4.5. Preparation of the 5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridines 19a,b

4.5.1. 2-[(1*E*)-3,3-Dimethylbut-1-en-1-yl]-4-phenylnicotinonitrile (17a). Potassium *tert*-butoxide (0.34 g, 3 mmol) was added to a solution of 2-methyl-4-phenylnicotinonitrile (0.5 g, 2.57 mmol) in anhydrous THF (5 mL). Trimethylacetic aldehyde (0.29 mL, 2.7 mmol) was added dropwise to this bright red reaction mixture that was then stirred at room temperature for 2 h. The mixture was diluted with water (5 mL) and treated with ethyl acetate (4× 10 mL). The extract was dried over $MgSO_4$ and concentrated under reduced pressure (60 °C/10 Torr). The residue was chromatographed (silica gel, hexane/ethyl acetate 4:1) to give the product **17a** (0.63 g, 94%) as white powder, mp 173–175 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.16 (s, 9H, $(CH_3)_3$), 6.79 (d, 1H, $J=15.4$ Hz, CH=CH), 7.27 (d, 1H, $J=15.4$ Hz, CH=CH), 7.49 (d, 1H, $J=5.1$ Hz, 5-H), 7.54–7.61 (m, 3H, Ph), 7.62–7.69 (m, 2H, Ph), 8.79 (d, 1H, $J=$ 5.1 Hz, 6-H). Analysis found: C, 82.29; H, 6.97; N, 10.59%. Calcd for $C_{18}H_{18}N_2$ (262.36): C, 82.41; H, 6.92; N, 10.68%.

4.5.2. 4-*tert*-Butyl-2-[(*E*)-2-phenylvinyl]nicotinonitrile (17b). Potassium *tert*-butoxide (0.77 g, 6.88 mmol) was added to a solution of 4-*tert*-butyl-2-methylnicotinonitrile (1.0 g, 6.25 mmol) in anhydrous THF (10 mL) at 0 °C. The bright red reaction mixture was stirred at 0 °C for 15 min, and benzaldehyde (0.67 mL, 6.6 mmol) was added dropwise. The mixture was stirred at 0 °C for 10 min then at room temperature for 1 h. The mixture was diluted with water (10 mL) and treated with diethyl ether (4×20 mL). The extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed (silica gel, chloroform) to give the product **17b** (1.03 g, 63%) as white crystals, mp 130–131 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.47 (s, 9H, $(CH_3)_3$), 7.36–7.49 (m, 3H, Ph), 7.41 (d, 1H, $J=5.1$ Hz, 5-H), 7.58 (d, 1H, $J=15.5$ Hz, CH=CH), 7.66–7.72 (m, 2H, Ph), 7.97 (d, 1H, $J=15.5$ Hz, CH=CH), 8.73 (d, 1H, $J=5.1$ Hz, 6-H). Analysis found: C, 82.56; H, 7.12; N, 10.49%. Calcd for $C_{18}H_{18}N_2$ (262.36): C, 82.41; H, 6.92; N, 10.68%.

4.5.3. 5-*tert*-Butyl-10-phenyl-5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine (19a). Dibutyltin oxide (0.068 g, 0.25 mmol) and trimethylsilyl azide (0.4 mL, 3 mmol) were added to a solution of nitrile **17a** (0.20 g, 0.76 mmol) in anhydrous 1,4-dioxane (2 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 2 h at 140 °C with stirring then cooled to room temperature. The solvent was removed to dryness. The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was chromatographed (silica gel, hexane then hexane/ethyl acetate in gradient 2:1–1:100) to give the titled product **19a** (0.12 g, 52%) as white crystals, mp 174–176 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.90 (s, 9H, $(CH_3)_3$), 3.51 (dd, 1H, $J=17.4$, 1.7 Hz, CH_2), 3.80 (dd, 1H, $J=17.4$, 8.1 Hz, CH_2), 4.93 (dd, 1H, $J=8.1$, 1.7 Hz, CH), 7.32–7.40 (m, 3H, Ph), 7.44–7.51 (m, 2H, Ph), 7.48 (d, 1H, $J=5.2$ Hz, 5-H), 8.67 (d, 1H, $J=5.2$ Hz, 6-H). Analysis found: C, 70.68; H, 6.14; N, 22.79%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%. Crystallographic data for compound **19a**: $C_{18}H_{19}N_5$, monoclinic, space group $P2(1)/n$, $a=$ 9.1730(18), $b=9.4000(19)$, $c=18.803(4)$ Å, $\alpha=90°$, $\beta=$ 93.32(3)°, $\gamma=90°$, volume 1618.6(6) Å^3, $T=293(2)$ K, $Z=4$, $D_c=1.253$ Mg/m^3, $\mu=0.078$ mm^{-1}, $\theta_{max}=25.23°$, 3101 reflections measured and 2885 unique ($R_{int}=0.0401$) reflections, full matrix least-squares refinement on F^2, R_1 (obsd)=0.0474, and wR_2 (all data)=0.1333. Crystallographic data (excluding structure factors) for the structure in this paper in the form of a CIF have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 276729. 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].

4.5.4. 2-[(1*E*)-3,3-Dimethylbut-1-en-1-yl]4-phenyl-3-(2*H*-tetrazol-5-yl)pyridine (18). The title compound was also isolated from the reaction mixture (0.05 g, 22%) as white powder, mp 165–167 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 0.96 (s, 9H, $(CH_3)_3$), 5.88 (d, 1H, $J=15.5$ Hz, CH=CH), 6.97 (d, 1H, $J=15.5$ Hz, CH=CH), 7.06–7.12 (m, 2H, Ph), 7.22–7.28 (m, 3H, Ph), 7.34 (d, 1H, $J=5.0$ Hz, 5-H), 8.67 (d, 1H, $J=5.0$ Hz, 6-H). Analysis found: C, 70.84; H, 6.27; N, 22.78%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%.

4.5.5. 10-*tert*-Butyl-5-phenyl-5,6-dihydrotetrazolo[5,1-*f*]-1,6-naphthyridine (19b). Dibutyltin oxide (0.23 g, 0.9 mmol) and trimethylsilyl azide (0.4 mL, 3 mmol) were added to a solution of nitrile **17b** (0.20 g, 0.76 mmol) in anhydrous 1,4-dioxane (2 mL). The reaction mixture was subjected to microwave irradiation in a tightly sealed glass vessel for 4 h at 140 °C with stirring then cooled to room temperature. The solvent was removed to dryness. The residue was treated with methanol (5 mL), and the mixture was evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate 2:1) to give the titled product **19b** (0.16 g, 68%) as pale yellow crystals, mp 175–177 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.56 (s, 9H, $(CH_3)_3$), 3.73 (dd, 1H, $J=16.4$, 5.6 Hz, CH_2), 3.93 (dd, 1H, $J=16.4$, 5.6 Hz, CH_2), 4.93 (t, 1H, $J=5.6$ Hz, CH), 7.07–7.12 (m, 2H, Ph), 7.27–7.37 (m, 3H, Ph), 7.53 (d, 1H, $J=$ 5.5 Hz, 5-H), 8.53 (d, 1H, $J=5.5$ Hz, 6-H). Analysis found: C, 70.84; H, 6.31; N, 22.94%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 22.93%.

4.6. General procedure for alkylation of model tetrazoles 7a–f

Freshly calcined K_2CO_3 (0.15 g, 1.08 mmol) was added to a solution of the tetrazole (1.08 mmol) in acetone (2 mL). The mixture was refluxed under stirring for 2 h, and then benzyl bromide (0.13 mL, 1.13 mmol) was added to the reaction mixture. The latter was refluxed for 6 h then cooled to room temperature, diluted with acetone (10 mL) and filtered. The filtrate was evaporated to dryness. The residue was

chromatographed (silica gel, hexane/ethyl acetate in gradient 4:1 to 3:1) to give the isomeric products.

4.6.1. 1-Benzyl-5-(1-phenylcyclopropyl)-1*H*-tetrazole (20a). Yield 37%; pale yellow oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.42–1.48 (m, 2H, CH_2), 1.48–1.53 (m, 2H, CH_2), 5.38 (s, 2H, $PhCH_2$), 6.92–6.97 (m, 2H, Ph), 7.05–7.10 (m, 2H, Ph), 7.20–7.33 (m, 6H, Ph). ^{13}C NMR (DMSO-d_6, δ ppm): 15.1 (CH_2), 18.6 (Ph*C*), 50.3 (Ph*C*H_2), 126.7, 127.0, 127.8, 128.2, 128.6, 128.8, 133.8, 139.3 (Ph), 157.2 (CN_4H). IR ν_{max} (film) 3444, 3061, 3031, 1602, 1523, 1451, 1333, 1175, 1030, 931, 725, 700. Analysis found: C, 73.75; H, 5.69; N, 20.11%. Calcd for $C_{17}H_{16}N_4$ (276.34): C, 73.89; H, 5.84; N, 20.27%.

4.6.2. 2-Benzyl-5-(1-phenylcyclopropyl)-2*H*-tetrazole (21a). Yield 47%; pale yellow oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.37–1.41 (m, 2H, CH_2), 1.47–1.52 (m, 2H, CH_2), 5.83 (s, 2H, $PhCH_2$), 7.22–7.41 (m, 10H, Ph). ^{13}C NMR (DMSO-d_6, δ ppm): 16.2 (CH_2), 22.1 (Ph*C*), 55.8 (Ph*C*H_2), 126.8, 128.1, 128.3, 128.8, 129.1, 134.2, 140.9 (Ph), 169.9 (CN_4H). IR ν_{max} (film) 3421, 3060, 3031, 1602, 1503, 1454, 1335, 1212, 1057, 1026, 935, 755, 723, 698. Analysis found: C, 73.85; H, 5.97; N, 20.28%. Calcd for $C_{17}H_{16}N_4$ (276.34): C, 73.89; H, 5.84; N, 20.27%.

4.6.3. 1-Benzyl-5-(1-phenylcyclobutyl)-1*H*-tetrazole (20b). Yield 33%; white crystals, mp 108–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.88–2.06 (m, 2H, CH_2), 2.66–2.77 (m, 2H, CH_2), 2.82–2.93 (m, 2H, CH_2), 5.16 (s, 2H, $PhCH_2$), 6.72–6.77 (m, 2H, Ph), 7.16–7.39 (m, 8H, Ph). IR ν_{max} (film) 3420, 3031, 2993, 2947, 2866, 1699, 1493, 1445, 1410, 1306, 1230, 1107, 829, 723, 699. Analysis found: C, 74.18; H, 6.15; N, 18.98%. Calcd for $C_{18}H_{18}N_4$ (290.37): C, 74.46; H, 6.25; N, 19.29%.

4.6.4. 2-Benzyl-5-(1-phenylcyclobutyl)-2*H*-tetrazole (21b). Yield 58%; white crystals, mp 104–106 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.86–2.04 (m, 2H, CH_2), 2.65–2.76 (m, 2H, CH_2), 2.79–2.88 (m, 2H, CH_2), 5.87 (s, 2H, $PhCH_2$), 7.16–7.22 (m, 1H, Ph), 7.24–7.41 (m, 9H, Ph). IR ν_{max} (film) 3445, 3022, 2978, 2939, 2863, 1599, 1550, 1486, 1445, 1320, 1196, 1147, 1077, 1020, 745, 722, 696. Analysis found: C, 74.48; H, 6.31; N, 19.17%. Calcd for $C_{18}H_{18}N_4$ (290.37): C, 74.46; H, 6.25; N, 19.29%.

4.6.5. 1-Benzyl-5-(1-phenylcyclopentyl)-1*H*-tetrazole (20c). Yield 23%; white crystals, mp 85–87 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.62–1.78 (m, 4H, CH_2), 2.25–2.35 (m, 2H, CH_2), 2.41–2.53 (m, 2H, CH_2), 5.14 (s, 2H, $PhCH_2$), 6.70–6.77 (m, 2H, Ph), 7.17–7.30 (m, 6H, Ph), 7.30–7.40 (m, 2H, Ph). IR ν_{max} (film) 3059, 2967, 2873, 1493, 1445, 1409, 1240, 1090, 1030, 748, 726, 703. Analysis found: C, 75.01; H, 6.54; N, 18.48%. Calcd for $C_{19}H_{20}N_4$ (304.40): C, 74.97; H, 6.62; N, 18.41%.

4.6.6. 2-Benzyl-5-(1-phenylcyclopentyl)-2*H*-tetrazole (21c). Yield 72%; white crystals, mp 109–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.44–1.57 (m, 2H, CH_2), 1.67–1.81 (m, 2H, CH_2), 2.09–2.21 (m, 2H, CH_2), 2.65–2.76 (m, 2H, CH_2), 5.87 (s, 2H, $PhCH_2$), 7.14–7.20 (m, 1H, Ph), 7.23–7.33 (m, 6H, Ph), 7.33–7.41 (m, 3H, Ph). IR ν_{max} (film) 3058, 3021, 2961, 2915, 2873, 1598, 1484, 1459, 1382, 1349, 1319, 1189, 1070, 1028, 745, 725, 696. Analysis found: C, 74.89; H, 6.45; N, 18.50%. Calcd for $C_{19}H_{20}N_4$ (304.40): C, 74.97; H, 6.62; N, 18.41%.

4.6.7. 1-Benzyl-5-(1-phenylcyclohexyl)-1*H*-tetrazole (20d). Yield 20%; white crystals, mp 102–103 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.27–1.40 (m, 1H, 4-H), 1.41–1.60 (m, 5H, CH_2, 4-H), 1.97–2.10 (m, 2H, CH_2), 2.41–2.50 (m, 2H, CH_2), 5.10 (s, 2H, $PhCH_2$), 6.72–6.78 (m, 2H, Ph), 7.17–7.21 (m, 2H, Ph), 7.21–7.31 (m, 4H, Ph), 7.31–7.39 (m, 2H, Ph). IR ν_{max} (film) 3063, 3010, 2947, 2926, 2862, 1596, 1492, 1443, 1399, 1278, 1235, 1112, 895, 743, 723, 700. Analysis found: C, 75.51; H, 7.07; N, 17.68%. Calcd for $C_{20}H_{22}N_4$ (318.43): C, 75.44; H, 6.96; N, 17.59%.

4.6.8. 2-Benzyl-5-(1-phenylcyclohexyl)-2*H*-tetrazole (21d). Yield 79%; white crystals, mp 92–93 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.17–1.39 (m, 3H, CH_2, 4-H), 1.46–1.56 (m, 1H, 4-H), 1.56–1.66 (m, 2H, CH_2), 1.96–2.09 (m, 2H, CH_2), 2.54–2.65 (m, 2H, CH_2), 5.91 (s, 2H, $PhCH_2$), 7.13–7.19 (m, 1H, Ph), 7.20–7.31 (m, 6H, Ph), 7.31–7.42 (m, 3H, Ph). IR ν_{max} (film) 3060, 2940, 2861, 1580, 1495, 1452, 1346, 1318, 1185, 1133, 1067, 1026, 895, 743, 724, 692. Analysis found: C, 75.57; H, 6.91; N, 17.69%. Calcd for $C_{20}H_{22}N_4$ (318.43): C, 75.44; H, 6.96; N, 17.59%.

4.6.9. 1-Benzyl-5-(4-phenyltetrahydro-2*H*-pyran-4-yl)-1*H*-tetrazole (20e). Yield 11%; white crystals, mp 113–115 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.19–2.30 (m, 2H, CH_2), 2.37–2.45 (m, 2H, CH_2), 3.66–3.81 (m, 4H, CH_2OCH_2), 4.95 (s, 2H, $PhCH_2$), 6.79–6.85 (m, 2H, Ph), 7.12–7.18 (m, 2H, Ph), 7.22–7.28 (m, 3H, Ph), 7.28–7.40 (m, 3H, Ph). IR ν_{max} (film) 3032, 2956, 2889, 2866, 1597, 1493, 1447, 1412, 1296, 1242, 1201, 1135, 1098, 1025, 922, 749, 721, 697. Analysis found: C, 71.37; H, 6.22; N, 17.29%. Calcd for $C_{19}H_{20}N_4O$ (320.40): C, 71.23; H, 6.29; N, 17.49%.

4.6.10. 2-Benzyl-5-(4-phenyltetrahydro-2*H*-pyran-4-yl)-2*H*-tetrazole (21e). Yield 79%; white crystals, mp 92–94 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.17–2.27 (m, 2H, CH_2), 2.59–2.67 (m, 2H, CH_2), 3.23–3.29 (m, 2H, CH_2), 3.77–3.85 (m, 2H, CH_2), 5.92 (s, 2H, $PhCH_2$), 7.17–7.23 (m, 1H, Ph), 7.25–7.31 (m, 6H, Ph), 7.31–7.41 (m, 3H, Ph). IR ν_{max} (film) 3064, 3035, 2958, 2923, 2845, 2769, 1597, 1462, 1389, 1352, 1246, 1142, 1102, 1037, 933, 742, 721, 692. Analysis found: C, 71.20; H, 6.38; N, 17.52%. Calcd for $C_{19}H_{20}N_4O$ (320.40): C, 71.23; H, 6.29; N, 17.49%.

4.7. General procedure for alkylation of 3-(5-tetrazolyl)pyridines 8a,g

Freshly calcined K_2CO_3 (0.23 g, 1.68 mmol) was added to a solution of the 3-(5-tetrazolyl)pyridine (0.84 mmol) in acetone (2 mL). The mixture was heated in sealed tube at 70 °C under stirring for 2 h, and then benzyl bromide (0.10 mL, 0.84 mmol) was added to the reaction mixture. The latter was refluxed for 4 h then cooled to room temperature, diluted with acetone (10 mL) and filtered. The filtrate was evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 3:1–1:1) to give the isomeric products.

4.7.1. 3-(1-Benzyl-1*H*-tetrazol-5-yl)-2-methyl-4-phenylpyridine (22a). Yield 44%; white crystals, mp 155–157 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 2.98 (s, 3H, Me), 4.42 (d, 1H, J=14.8 Hz, $PhCH_2$), 5.12 (d, 1H, J=14.8 Hz, $PhCH_2$), 6.27–6.77 (m, 2H, Ph), 7.14–7.20 (m, 4H, Ph), 7.21–7.25 (m, 1H, Ph), 7.29–7.39 (m, 3H, Ph), 7.34 (d, 1H, J=5.5 Hz, 5-H), 8.71 (d, 1H, J=5.5 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 22.7 (CH_3), 51.1 (Ph*C*H_2), 118.0, 121.5, 127.8, 128.3, 128.9, 129.0, 129.1, 132.5, 136.5, 150.0, 151.5, 152.1 (Ph), 159.2 (CN_4H). Analysis found: C, 73.38; H, 5.19; N, 21.43%. Calcd for $C_{20}H_{17}N_5$ (327.39): C, 73.37; H, 5.23; N, 21.39%.

4.7.2. 3-(2-Benzyl-2*H*-tetrazol-5-yl)-2-methyl-4-phenylpyridine (23a). Yield 18%; light brown oil; ^{1}H NMR ($CDCl_3$, δ ppm): 2.45 (s, 3H, Me), 5.72 (s, 2H, $PhCH_2$), 7.01–7.06 (m, 2H, Ph), 7.10–7.16 (m, 4H, Ph), 7.18–7.22 (m, 1H, Ph), 7.24 (d, 1H, J=5.1 Hz, 5-H), 7.29–7.37 (m, 3H, Ph), 8.64 (d, 1H, J=5.1 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 23.3 (CH_3), 56.7 (Ph*C*H_2), 122.0, 122.1, 127.8, 128.0, 128.1, 128.5, 129.8, 130.0, 133.3, 138.1, 149.6, 151.2 (Ph), 158.5 (CN_4H), 163.1 (Ph). Analysis found: C, 73.02; H, 5.08; N, 21.28%. Calcd for $C_{20}H_{17}N_5$ (327.39): C, 73.37; H, 5.23; N, 21.39%.

4.7.3. 4-(1-Benzyl-1*H*-tetrazol-5-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (22b). Yield 31%; grey crystals, mp 102–104 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.79–2.10 (m, 3H, CH_2), 1.99 (s, 3H, Me), 2.36–2.46 (m, 1H, CH_2), 2.83–2.97 (m, 2H, CH_2), 5.48 (d, 1H, J=15.2 Hz, $PhCH_2$), 5.57 (d, 1H, J=15.2 Hz, $PhCH_2$), 6.96–7.02 (m, 2H, Ph), 7.24–7.33 (m, 3H, Ph), 8.50 (s, 1H, 6-H). IR ν_{max} (film) 3034, 2962, 2864, 1578, 1495, 1452, 1404, 1240, 1115, 988, 937, 727, 702. Analysis found: C, 70.19; H, 5.88; N, 23.93%. Calcd for $C_{17}H_{17}N_5$ (291.36): C, 70.08; H, 5.88; N, 24.04%.

4.7.4. 4-(2-Benzyl-2*H*-tetrazol-5-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (23b). Yield 52%; brown oil; ^{1}H NMR (DMSO-d_6, δ ppm): 1.97–2.06 (m, 2H, CH_2), 2.54 (s, 3H, Me), 2.89–2.96 (m, 4H, CH_2), 6.04 (s, 2H, $PhCH_2$), 7.34–7.44 (m, 5H, Ph), 8.42 (s, 1H, 6-H). IR ν_{max} (film) 3420, 3033, 2957, 1720, 1581, 1498, 1456, 1437, 1152, 1030, 939, 723, 692. Analysis found: C, 69.83; H, 6.03; N, 23.74%. Calcd for $C_{17}H_{17}N_5$ (291.36): C, 70.08; H, 5.88; N, 24.04%.

4.8. Alkylation of the 5*H*-tetrazolo[1′,5′:1,5]pyrrolo[3,4-*b*]pyridine 16l

4.8.1. 5-Benzyl-9-*tert*-butyl-5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (24). Potassium *tert*-butoxide (0.112 g, 1.0 mmol) was added to a solution of compound **16l** (0.20 g, 1.0 mmol) in anhydrous THF (2 mL) at −10 °C. The ice-cold mixture was stirred for 30 min, and benzyl bromide (0.12 mL, 1.0 mmol) was added to the mixture under stirring. The mixture was then stirred at −10 °C for 3 h and treated with water (2 mL). The product was extracted with ethyl acetate (3×4 mL), the extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed (silica gel, hexane/ethyl acetate 3:1) to give the titled product **24** (0.1 g, 33%) as pale yellow solid, mp 113–114 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 1.43 (s, 9H, *t*-Bu), 3.65 (dd, 1H, J=14.2, 4.5 Hz, CH_2), 3.87 (dd, 1H, J=14.2, 4.5 Hz, CHH_2), 5.72 (t, 1H, J=4.5 Hz, CH), 6.61–6.65 (m, 2H, Ph), 6.93–7.05 (m, 3H, Ph), 7.36 (d, 1H, J=5.4 Hz, 5-H), 8.64 (d, 1H, J=5.4 Hz, 6-H). Analysis found: C, 75.61; H, 6.28; N, 17.70%. Calcd for $C_{18}H_{19}N_5$ (305.39): C, 70.80; H, 6.27; N, 23.00%.

4.8.2. 5,5-Dibenzyl-9-*tert*-butyl-5*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (25). The title compound was also isolated (0.1 g, 25%) as white crystals, mp 195–197 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.12 (s, 9H, *t*-Bu), 3.85 (dd, 4H, J=17.1, 13.8 Hz, $2CH_2$), 6.43–6.48 (m, 4H, Ph), 6.86–6.98 (m, 6H, Ph), 7.38 (d, 1H, J=5.4 Hz, 5-H), 8.81 (d, 1H, J=5.4 Hz, 6-H). Analysis found: C, 75.70; H, 6.59; N, 17.70%. Calcd for $C_{25}H_{25}N_5$ (395.51): C, 75.92; H, 6.37; N, 17.71%.

4.8.3. 6-Benzyl-9-*tert*-butyl-6*H*-tetrazolo[1′,5′:1,5]-pyrrolo[3,4-*b*]pyridine (26). Benzyl bromide (0.024 mL, 0.2 mmol) was added to a solution of compound **16l** (0.04 g, 0.2 mmol) in anhydrous acetone (1 mL). The mixture was heated in sealed tube at 65 °C for 80 h then cooled and diluted with anhydrous ether (1 mL). The precipitate formed was filtered off, washed with cold ether (2 mL) and dried to give an intermediate pyridinium bromide (0.02 g, 29%) as white crystals, mp 175–180 °C (decomp.); ^{1}H NMR (DMSO-d_6, δ ppm): 1.62 (s, 9H, *t*-Bu), 6.01 (s, 2H, CH_2), 6.25 (s, 2H, CH_2), 7.30–7.62 (m, 5H, Ph), 8.29 (d, 1H, J=6.7 Hz, 5-H), 9.20 (d, 1H, J=6.7 Hz, 6-H). The salt obtained was treated with saturated aqueous solution of $NaHCO_3$ (1 mL), and the product was extracted with ethyl acetate (4×1 mL). The extract was evaporated to give the title product (**26**) (0.015 g, 26% for two steps) as deep red crystals, mp 170–175 °C (decomp.); ^{1}H NMR ($CDCl_3$, δ ppm): 1.72 (s, 9H, *t*-Bu), 5.28 (s, 2H, CH_2), 6.69 (d, 1H, J=6.8 Hz, 5-H), 7.27–7.31 (m, 2H, Ph), 7.32 (s, 1H, 7-CH), 7.38–7.45 (m, 3H, Ph), 7.64 (d, 1H, J=6.8 Hz, 6-H). ^{13}C NMR ($CDCl_3$, δ ppm): 28.6 (9-C, 10-C, 11-C), 36.6 (8-C), 58.5 (13-C), 84.8 (7-C), 103.9 (5-C), 104.3 (3-C), 127.9 (Ph), 129.2 (Ph), 129.5 (Ph), 132.4 (Ph), 134.1 (4-C), 137.1 (6-C), 161.3 (2-C), 174.0 (12-C) (atom numbering see Scheme 11). Analysis found: C, 70.42; H, 6.78; N, 22.59%. Calcd for $C_{18}H_{19}N_5$ +0.1 mol Et_2O (312.79): C, 70.65; H, 6.44; N, 22.39%.

4.9. Preparation of 3-(1,3,4-oxadiazol-2-yl)pyridines 27a–f

4.9.1. 2-Methyl-3-(5-methyl-1,3,4-oxadiazol-2-yl)-4-phenylpyridine (27a). Acetic anhydride (0.12 mL, 1.26 mmol) was added to a solution of compound **8a** (0.2 g, 0.84 mmol) in anhydrous acetonitrile (2 mL). The solution was subjected to microwave irradiation in sealed reactor at 120 °C for 1 h. The reaction mixture was evaporated to dryness, the residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27a** (0.2 g, 95%) as white crystals, mp 104–105 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.41 (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 7.16–7.23 (m, 2H, Ph), 7.35–7.42 (m, 3H, Ph), 7.45 (d, 1H, J=5.1 Hz, 5-H), 8.72 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 71.76; H, 5.15; N, 16.69%. Calcd for $C_{15}H_{13}N_3O$ (251.29): C, 71.70; H, 5.21; N, 16.72%.

4.9.2. 2-Methyl-4-phenyl-3-[5-(trifluoromethyl)-1,3,4-oxadiazol-2-yl]pyridine (27b). Trifluoroacetic anhydride (0.23 mL, 1.68 mmol) was added to a solution of compound **8a** (0.2 g, 0.84 mmol) in anhydrous acetonitrile (2 mL). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure to dryness. The residue was treated with saturated aqueous solution of $NaHCO_3$ (3 mL), the mixture was extracted with ethyl acetate (4× 5 mL). The extract was dried over $MgSO_4$ and evaporated. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27b** (0.32 g, 100%) as white solid, mp 109–110 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.65 (s, 3H, CH_3), 7.15–7.22 (m, 2H, Ph), 7.37–7.45 (m, 3H, Ph), 7.52 (d, 1H, J=5.1 Hz, 5-H), 8.80 (d, 1H, J=5.1 Hz, 6-H). Analysis found: C, 58.98; H, 3.24; F, 18.53; N, 13.71%. Calcd for $C_{15}H_{10}F_3N_3O$ (305.26): C, 59.02; H, 3.30; F, 18.67; N, 13.77%.

4.9.3. 1-(5-*tert*-Butyl-1,3,4-oxadiazol-2-yl)-2-methyl-5,6-dihydrobenzo[*f*]isoquinoline (27c). 2,2-Dimethylpropanoic anhydride (0.16 g, 0.84 mmol) was added to a suspension of compound **8b** (0.2 g, 0.76 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. Additional 2,2-dimethylpropanoic anhydride (0.16 g, 0.84 mmol) was added to the mixture that then irradiated at the same temperature for 2 h again. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (5 mL), and the mixture was extracted with ethyl acetate (4×5 mL). The extract was washed with brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:1) to give the target product **27c** (0.23 g, 96%) as light creamy crystals, mp 110–111 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 1.31 (s, 9H, $(CH_3)_3$), 2.45 (s, 3H, CH_3), 2.77–2.88 (m, 4H, CH_2), 6.46 (m, 1H, Ph), 7.12 (m, 1H, Ph), 7.31 (m, 1H, Ph), 7.39 (m, 1H, Ph), 8.63 (s, 1H, 6-H). Analysis found: C, 75.11; H, 6.64; N, 13.14%. Calcd for $C_{20}H_{21}N_3O$ (319.41): C, 75.21; H, 6.63; N, 13.16%.

4.9.4. 1-[5-(2-Methoxyethyl)-1,3,4-oxadiazol-2-yl]-2-methyl-5*H*-chromeno[3,4-*c*]pyridine (27d). 3-Methoxypropanoic anhydride (0.16 g, 0.84 mmol) was added to a suspension of compound **8c** (0.2 g, 0.75 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. Additional 3-methoxypropanoic anhydride (0.08 g, 0.42 mmol) was added to the mixture that then irradiated at the same temperature for 1 h again. The reaction mixture was poured into saturated aqueous solution of $NaHCO_3$ (5 mL), and the mixture was extracted with ethyl acetate (4×5 mL). The extract was washed with brine (10 mL), dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:100) to give the target product **27d** (0.2 g, 80%) as light yellow crystals, mp 89–91 °C; ^{1}H NMR (DMSO-d_6, δ ppm): 2.38 (s, 3H, CH_3), 3.22 (t, 2H, J= 6.2 Hz, CH_2CH_2O), 3.25 (s, 3H, CH_3O), 3.69 (t, 2H, J= 6.2 Hz, CH_2–CH_2O), 5.17 (s, 2H, CH_2O, dihydropyrane ring), 6.45 (m, 1H, Ph), 6.90 (m, 1H, Ph), 7.11 (m, 1H, Ph), 7.38 (m, 1H, Ph), 8.67 (s, 1H, 6-H). Analysis found: C, 66.75; H, 5.13; N, 12.83%. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00%.

4.9.5. 4-(5-Isopropyl-1,3,4-oxadiazol-2-yl)-3-methyl-6,7-dihydro-5*H*-cyclopenta[*c*]pyridine (27e). 2-Methylpropanoic anhydride (0.25 mL, 1.5 mmol) was added to a solution of compound **8g** (0.20 g, 1.0 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 2 h. The reaction mixture was evaporated to dryness, and the residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 7:3–1:100) to give the target product **27e** (0.24 g, 99%) as dark brown oil; ^{1}H NMR ($CDCl_3$, δ ppm): 1.46 (d, 6H, J=7.1 Hz, $CH(CH_3)_2$), 2.16 (m, 2H, J=7.6 Hz, CH_2), 2.80 (s, 3H, Me), 3.00 (t, 2H, J=7.6 Hz, CH_2), 3.18 (t, 2H, J=7.6 Hz, CH_2), 3.30 (m, 1H, J=7.1 Hz, $CH(CH_3)_2$), 8.45 (s, 1H, 6-H). Analysis found: C, 69.04; H, 6.95; N, 17.27%. Calcd for $C_{14}H_{17}N_3O$ (243.31): C, 69.11; H, 7.04; N, 17.27%.

4.9.6. 4-[5-(4-Chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-methyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*c*]pyridine (27f). 4-Chlorobenzoic anhydride (0.31 g, 1.05 mmol) was added to a suspension of compound **8i** (0.2 g, 0.87 mmol) in anhydrous acetonitrile (2 mL). The mixture was subjected to microwave irradiation in sealed reactor at 120 °C for 3 h. The reaction mixture was evaporated to dryness, and the residue was treated with saturated aqueous solution of $NaHCO_3$ (5 mL). The mixture was extracted with ethyl acetate (4×5 mL). The extract was dried over $MgSO_4$ and evaporated to dryness. The residue was chromatographed (silica gel, hexane/ethyl acetate in gradient 2:1–1:100) to give the target product **27f** (0.2 g, 68%) as light yellow crystals, mp 105–107 °C; ^{1}H NMR ($CDCl_3$, δ ppm): 1.60 (m, 4H, $(CH_2)_2$), 1.82–1.91 (m, 2H, CH_2), 2.49 (s, 3H, Me), 2.64–2.70 (m, 2H, CH_2), 2.83–2.90 (m, 2H, CH_2), 7.52 (d, 2H, J=8.6 Hz, Ph), 8.04 (d, 2H, J=8.6 Hz, Ph), 8.38 (s, 1H, 6-H). Analysis found: C, 67.18; H, 5.37; Cl, 10.46; N, 12.24%. Calcd for $C_{19}H_{18}ClN_3O$ (339.83): C, 67.16; H, 5.34; Cl, 10.43; N, 12.37%.

References and notes

1. McManus, J. M.; Herbst, R. M. *J. Org. Chem.* **1959**, *24*, 1462–1464.
2. Holland, G. F.; Pereira, J. N. *J. Med. Chem.* **1967**, *10*, 149–154.
3. Butler, R. N.; Garvin, V. C. *J. Chem. Res. (S)* **1982**, 122–123.
4. Demko, Z. P.; Sharpless, K. B. *J. Org. Chem.* **2001**, *66*, 7945–7950.
5. Moltzen, E. K.; Pedersen, H.; Bøgesø, K. P.; Meier, E.; Frederiksen, K.; Sánchez, C.; Lembøl, H. L. *J. Med. Chem.* **1994**, *24*, 4085–4099.
6. Wittenberger, S. J. *Org. Prep. Proced. Int.* **1994**, *26*, 499–531.
7. Thornber, C. W. *Chem. Soc. Rev.* **1979**, *8*, 563–580.
8. Butler, R. N. *Adv. Heterocycl. Chem.* **1977**, *21*, 323–425.
9. Herr, R. J. *Bioorg. Med. Chem.* **2002**, *10*, 3379–3393.
10. Duncia, J. V.; Pierce, M. E.; Santella, J. B., III *J. Org. Chem.* **1991**, *56*, 2395–2400.
11. Wittenberger, S. J.; Donner, B. G. *J. Org. Chem.* **1993**, *58*, 4139–4141.
12. Russell, R. K.; Murray, W. V. *J. Org. Chem.* **1993**, *58*, 5023–5024.

13. Bliznets, I. V.; Vasil'ev, A. A.; Shorshnev, S. V.; Stepanov, A. E.; Lukyanov, S. M. *Tetrahedron Lett.* **2004**, *45*, 2571–2573.
14. Katritzky, A. R.; Denisenko, A.; Arend, M. *J. Org. Chem.* **1999**, *64*, 6076–6079.
15. Himo, F.; Demko, Z. P.; Noodleman, L.; Sharpless, K. B. *J. Am. Chem. Soc.* **2003**, *125*, 9983–9987.
16. Ek, F.; Manner, S.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* **2004**, *69*, 1346–1352.
17. Alterman, M.; Hallberg, A. *J. Org. Chem.* **2000**, *65*, 7984–7989.
18. Schulz, M. J.; Coats, S. J.; Hlasta, D. J. *Org. Lett.* **2004**, *6*, 3265–3268.
19. Bliznets, I. V.; Shorshnev, S. V.; Aleksandrov, G. G.; Stepanov, A. E.; Lukyanov, S. M. *Tetrahedron Lett.* **2004**, *45*, 9127–9130.
20. (a) Fontenas, C.; Bejan, E.; Haddou, H. A.; Balavoine, G. G. A. *Synth. Commun.* **1995**, *25*, 629–633. (b) Mayer, P.; Loubat, C.; Imbert, T. *Heterocycles* **1998**, *48*, 2529–2534.
21. (a) Furukawa, S *J. Pharm. Soc. Jpn.* **1956**, *76*, 900–902; *Chem. Abstr.* **1957**, *51*, 2770b. (b) Epsztajn, J.; Bieniek, A. *J. Chem. Soc., Perkin Trans. 1* **1985**, 213–220. (c) Nicolaou, K. C.; Hwang, C.-K.; Smith, A. L.; Wendeborn, S. V. *J. Am. Chem. Soc.* **1990**, *112*, 7416–7418. (d) Nicolaou, K. C.; Smith, A. L.; Wendeborn, S. V.; Hwang, C.-K. *J. Am. Chem. Soc.* **1991**, *113*, 3106–3114. (e) Nicolaou, K. C.; Maligres, P.; Suzuki, T.; Wendeborn, S. V.; Dai, W.-M.; Chadha, R. K. *J. Am. Chem. Soc.* **1992**, *114*, 8890–8907. (f) Nicolaou, K. C.; Dai, W.-M. *J. Am. Chem. Soc.* **1992**, *114*, 8908–8921.
22. (a) Demko, Z. P.; Sharpless, K. B. *Org. Lett.* **2001**, *3*, 4091–4094. (b) Himo, F.; Demko, Z. P.; Noodleman, L. *J. Org. Chem.* **2003**, *68*, 9076–9080.
23. (a) Földi, Z. (Chinoin) U.S. Patent 2,020,937, 1936; *Chem. Abstr.* **1936**, *30*, 575[1]; see also *Chem. Abstr.* **1935**, *29*, 5995[1]. (b) Bruché, L.; Garanti, L.; Zecchi, G. *J. Chem. Res. (S)* **1983**, 202–203.
24. (a) Voitenko, Z. V.; Yegorova, T. V.; Kysil, A. I.; Andre, C.; Wolf, J. G. *Tetrahedron* **2004**, *60*, 195–201. (b) Babichev, F. S.; Romanov, N. N. *Ukr. Khim. Zh.* **1973**, *39*, 49–52.
25. (a) Myznikov, L. V.; Artamonova, T. V.; Koldobsky, G. I.; Grabalek, A. *Zh. Org. Khim.* **2004**, *40*, 580–583. (b) Koren, A. O.; Gaponik, P. N. *Khim. Geterocycl. Soedin.* **1991**, 1280–1281.
26. Butler, R. N. In Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996; Vol. 4, pp 621–678.
27. Moderhack, D. *J. Prakt. Chem.* **1998**, *340*, 687–709.
28. (a) Poroikov, V. V.; Filimonov, D. A.; Ihlenfeldt, W. D.; Gloriozova, T. A.; Lagunin, A. A.; Borodina, Yu. V.; Stepanchikova, A. V.; Nicklaus, M. C. *J. Chem. Inf. Comput. Sci.* **2003**, *43*, 228–236. (b) Stepanchikova, A. V.; Laginin, A. A.; Filimonov, D. A.; Poroikov, V. V. *Curr. Med. Chem.* **2003**, *10*, 225–233.
29. Sheldrick, G. M., *SHELX97*, Program for the Solution and for the Refinement of Crystal Structures, Göttingen University: Göttingen, Germany, 1997.
30. Butler, D. E.; Pollatz, J. C. *J. Org. Chem.* **1971**, *36*, 1308–1309.
31. Allen, C. F. H.; Kibler, C. J.; McLachlin, D. M.; Wilson, C. V. *Org. Synth.* **1946**, *26*, 1–3.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron 62 (2006) 1864–1876
Tetrahedron

Asymmetric transfer hydrogenation of α,β-unsaturated, α-tosyloxy and α-substituted ketones

Philip Peach,[a] David J. Cross,[a] Jennifer A. Kenny,[a] Inderjit Mann,[b] Ian Houson,[c] Lynne Campbell,[c] Tim Walsgrove[b] and Martin Wills[a,*]

[a]*Department of Chemistry, University of Warwick, Coventry CV4 7AL, UK*
[b]*GlaxoSmithKline Pharmaceuticals, Old Powder Mills, Nr. Leigh Tonbridge, Kent TN11 9AN, UK*
[c]*Avecia Huddersfield Works, PO Box A38, Leeds Road, Huddersfield, Yorkshire HD2 1FF, UK*

Received 22 July 2005; revised 31 October 2005; accepted 17 November 2005

Available online 13 December 2005

Abstract—Asymmetric transfer hydrogenation of cyclic and acyclic α,β-unsaturated ketones catalysed by η^6-*p*-cymene/ruthenium(II) and η^5-pentamethylcyclopentadienyl/rhodium(III) complexes have been investigated. Cyclic α,β-unsaturated ketones appeared to be more suitable substrates for the synthesis of enantiomerically pure allylic alcohols than do acyclic α,β-unsaturated ketones. A proposed mechanism for the formation of 4-phenyl-[1,3]-dioxolan-2-one from α-tosyloxy- and halo-substituted acetophenones is discussed. The results of further investigations into the reduction of a range of α-tosyloxyacetophenones and the dynamic kinetic resolution of α-substituted ketones is presented.

1. Introduction

Asymmetric transfer hydrogenation (ATH) is a valuable synthetic tool for the catalytic asymmetric reduction of ketones and imines.[1] The extension of this methodology to the preparation of a wide range of enantiomerically pure secondary alcohols and amines, has resulted from the introduction of highly active and enantioselective η^5-pentamethylcyclopentadienyl/rhodium(III) and η^6-arene/ruthenium(II) complexes of monotosylated 1,2-diamines such as **1** (in propan-2-ol or formic acid) or β-amino alcohols such as **2** (in propan-2-ol).[2,3] Most of the reductions catalysed by these systems involve the synthesis of chiral, non racemic benzylic alcohols;[4] mainly substituted aryl/alkyl alcohols,[2a–c,3a] or aryl/substituted alkyl alcohols.[2h,3c,5,6]

However, very few reports have appeared on the reduction of conjugated ketonic substrates via asymmetric transfer hydrogenation.[7] With the exception of Noyori's propargylic ketone reductions[7a] and their synthetic applications,[8] these studies focus mainly on the reduction of cyclic α,β-unsaturated ketones,[7b–e] which give consistently better results than acyclic substrates. The effective kinetic resolution of racemic secondary allylic alcohols, reported by Noyori et al. affords also better enantioselectivity with cyclic substrates than acyclic substrates.[9]

This may reflect a preference for hydride transfer to occur via a 1,2-reduction mechanism for a cyclic enone due to geometric restraint (i.e., enforced *s*-trans conformation). In contrast, acyclic enones have a less rigid structure that may allow a 1,4-reduction to take place and so to compete with the 1,2-reduction pathway (Fig. 1).

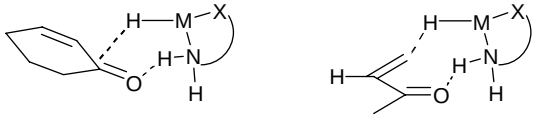
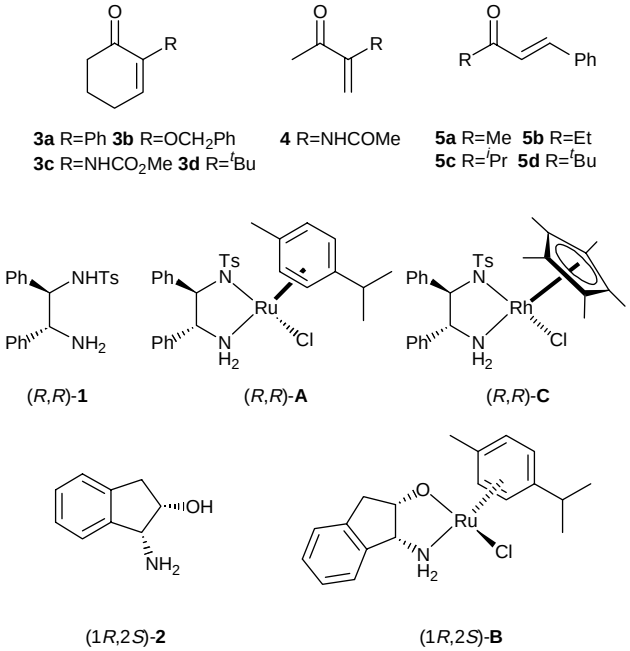


Figure 1. Preferred reduction pathway according to the nature of the substrate structure (M=metal; X=O or NTs; auxiliary ligands are omitted for clarity).

We examined the reduction of cyclic and acyclic α,β-unsaturated ketones **3**–**5** by ATH using well-established catalysts **A**–**C**.[10] Some of the results have been presented in a preliminary paper.[7e] The catalytic systems were prepared in situ in the reaction mixture by combination of the dimers $[RuCl_2(p\text{-cymene})]_2$ or $[RhCl_2(\text{pentamethylcyclopentadiene})]_2$ with the appropriate ligand (*R*,*R*)-**1** or (1*R*,2*R*)-**2**.[2c,2f,3a]

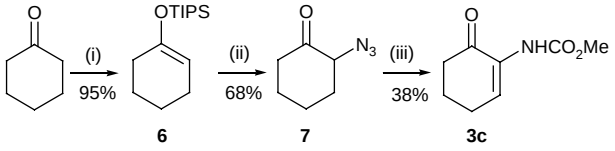
Keywords: Asymmetric; Ketone; Reduction; Hydrogenation; Transfer; Ruthenium.
* Corresponding author. Tel.: +44 2476523260; fax: +44 2476524112; e-mail: m.wills@warwick.ac.uk

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.036



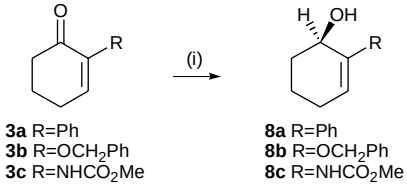
2. Results and discussion

Unsaturated ketone **3a** was prepared by allylic oxidation of 1-phenyl-cyclohexene using a 1:1 molar combination of *tert*-butyl hydroperoxide and pyridinium dichromate.[11] Ether **3b** was obtained by treatment of 1,2-cyclohexanedione with benzyloxy trimethylsilane in the presence of a catalytic amount of trifluoromethanesulphonic acid.[12] Ketone **3c** was synthesised in three steps from commercially available cyclohexanone (Scheme 1) via silyl enol ether **6**.[13] Oxidative azidation of **6** gave the 2-azido-cyclohexan-1-one **7**.[14,15] The last step of the synthesis of **3c** from **7**, required heating in methyl chloroformate in the presence of a catalytic amount of trifluoroacetic acid and sodium perrhenate. The last cyclic enone **3d** bearing a *tert*-butyl group was obtained by addition of ^{t}BuLi to 7-oxabicyclo [4.1.0]heptan-2-one, followed by water elimination.[16]



Scheme 1. Synthesis of cyclic α,β-unsaturated ketone **3c**. Conditions: (i) TIPS triflate (1.1 equiv), Et_3N (2.0 equiv), CH_2Cl_2, 0 °C, 1 h; (ii) NaN_3 (4.5 equiv), $(NH_4)_2Ce(NO_3)_6$ (3.0 equiv), MeCN, −20 °C, 1.5 h; (iii) $NaReO_4$ (1 mol%), TFA (1 mol%), $ClCO_2Me$, 55 °C, 6 h.

Enone **3a** was selectively reduced at the carbonyl moiety by either catalyst (*R*,*R*)-**A** or (1*R*,2*S*)-**B** to the corresponding allylic alcohol **8a** (Scheme 2), in modest yields and ees (Table 1, entry 1 and 2). In neither case was 1,4-reduction product observed in the crude reaction mixture although some unreacted starting material was recovered. Replacement of the α-aryl group of **3a** by a benzyloxy group (**3b**) does not influence the regioselectivity of catalyst (*R*,*R*)-**A** towards the carbonyl moiety. Thus, **3b** was selectively reduced to allylic alcohol **8b** (Scheme 2) with very high ee



Scheme 2. Reduction of α,β-unsaturated ketones **3a–c** with catalysts **A–B**. Conditions: (i) 0.5 mol% (*R*,*R*)-**A** or (1*R*,2*S*)-**B**, see Table 1.

Table 1. Reduction of cyclic α,β-unsaturated ketones **3a–d** with catalysts (*R*,*R*)-**A** and (1*R*,2*R*)-**B**

Entry	Ketone	Catalyst	% Yield[a]	% Conv.[b] **8**	% ee	Confign.[c]
1	**3a**	**A**[d]	47	62	72[e]	*R*
2	**3a**	**B**[f]	27	33	70[e]	*S*
3	**3b**	**A**[d]	78	—	99[e]	*R*
4	**3b**	**B**[f]	0	0	—	—
5	**3c**	**A**[d]	54	80	>99[g]	*R*
6	**3c**	**B**[f]	0	0	—	—
7	**3d**	**A**[d] or **B**[f]	0	0	—	—

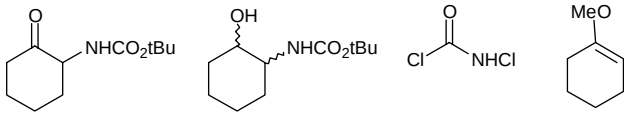
[a] Isolated yield.
[b] Determined by ^{1}H NMR.
[c] Predicted using Refs. 3a and 5i.
[d] The reaction was carried out overnight at 28 °C using 1 mol L^{-1} solution of unsaturated ketone in formic acid:triethylamine mixture (5:2).
[e] Determined by HPLC analysis using a Daicel chiralcel OD 4.6×250 mn column (propan-2-ol:hexane 10:90; 0.5 mL min^{-1}).
[f] The reaction was carried out for 3 h at rt using 0.1 mol L^{-1} solution of unsaturated ketone in propon-2-ol with KOH (2.5 mol%).
[g] HPLC analysis using Daicel chiralcel OD (EtOH:hexane 10:90; 0.5 mL min^{-1}).

(99%) and good yield (78%) (Table 1, entry 3). Nevertheless, no reduction of substrate **3b** was obtained with catalyst (1*R*,2*S*)-**B** (Table 1, entry 4).

We have observed similar failures with **B** in the reduction of α-chloro- and α-methoxyacetophenone. In these cases, we suggested an inhibition of the reduction process due to the chelation of either the methoxy substituted derivative or the reduction product to the catalyst.[5g] Since our report, a similar mechanism has been proposed by others.[3c] The chelation of ketone **3b** or its 1,2-reduction product **8b** to the ruthenium, may be followed by decomposition of the catalyst. The reduction of 2-(methoxycarbonylamino)-cyclohex-2-en-1-one **3c** with catalyst (*R*,*R*)-**A** gave the allylic alcohol **8c** (Scheme 2) in 80% conversion and with excellent ee (>99%) (Table 1, entry 5). In this case, it is interesting to note that 20% of the starting material was reduced via a 1,4-reduction process. Catalyst (1*R*,2*S*)-**B** was also an inefficient catalyst for the reduction of substrate **3c** (Table 1, entry 6). Finally, the introduction of a *tert*-butyl group (**3d**) at the α-position gave an incompatible substrate for ruthenium(II)-catalysed transfer hydrogenation and no reduction occurred using either catalyst (*R*,*R*)-**A** or (1*R*,2*S*)-**B** (Table 1, entry 7).

The reduction of **3c** using rhodium catalyst (*R*,*R*)-**C** was not as regioselective, and the allylic alcohol **8c** was obtained in only 7% yield despite excellent enantioselectivity (92%, *S*). The isolated by-products were the 1,4-reduction ketonic product **9** (20%), found to be racemic by HPLC analysis

and the saturated alcohol carbamate derivatives **10**. Unfortunately, the ee of *cis*-**10** (26%) and *trans*-**10** (13%) could not be determined. Similar differences in reactivity with the same catalytic systems have been previously observed in the reduction of α-substituted acetophenones.[2h,5h]

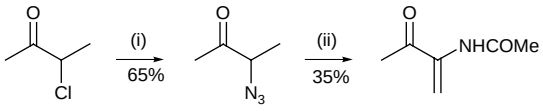


9 *cis*/*trans*-**10** **11** **12**

In order to gain an insight into the mechanism of formation of the by-products, allylic alcohol **8c** and ketone **9** were independently synthesised and exposed to the reaction conditions employed for the asymmetric transfer hydrogenation of **3c**. Ketone **9** was synthesised by chromous chloride promoted radical addition of *N*-chloromethylcarbamate **11** to 1-methoxycyclohexene **12**.[17–19] Allylic alcohol **8c** was prepared by the sodium borohydride reduction of compound **3c**, in the presence of catalytic amount of cerium chloride hydrate.[20]

The carbonyl moiety of ketone **9** was partially reduced by rhodium catalyst (*R*,*R*)-**C** whilst the carbon–carbon double bond of alcohol **8c** was inert to these conditions. From these experiments, it was deduced that *cis*/*trans*-**10** were formed via the reduction of ketone **9**, and not via the reduction of the carbon–carbon double bond of **8c**. No isomerisation of alcohol **8c** to ketone **9** was observed. Some examples of isomerisation of allylic alcohols to saturated carbonyl compounds have been reported with some ruthenium catalyst precursors used in transfer hydrogenation.[21]

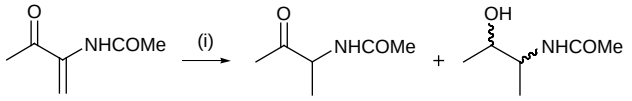
We next, examined the reduction of acyclic α,β-unsaturated ketone **4** having, as far as possible, similar functional groups to cyclic α,β-unsaturated ketone **3c**. The acyclic α,β-unsaturated ketone **4** was synthesised in two steps from commercially available 3-chlorobutan-2-one (Scheme 3).[22,23]



13 **4**

Scheme 3. Synthesis of acyclic α,β-unsaturated ketone **4**. Conditions: (i) NaN_3 (1.5 equiv), acetone, rt, 2 days; (ii) $NaReO_4$ (1 mol%), TFMS (1 mol%), Ac_2O, 50 °C, overnight.

Asymmetric transfer hydrogenation of 3-(acetylamino)-but-3-en-2-one **4** with catalyst (*R*,*R*)-**A** afforded the ketone **14** and the saturated alcohol **15** in 33 and 67% conversion, respectively (Scheme 4, Table 2). No allylic alcohol was detected in the reaction mixture. The reaction most probably proceeds via a 1,4-reduction process, even though a 1,2-reduction pathway, followed by a rapid isomerisation of the allylic alcohol product to a saturated ketone, is still a possibility. Unlike the ruthenium catalyst, the reduction of compound **4** with rhodium catalyst (*R*,*R*)-**C** gave only ketone **14**, in >99% conversion. Catalyst **B** failed to give any reduction products.



4 **14** **15**

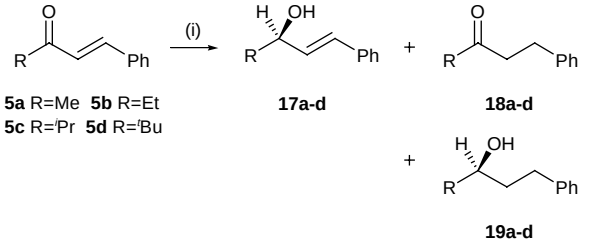
Scheme 4. Reduction of acyclic α,β-unsaturated ketone **4** with catalysts (*R*,*R*)-**A** and (*R*,*R*)-**C**. Conditions: see Table 2.

Table 2. Reduction of acyclic α,β-unsaturated ketone **4** with catalysts (*R*,*R*)-**A** and (*R*,*R*)-**C**

Entry	Catalyst[a]	% Conv. **14**[b]	% Conv. **15**[b]
1	**A**[c]	33	67[d]
2	**C**[e]	>99	0

[a] 0.25 mol% of catalyst, 2 days with 1 mol L^{-1} solution of unsaturated ketone in formic acid:triethylamine mixture (5:2).
[b] Determined by ^1H NMR.
[c] 28 °C.
[d] Diastereomeric ratio = 1:1.
[e] rt.

During the work on the reduction of acyclic α,β-unsaturated ketones, we observed that the asymmetric transfer hydrogenation of benzylidene acetophenone (chalcone) and benzylidene acetone **5a** gave different chemoselectivity with catalyst (*R*,*R*)-**A**. Indeed, chalcone was preferentially reduced via a 1,4-reduction pathway whilst benzylidene acetone **5a** mainly gave the corresponding allylic alcohol **17a** (Scheme 5, Table 3). Similar observations were previously made by others on the same substrates, during the hydrogen-transfer hydrogenation assisted by an iron(II) complex.[24]



5a R=Me **5b** R=Et **5c** R=^{i}Pr **5d** R=^{t}Bu

17a-d **18a-d** **19a-d**

Scheme 5. Reduction of α,β-unsaturated ketones **5a–d** with catalyst (*R*,*R*)-**A**. Conditions: 0.5 mol% (*R*,*R*)-**A**, HCO_2H–Et_3N (5/2), 28 °C, 7 days, for ratios see Table 3.

Table 3. Reduction of cyclic α,β-unsaturated ketones **5a–d** with catalyst (*R*,*R*)-**A**

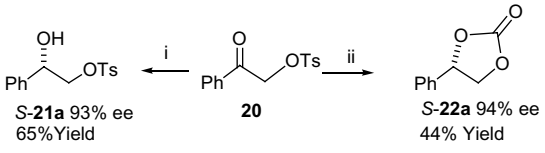
Entry	Ketone	% Conv. **17**[a]	% Conv. **18**[a]	% Conv. **19**[a]	% ee **17**	Confign.[b]
1	**5a**	75	0	25	30[c]	*R*
2	**5b**	90	4	6	6[d]	*R*
3	**5c**	48	30	16	28[d]	*R*
4	**5d**	13	71	3	57[d]	—

[a] Determined by ^1H NMR.
[b] Assigned by the sign of optical rotation.
[c] Determined by HPLC analysis using a Daicel chiralcel OD 4.6×250 mn column (eluent 10:90 EtOH:hexane; flow rate 0.5 mL min^{-1}).
[d] Determined by HPLC analysis using Daicel chiralcel OD (eluent 5:95 EtOH:hexane; flow rate 0.5 mL min^{-1}).

Bearing this in mind, we were interested in studying the reduction of benzylidene acetone derivatives with different alkyl substituents at the α-position. We synthesised three acyclic benzylidene acetone derivatives in order to study the influence of the bulkiness of the alkyl substituent on the chemo- and enantioselectivity of their reduction. Ketone **5b** was synthesised in 55% yield through a palladium-catalysed vinylic substitution reaction with phenyl iodide and pent-1-en-3-one.[25] Ketones **5c** and **5d** were synthesised by aldol condensation of benzaldehyde with respectively 3-methyl-butan-2-one (58% yield) and pinacolone (50% yield).

ATH of acyclic α,β-unsaturated ketones **5a–d** with catalyst (*R*,*R*)-**A** afforded mixtures different ratios of 1,2 and 1,4-reduction products (Scheme 5, Table 3). Enone **5b** with an ethyl group, afforded the allylic alcohol **17b** in 90% conversion whilst enone **5d** with a *tert*-butyl group gave the saturated ketone **18d** in 71% conversion. Enone **5c** with an *iso*-propyl substituent, gave a 50% mixture of 1,2 and 1,4 reduction products. It appears that, as the bulkiness of the alkyl group increases from ethyl to *iso*-propyl to *tert*-butyl, the chemoselectivity towards the carbonyl functionality decreases although the extent of the ee of the allylic alcohol **17** increases. The sense of reduction (*R*) is the same for compounds **5a–c**. The configuration of the reduction product of **5d** has not yet been confirmed.

In a previous paper,[5h] we reported that the transfer hydrogenation of α-tosyloxy acetophenone (**20a**) with a Rh(III) based catalyst gave the alcohol (**21a**), whilst the Ru(II) based catalyst gave the dioxolan-2-one (**22a**) (Scheme 6). We have investigated of the mechanism of the dioxolan-2-one formation, and the extension of the scope of this reduction to a range of α-tosyloxy ketones.



Scheme 6. Conditions: (i) 0.25 mol% $[Rh(C_5Me_5)Cl_2]_2$, 0.5 mol% (*R*,*R*)-TsDPEN, HCO_2H, Et_3N, (5:2 molar ratio), rt, 200 °C; (ii) 0.25 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 0.5 mol% (*R*,*R*)-TsDPEN, HCO_2H, Et_3N, (5:2 molar ratio), rt, 30 °C.

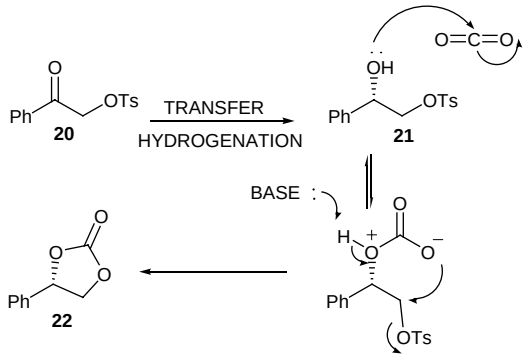
We were concerned that the temperature might be influencing the reaction, since the Rh-catalysed reactions are generally performed at rt, ca. 20 °C, and the Ru-catalysed reactions at slightly higher temperature, ca. 30 °C To prove that the temperature was not the decisive factor, the rhodium catalysed transfer hydrogenation was repeated at 30 °C. This resulted in formation of the **21** in a lower yield of 35% but in identical ee. Hence the only difference between the two reaction conditions is the metal complex employed.

Preliminary studies led us to conclude that the mechanism for the formation of **22** is likely to be via the alcohol **21**, followed by trapping out of free carbon dioxide in the reaction mixture. However, we were also anxious to establish whether the Ru(II) catalyst was also playing a part in the carbon dioxide trapping process. We therefore, conducted a series of experiments on 2-bromo-2-phenyl-ethanol to see, which reagents are essential for dioxolan-2-one formation. Table 4 summarises the results of this study, in which we measured the conversion to dioxolan-2-one. In all cases the mass balance was completed by unreacted alcohol starting material. Epoxide formation was not observed.

Table 4. Cyclic carbonate formation from α-bromophenylethanol

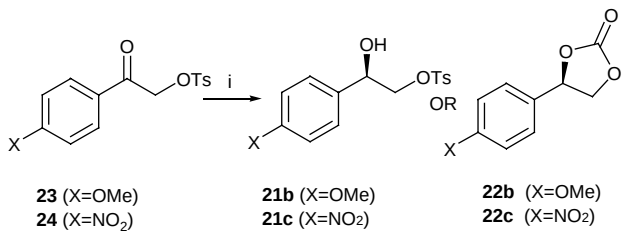
Reaction conditions	Yield (%)
$[Ru(p\text{-cymene})Cl_2]_2$, TsDPEN, HCO_2H:Et_3N, 28 °C, 24 h	51
$[RhCp^*Cl_2]_2$, TsDPEN, HCO_2H:Et_3N, 21 °C, 24 h	17
HCO_2H:Et_3N, 28 °C, 24 h	0
CO_2, Et_3N, DCM, 21 °C, 6 h	14–40
CO_2, DCM, 21 °C, 6 h	0

As the results show, the catalyst (either ruthenium or rhodium based) is not required to produce the dioxolan-2-one, nor is formic acid. The only essential additives are carbon dioxide (solid pellets added) and triethylamine. This suggests that the mechanism involves trapping of carbon dioxide by the alcohol, with the bromide (or tosylate) acting as a subsequent leaving group (Scheme 7). The catalyst system in these reactions must therefore act only as a source of carbon dioxide by decomposing formic acid to hydrogen and carbon dioxide. Both the ruthenium and the rhodium transfer hydrogenation systems yield the dioxolan-2-one, however, the ruthenium system gives it in a much greater yield, possibly due to more rapid decomposition of the formic acid.



Scheme 7.

We have also investigated the scope of the reaction by testing two further α-tosyloxy acetophenone derivatives (Scheme 8, Table 5; note that TsDPEN of *S*,*S* configuration was used for these reductions). These were prepared in a good yield from their respective acetophenone derivatives and HTIB. The ketones were reduced using standard ATH conditions. Using Rh(III) catalysts, the enantiomerically enriched alcohols were formed in moderate to good yields (78–41%), and dramatically variable ee (>99–15%). The reduction using Ru(II) catalysis also gave only the alcohol in good ee for the *p*-nitro derivative **24** (82%), but the *p*-methoxy derivative **23** yielded the dioxolan-2-one **22a**, in a moderate yield (28%) and ee (52%). The lack of formation of a dioxolan-2-one in the case of the *p*-nitro substrate may be due to the lower nucleophilicity of the alcohol in this case.



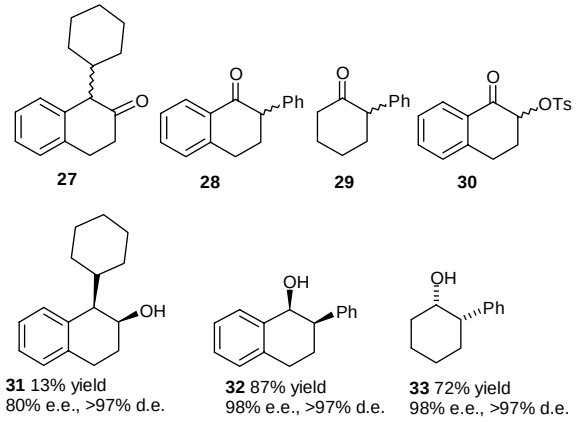
Scheme 8. Conditions: (i) 0.25 mol% $[Ru(p\text{-cymene})Cl_2]_2$, 0.5 mol% (*S*,*S*)-TsDPEN, HCO_2H, Et_3N, (5:2 molar ratio), 28 °C or 0.25 mol% $[Rh(C_5Me_3)Cl_2]_2$, 0.5 mol% (*S*,*S*)-TsDPEN, HCO_2H, Et_3N, (5:2 molar ratio), rt.

Table 5. Investigation into the role of different electronic effects on dioxolan-2-one formation

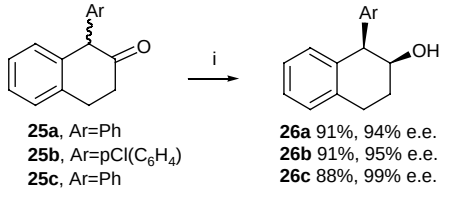
Ketone	Metal	Product	Yield (%)	ee
23	Ru	**22b**	28	52
	Rh	**21b**	59	15
24	Ru	**21c**	55	82
	Rh	**21c**	78	51

2.1. Dynamic kinetic resolutions

Dynamic kinetic resolution—transfer hydrogenation (DKR-TH) of β-tetralone derivatives has been successfully demonstrated in our group.[5k] In our previous report on this subject, the best result was obtained using substrates of type **25**, for which both high yields and ees were achieved (Scheme 9). The scope of this work has now been extended to ketones **27**–**30**. This selection was made on the basis of the diversity of the substrates. In particular, compound **27** should have a higher pK_a than the 1-aryl substrates, and thus be a more challenging substrate.



Substrates **28** and **29** are relatively simple ketones in which the α-aryl group is designed to increase the acidity of the a-proton in order to make it more likely to epimerise under the reaction conditions. In the cases of compounds **27**–**29**, the DKR reactions were carried out using 0.5 mol% catalyst in the case of **29** and 2 mol% for the other two substrates. Product **31** was isolated in only 13% yield and 80% ee (absolute configuration assigned by comparison with related structures), which does not indicate a dynamic resolution. The unreacted starting material was found to have an optical rotation of +13.3 (c=0.08, chloroform) and by chiral HPLC had an ee of 5%. This ketone was redissolved in formic acid–triethylamine (5/2) and stirred for 24 h at rt. The substrate was found to have no optical rotation and was racemic by chiral HPLC. This suggests that the ketone does racemise under the reaction conditions, but is not well matched to the catalyst. The absolute configuration of the 2-phenylcyclohexanol **33** was found to be (1*S*,2*S*) by X-ray analysis of the tosyl ester.[32] The absolute configuration of **32** could not be confirmed in a satisfactory way, therefore the assigned configuration represents that matched to the fused tetralone ring (see below). The reduction of **30** gave a mixture of the alcohol (51%) and the carbamate (16%) in ees of only 6 and 5%, respectively, indicating that no DKR was taking place, only a diastereoselective reduction.



Scheme 9. Conditions: (i) 0.25 mol% $[Ru(Cymene)Cl_2]_2$, 0.5 mol% (*S*,*S*)-TsDPEN, HCO_2H, Et_3N, (5:2 molar ratio), rt, 20 °C.

Figure 2 illustrates the possible transition states for the formation of **26a**, **32** and **33**. In the first and second cases, an established π-interaction between the η^6-arene (on ruthenium) and the aryl ring of the substrate serves to stabilise the transition state with the latter ring occupying the higher position (as illustrated).[2e] The enantiomer of product, which is preferably reduced is that in which the exocyclic phenyl ring is furthest from the catalyst, thus minimising any steric obstacles to the approach of the ruthenium hydride to the ketone. In the case of **33**, the exocyclic arene is presumed to engage in a stabilising interaction with the η^6-arene. However, the ketone is reduced on the face opposite this ring, resulting in formation of a cis product.

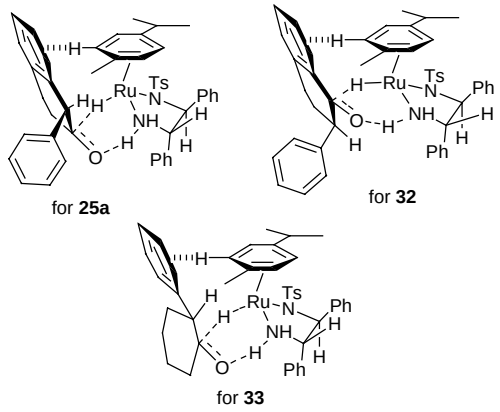


Figure 2. Preferred reduction transition states for **26a**, **32**, and **33**.

3. Experimental

3.1. General

All reactions were run under an atmosphere of nitrogen in flame or oven dried glassware (round bottomed flasks or

Schlenk tubes) unless otherwise stated. Room temperature refers to ambient rt (20–22 °C). 0 °C refers to an ice slush bath, −78 °C and −10 °C refer to a dry-ice acetone bath and ice-acetone bath, respectively. Heated experiments were conducted using thermostatically controlled oil baths. Reagents were used as received from commercial sources (Aldrich, Fluka, Lancaster) unless otherwise stated. Formic acid–triethylamine mixture (5/2) is a commercially available azeotrope (Fluka). All anhydrous solvents were used as supplied by Romil in HyDry™ form, except anhydrous propan-2-ol, which was supplied by Aldrich. Tetrahydrofuran (THF) was freshly distilled from sodium using benzophenone. Flash column chromatography was carried out routinely using 60 Å silica gel (Merck). Determination of ees was achieved by HPLC analysis (Waters 501 HPLC pump, a Waters 486 tuneable absorbance detector, a Waters 746 data module and a Daicel chiralcel OD 4.6×250 mm column). Chiral shift reagent Eu(hfc)$_3$ is Europium tris [3-(heptafluoropropyl-hydroxymethylene)-(−)-camphorate]. Optical rotations ($[\alpha]_D$) were measured on a Perkin-Elmer 241 polarimeter (sodium D line) at ambient temperature with a 10 cm rotation cell and are reported in 10^{-1} deg cm^2 g^{-1} with c (concentration) in g/100 mL. Elemental analyses were performed using the Exeter Analytical Model CE 440. Infrared spectra (IR) were recorded on a Nicolet Model Avatar 320 FTIR instrument. Nuclear magnetic resonance (NMR) spectra were recorded either on a Bruker AC-250 (250 MHz), Bruker DPX-300 (300 MHz) or DXP 400 (400 MHz) spectrometer. Chemical shifts values are reported in δ units, parts per million (ppm) downfield from the standard tetramethylsilane (Me_4Si). Coupling constants (J) are measured in Hertz (Hz). All mass spectra and high resolution mass spectra were recorded on a Micromass AutoSpec instrument. Compounds **3a**,[11] **3b**,[12] **3c**,[14] **6**,[13] **7**,[14,15] **11**,[17] **12**,[19] **20**,[5h] **21a**,[5h] and **22a**[5h] have been reported previously.

3.1.1. (±)-2-(Methoxycarbonylamino)-cyclohexan-1-one 9. To a −78 °C cooled solution of methylcarbamate and *N*-chloromethylcarbamate **11** (78/22 mol/mol, respectively) (0.540 g, 1.3 mmol of *N*-chloromethylcarbamate) in chloroform (3 mL) and absolute methanol (1 mL) was added a solution of 1-methoxy-cyclohex-1-ene **11** (0.409 g, 3.6 mmol) in chloroform (1 mL), pre-cooled to −78 °C. A solution of chromous chloride (0.310 g, 2.5 mmol) in methanol (4.5 mL) was added dropwise during 1 h at −78 °C and the reaction mixture was stirred for another hour at the same temperature. The cooling bath was removed and air was allowed in the reaction vessel. A 1 M aqueous solution of sulphuric acid (1 mL) was added and the reaction mixture was stirred for 4 h. Water was added (20 mL) and the mixture was extracted with dichloromethane (3×40 mL). The organic extracts were washed with water (2×15 mL), then combined, dried over anhydrous sodium sulphate and filtered. The solvent was removed in vacuo to give a colourless oil, which was purified by flash chromatography (10→30% v/v ethyl acetate/hexane) to afford the product as white crystals (0.123 g, 55%). For characterisation, see reduction of 2-(methoxycarbonylamino)-cyclohex-2-en-1-one **3c** with catalyst (*R*,*R*)-**C** (vide infra).

3.1.2. 3-Azido-butan-2-one 13. To a stirred solution of 3-chlorobutan-2-one (5 mL, 50 mmol) in acetone (50 mL) was added sodium azide (4.9 g, 75 mmol) at rt. The reaction mixture was stirred for 2 days and filtered off. The solvent was removed in vacuo to give a slightly yellow oil (4.3 g, 75%). The product was sufficient pure to be used in the next step without any further purification. ν_{max} (film) 2989, 2941, 2098 (N_3), 1726 (CO), 1360, 1256 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.95 (1H, q, J=7.1 Hz, C*H*N$_3$), 2.24 (3H, s, COC*H*$_3$), 1.44 (3H, d, J=7.0 Hz, C*H*$_3$CHN$_3$); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 205.8, 64.1, 26.8 and 16.1.

3.1.3. 3-(Acetylamino)-but-3-en-2-one 4. To a stirred solution of 3-azido-butan-2-one **13** (3.00 g, 26 mmol) in acetic anhydride (40 mL) was added sodium perrhenate (0.071 g, 0.26 mmol) at rt, followed by trifluoromethanesulphonic acid (23 μL, 0.26 mmol). The reaction mixture was stirred overnight at 50 °C, concentrated in vacuo to give the crude product, which was purified by flash column chromatography (25→45% v/v ethyl acetate/hexane) to afford a yellow oil (1.155 g, 35%). ν_{max} (Nujol) 3330, 3180, 1714 (CO), 1660 (NHCO) cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.05 (1H, br s, N*H*), 6.91 (1H, s, C*H*), 5.78 (1H, s, C*H*), 2.42 (3H, s, C*H*$_3$CO), 2.14 (3H, s, C*H*$_3$CONH); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 195.2, 169.4, 138.6, 110.4, 25.1, 24.1; *m/z* (CI, NH_3) 144 ([M+NH$_3$]$^+$, 8%), 128 ([M+H]$^+$, 100), 112 ([M−Me]$^+$, 12), 79 (23), 60 (48), 35 (80); HRMS (CI, NH_3): [NH]$^+$, found 128.0711. $C_6H_{10}O_2N$ requires 128.0711.

3.1.4. 1-Phenyl-pent-1-en-3-one 5b. To a mixture of phenyl iodide (2 mL, 17 mmol) and triethylamine (3.4 mL, 24 mmol) was added vinyl ethyl ketone (0.600 g, 7.1 mmol), followed by palladium(II) diacetate (8 mg, 0.035 mmol) and acetonitrile (2 mL) at rt. The mixture was refluxed for 7 h then ethyl acetate (5 mL) and water (5 mL) were added. The organic layer was washed with water, dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo to give a yellow oil, which was purified by flash chromatography (5→20% v/v ethyl acetate/hexane) to afford yellow crystals (0.639 g, 56%). Mp 35–36 °C (lit.,[25] 38–40 °C); ν_{max} (neat) 3057, 2974, 1689, 1664, 1607, 1447, 1121 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.58–7.54 (3H, m, aryl C*H*, PhC*H*), 7.40–7.38 (3H, m, aryl C*H*), 6.75 (1H, d, J=16.0 Hz, COC*H*), 2.70 (2H, q, J=7.3 Hz, C*H*$_2$), 1.17 (3H, t, J=7.3 Hz, C*H*$_3$); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 201.2, 142.5, 135.0, 130.7, 129.3, 128.6, 126.4, 34.4, 8.6; *m/z* (EI) 161 ([M+H]$^+$, 49%), 160 ([M]$^+$, 52), 131 ([M−C$_2$H$_5$]$^+$, 100), 103 ([M−C$_3$H$_5$O]$^+$, 44), 77 ([C$_6$H$_5$]$^+$, 30), 57 ([C$_2$H$_5$CO]$^+$, 7); HRMS (EI): [M]$^+$, found 160.0900. $C_{11}H_{12}O$ requires 160.0888.

3.1.5. 4-Methyl-1-phenyl-pent-1-en-3-one 5c. To a stirred solution of benzaldehyde (1.2 g, 11 mmol) in ethanol (40 mL) was added 3-methyl-butan-2-one (0.974 g, 11 mmol), followed by the addition of a 10% aqueous solution of sodium hydroxide (11.2 mL, 2.7 mmol) at rt. The reaction mixture was stirred at reflux for 2 days and a saturated aqueous solution of sodium chloride was added (30 mL). The product was extracted with ethyl acetate (3× 20 mL) and the combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo. Purification via flash column chromatography

(0→5% v/v ethyl acetate/hexane) affords the product as a yellow oil (1.1 g, 58%). ν_{max} (neat) 2967, 1686, 1661, 1610, 1448, 1053 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.61 (1H, d, J=16.0 Hz, C*H*Ph), 7.57–7.55 (2H, m, aryl C*H*), 7.40–7.38 (3H, m, aryl C*H*), 6.82 (1H, d, J=15.8 Hz, C*H*), 2.97–2.90 (1H, m, C*H*Me_2), 1.19 (6H, d, J=7.0 Hz, 2×CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 204.2, 142.8, 135.1, 130.7, 129.3, 128.7, 124.8, 39.7, 18.9; *m/z* (EI) 174 ($[M]^+$, 14%), 131 ($[M-C_3H_7]^+$, 100), 103 ($[M-C_4H_7O]^+$, 30), 76 ($[C_6H_4]^+$, 16); HRMS (EI): $[M]^+$, found 174.1060. $C_{12}H_{14}O$ requires 174.1045.

3.1.6. 4,4-Dimethyl-1-phenyl-pent-1-en-3-one 5d. To a stirred solution of benzaldehyde (0.300 g, 2.8 mmol) in ethanol (10 mL) was added pinacolone (0.280 g, 2.8 mmol), followed by the addition of a 10% aqueous solution of sodium hydroxide (2.8 mL, 0.7 mmol). The reaction mixture was stirred at reflux overnight and a saturated aqueous solution of sodium chloride was added (10 mL). The product was extracted with ethyl acetate (3×10 mL) and the combined organic layers were dried over anhydrous magnesium sulphate, filtered and concentrated in vacuo. Purification via flash column chromatography (0→10% v/v ethyl acetate/hexane) affords the product as a yellow solid (0.263 g, 50%). Mp 38–40 °C (lit.,[27] 42–43 °C); ν_{max} (neat) 2966, 2867, 1681, 1608, 1576, 1495, 1073 cm^{-1}; δ_H (250 MHz; $CDCl_3$; Me_4Si) 7.69 (1H, d, J=15.6 Hz, PhC*H*), 7.62–7.53 (2H, m, aryl C*H*), 7.42–7.35 (3H, m, aryl C*H*), 7.13 (1H, d, J=15.55 Hz, C*H*), 1.23 (9H, s, 3×CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 204.6, 143.3, 135.3, 130.6, 129.2, 128.7, 121.1, 43.6, 26.7; *m/z* (EI) 189 ($[M+H]^+$, 16%), 189 ($[M]^+$, 4), 160 (7), 131 ($[M-C_4H_9]^+$, 100), 103 ($[M-C_5H_9O]^+$, 19), 76 ($[C_6H_4]^+$, 10), 56 ($[C_4H_8]^+$, 12); HRMS (EI): $[M]^+$, found 188.1195. $C_{13}H_{16}O$ requires 188.1201.

3.2. General procedure for the reduction of α,β-unsaturated ketones 3a–c and 5a–d and with catalyst (*R*,*R*)-A

A mixture of (*p*-cymene) ruthenium(II) chloride dimer ($2.5.10^{-3}$ equiv) and (*R*,*R*)-(−)-*N*-(*p*-toluenesulphonyl)-1,2-diphenylethylene-diamine (TsDPEN) (5.0×10^{-3} equiv) in a formic acid–triethylamine mixture (5/2 molar) was stirred for 20 min at 28 °C. The corresponding ketone (1.0 equiv) was added and the reaction mixture was stirred at 28 °C, filtered through a plug of silica gel and washed with ethyl acetate. The organic fractions were collected, combined and concentrated in vacuo to give the crude product.

3.2.1. (*R*)-(+)-2-Phenyl-cyclohex-2-en-1-ol 8a. 2-Phenyl-cyclohex-2-en-1-one **3a** (0.860 g, 5 mmol) was reacted overnight with (*p*-cymene) ruthenium(II) chloride dimer (7.7 mg, 12×10^{-3} mmol) and TsDPEN (9.2 mg, 25×10^{-3} mmol) in a formic acid:triethylamine mixture (2.5 mL) according to the general procedure described above. Purification by flash chromatography (0→15% v/v ethyl acetate/hexane) affords (*R*)-(+)-2-phenyl)-cyclohex-2-en-1-ol **8a** as a white solid (0.410 g, 47%). The product was determined to be of 72% ee by chiral HPLC analysis (chiral OD column, hexane/propan-2-ol=90:10, 0.5 mL/min), *S* isomer 17.1 min, *R* isomer 42.0 min. Mp 59 °C; $[\alpha]_D^{23}$ +9.8 (*c* 1.6, $CHCl_3$). [Found: C, 82.55; H, 8.1. $C_{12}H_{14}O$ requires C, 82.7; H, 8.1%]; ν_{max} (Nujol) 3172 (OH), 2341, 1160, 1052 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.38–7.23 (5H, m, Ar), 6.12 (1H, br s, C*H*), 4.38 (1H, br s, C*H*OH), 2.49–2.32 (2H, m, CH_2), 1.96–1.87 (2H, m, CH_2), 1.74–1.65 (3H, m, CH_2, O*H*); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 141.7, 140.5, 128.7, 127.8, 127.0, 125.8, 66.7, 32.08, 27.9, 19.9; *m/z* (EI) 174 ($[M]^+$, 98%), 145 (100), 131 (93), 115 (89), 91 (91), 77 (70), 51 (56).

3.2.2. (*R*)-(+)-2-Benzyloxy-cyclohex-2-en-1-ol 8b. 2-Benzyloxy-cyclohex-2-en-1-one **3b** (0.202 g, 1.0 mmol) was reacted overnight with (*p*-cymene) ruthenium(II) chloride dimer (1.5 mg, 2.5×10^{-3} mmol) and TsDPEN (1.8 mg, 5×10^{-3} mmol) in a formic acid:triethylamine mixture (0.5 mL) according to the general procedure described above. Purification by flash chromatography (0→5% v/v ethyl acetate/hexane) affords (*R*)-(+)-2-benzyloxy-cyclohex-2-en-1-ol **8b** as a colourless oil (0.156 g, 78%). The product was determined to be of 99% ee by chiral HPLC analysis (chiral OD column, hexane/propan-2-ol=90:10, 0.5 mL/min), *S* isomer 16.7 min, *R* isomer 22.7 min. $[\alpha]_D^{21}$ +74.4 (*c* 1, EtOH); ν_{max} (film) 3425, 3029, 2926, 1663, 1452, 1180 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.28–7.41 (5H, m, Ar), 4.85 (1H, t, J=4.1 Hz, CH_2CH), 4.74 (2H, s, CH_2Ph), 4.23 (1H, br s, C*H*OH), 2.37 (1H, s, O*H*), 2.02–1.99 (2H, m, CH_2), 1.97–1.63 (3H, m, CH_2C*H*H), 1.62–1.49 (1H, m, CH_2CH*H*); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 155.0, 137.5, 128.9, 128.3, 128.1, 97.9, 69.3, 66.9, 31.4, 24.3, 19.2; *m/z* (CI) 222 ($[M+NH_4]^+$, 52%), 204 ($[M]^+$, 39), 187 (25), 108 (67), 91 (72); HRMS (CI, NH_3): $[M+NH_4]^+$, found 222.1492. $C_{13}H_{20}O_2N$ requires 222.1494.

3.2.3. (*R*)-(+)-2-(Methoxycarbonylamino)-cyclohex-2-en-1-ol 8c. 2-(Methoxycarbonylamino)-cyclohex-2-en-1-one **3c** (0.170 g, 1 mmol) was reacted overnight with (*p*-cymene) ruthenium(II) chloride dimer (1.5 mg, 2.5×10^{-3} mmol) and TsDPEN (1.8 mg, 5×10^{-3} mmol) in a formic acid:triethylamine mixture (1 mL) according to the general procedure described above. Purification by flash chromatography (10→30% v/v ethyl acetate/hexane) affords (*R*)-(+)-2-(methoxycarbonylamino)-cylohex-2-en-1-ol **8c** as a colourless oil (0.093 g, 54%). The product was determined to be of >99% ee by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=90:10, 0.5 mL/min), *R* isomer 17.3 min, *S* isomer 35.6 min. $[\alpha]_D^{11}$ +37.5 (*c* 0.2, EtOH); ν_{max} (film) 3404, 2942, 2867, 1709, 1522, 1448, 1248, 1049 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.65 (1H, br s, N*H*), 5.78 (1H, t, J=4.1 Hz, C*H*), 4.22 (1H, br s, C*H*OH), 3.69 (3H, s, CH_3), 3.57 (1H, br s, O*H*), 2.20–1.96 (2H, m, CCHCH_2), 1.94–1.64 (3H, m, CH(OH)CH_2C*H*H), 1.64–1.49 (1H, m, CH(OH)CH_2CH*H*); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 155.4, 134.5, 113.4, 65.9, 52.6, 31.9, 24.6, 18.7; *m/z* (CI) 172 ($[M+H]^+$, 53%), 171 ($[M]^+$, 36), 157 ($[MH-Me]^+$, 62), 154 ($[M-OH]^+$, 100), 140 ($[M-OMe]^+$, 85), 112 ($[M-CO_2Me]^+$, 24), 96 ($[M-NH_2CO_2Me]^+$, 17), 84 (9), 68 (9); HRMS (CI, NH_3): $[M+H]^+$, found 172.0973. $C_8H_{14}O_3N$ requires 172.0974.

3.2.4. (*R*)-(+)-4-Phenyl-but-3-en-2-ol 17a. 4-Phenyl-but-3-en-2-one **5a** (0.234 g, 1.6 mmol) was reacted with (*p*-cymene) ruthenium(II) chloride dimer (2 mg, 3.9×10^{-3} mmol) and TsDPEN (3 mg, 8.0×10^{-3} mmol) in a formic

acid:triethylamine mixture (1.6 mL) for 4 days according to the general procedure described above. Purification by flash chromatography (0→40% v/v ethyl acetate/hexane) affords (*R*)-(+)-4-phenyl-but-3-en-2-ol **17a** as a white solid (0.141 g, 60%). The product was determined to be of 30% ee by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=90:10, 0.5 mL/min), *R* isomer 13.8 min, *S* isomer 18.6 min. Mp 32–33 °C (lit.,[28] 34–35 °C); $[\alpha]_D^{20}$ +4.7 (*c* 0.4, EtOH) (lit.,[29] $[\alpha]_D^{23}$ +30.5 (*c* 1.0 in $CHCl_3$), >99% ee (*R*)); ν_{max} (neat) 3338, 2971, 1493, 1448, 1265, 1140, 1056 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.37–7.26 (5H, m, aryl C*H*), 6.57 (1H, d, *J*=15.9 Hz, PhC*H*), 6.26 (1H, dd, *J*=15.9, 6.4 Hz, C*H*), 4.52–4.48 (1H, m, C*H*OH), 1.62 (1H, br s, O*H*), 1.38 (3H, d, *J*=6.4 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 137.1, 134.0, 129.9, 129.0, 128.1, 126.9, 69.4, 23.9; *m/z* (CI) 148 ($[M]^+$, 54%), 133 ($[M-Me]^+$, 27), 131 ($[M-OH]^+$, 100), 115 ($[C_9H_7]^+$, 20), 105 (23), 91 ($[C_7H_7]^+$, 44); HRMS (EI): M^+, found 148.0875. $C_{10}H_{12}O$ requires *m/z* 148.0888.

3.2.5. (*R*)-(+)-1-Phenyl-pent-1-en-3-ol 17b. 1-Phenyl-pent-1-en-3-one **5b** (0.200 g, 1.2 mmol) was reacted with (*p*-cymene) ruthenium(II) chloride dimer (2 mg, 3.1×10^{-3} mmol) and TsDPEN (2 mg, 6.2×10^{-3} mmol) in a formic acid:triethylamine mixture (1 mL) according to the general procedure described above. Purification by flash chromatography (2→20% v/v ethyl acetate/hexane) affords (*R*)-(+)-1-phenyl-pent-1-en-3-ol **17b** as a colourless oil (0.155 g, 80%). The product was determined to be of 6% ee by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=95:5, 0.5 mL/min), *R* isomer 17.7 min, *S* isomer 23.9 min. $[\alpha]_D^{20}$ +1.1 (*c* 0.3 in EtOH) (lit.,[30] $[\alpha]_D^{22}$ −6.30 (*c* 2.70 $CHCl_3$), 100% ee (*S*)); ν_{max} (neat) 3333, 2962, 2929, 1493, 1450, 962 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.41–7.24 (5H, m, aryl C*H*), 6.58 (1H, d, *J*=19.2 Hz, PhC*H*), 6.22 (1H, dd, *J*=19.2, 8.2 Hz, C*H*), 4.26–4.18 (1H, m, C*H*OH), 1.73–1.63 (2H, m, CH_2), 0.98 (3H, t, *J*=8.8 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 137.1, 132.6, 130.8, 129.0, 128.0, 126.85, 74.8, 30.6, 10.1; *m/z* (EI) 162 ($[M]^+$, 28%), 145 ($[M-OH]^+$, 100), 133 ($[M-C_2H_5]^+$, 20), 117 (19), 105 (18), 91 ($[C_7H_7]^+$, 24); HRMS (EI): M^+, found 162.1044. $C_{11}H_{14}O$ requires 162.1045.

3.2.6. (*R*)-(−)-4-Methyl-1-phenyl-pent-1-en-3-ol 17c. 4-Methyl-1-phenyl-pent-1-en-3-one **5c** (0.200 g, 1.1 mmol) was reacted with (*p*-cymene) ruthenium(II) chloride dimer (2 mg, 2.8×10^{-3} mmol) and TsDPEN (2 mg, 5.7×10^{-3} mmol) in a formic acid:triethylamine mixture (1 mL) according to the general procedure described above. Purification by flash chromatography (0→10% v/v ethyl acetate/hexane) affords an inseparable mixture of (*R*)-(−)-4-methyl-1-phenyl-pent-1-en-3-ol **17c** and 4-methyl-1-phenyl-pentan-3-ol **19c** in a 4:1 ratio, respectively, and in the form of a colourless oil (0.077 g, 40%). (*R*)-(−)-4-methyl-1-phenyl-pent-1-en-3-ol **17c** was determined to be of 28% ee by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=95:5, 0.5 mL/min), *R* isomer 16.5 min, *S* isomer 21.7 min. $[\alpha]_D^{20}$ −2.5 (*c* 0.4, EtOH) (lit.,[31] $[\alpha]_D^{24}$ −8.4 (*c* 1.02, $CHCl_3$); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.38–7.27 ($5H_{maj}+5H_{min}$, m, aryl C*H*), 6.57 ($1H_{maj}$, d, *J*=15.8 Hz, PhC*H*), 6.23 ($1H_{maj}$, dd, *J*=15.8, 6.9 Hz, C*H*), 4.05–4.01 ($1H_{maj}$, m, C*H*OH), 3.43–3.37 ($1H_{min}$, m, C*H*OH), 2.88–2.81 ($1H_{min}$, m, CH_2), 2.65–2.61 ($1H_{min}$, m, CH_2), 1.86–1.75 ($1H_{maj}+1H_{min}$, m, C*H*Me_2, CH_2), 1.71–1.67 ($2H_{min}$, m, C*H*Me_2, CH_2), 1.56 ($1H_{maj}$, br s, O*H*), 1.32 ($1H_{min}$, br s, O*H*), 0.99 ($3H_{maj}$, d, *J*=6.8 Hz, CH_3), 0.95 ($3H_{maj}$, d, *J*=6.8 Hz, CH_3), 0.91 ($6H_{min}$, d, *J*=6.8 Hz, $2\times CH_3$).

3.2.7. (−)-4,4-Dimethyl-1-phenyl-pent-1-en-3-ol 17d. 4,4-Dimethyl-1-phenyl-pent-1-en-3-one **5d** (0.200 g, 1.1 mmol) was reacted with (*p*-cymene) ruthenium(II) chloride dimer (2 mg, 2.9×10^{-3} mmol) and TsDPEN (2 mg, 5.7×10^{-3} mmol) in a formic acid:triethylamine mixture (1 mL) according to the general procedure described above. Purification by flash chromatography (0→10% v/v ethyl acetate/hexane) affords (−)-4,4-dimethyl-1-phenyl-pent-1-en-3-ol **17d** as a colourless oil (0.015 g, 7%). The product was determined to be of 57% ee by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=95:5, 0.5 mL/min), major isomer 15.0 min, minor isomer 19.2 min. $[\alpha]_D^{20}$ −18.0 (*c* 0.4, EtOH); ν_{max} (neat) 3406, 2952, 2867, 1477, 1362 cm^{-1}; δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.40–7.38 (2H, m, aryl C*H*), 7.33–7.30 (2H, m, aryl C*H*), 7.24–7.22 (1H, m, aryl C*H*), 6.58 (1H, d, *J*=15.8 Hz, PhC*H*), 6.29 (1H, dd, *J*=15.8, 7.3 Hz, C*H*), 3.94–3.91 (1H, m, C*H*OH), 1.55 (1H, br s, O*H*), 0.97 (9H, s, $3\times CH_3$); δ_C (100 MHz; $CDCl_3$; Me_4Si) 136.9, 131.8, 129.6, 128.6, 127.6, 126.4, 81.0, 35.3, 25.8; *m/z* (EI) 190 ($[M]^+$, 8%), 173 ($[M-OH]^+$, 90), 133 ($[M-C_4H_9]^+$, 100), 115 ($[C_9H_7]^+$, 15), 105 (11), 91 ($[C_7H_7]^+$, 8), 56 (13); HRMS (EI): M^+, found 190.1345. $C_{13}H_{18}O$ requires 190.1358.

3.2.8. (*S*)-(−)-2-Phenyl-cyclohex-2-en-1-ol 8a. A mixture of (*p*-cymene) ruthenium(II) chloride dimer (7.7 mg, 12×10^{-3} mmol) and (1*R*,2*S*)-*cis*-1-aminoindan-2-ol (7.5 mg, 5×10^{-3} mmol) in dry and degassed propan-2-ol (4 mL) was heated at 80 °C for 20 min. After cooling down to rt, a solution of 2-phenyl-cyclohex-2-en-1-one **3a** (0.860 g, 5 mmol) in dry and degassed propan-2-ol (45 mL) was added to the reaction mixture. Then a 0.1 M solution of potassium hydroxide in dry and degassed propan-2-ol (1.25 mL, 0.125 mmol) was added. The reaction mixture was stirred for 3 h at rt, filtered through a plug of silica gel and washed with ethyl acetate (2×50 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product, which was purified by flash chromatography (0→15% v/v ethyl acetate/hexane) to afford the product as a white solid (0.230 g, 27%) (0.400 g of starting material was recovered, 47%). The product was determined to be of 70% ee by chiral HPLC analysis (chiral OD column, hexane:propan-2-ol=90:10, 0.5 mL/min), *S* isomer 17.1 min, *R* isomer 41.7 min. $[\alpha]_D^{23}$ −9.1 (*c* 1.0 in $CHCl_3$).[1]H NMR spectrum is identical to (*R*)-(+)-2-phenyl-cyclohex-2-en-1-ol **8a**.

3.3. Reduction of α,β-unsaturated ketone 4 with catalyst (*R*,*R*)-A

A mixture of (*p*-cymene) ruthenium(II) chloride dimer (3.6 mg, 5.9×10^{-3} mmol) and *R*,*R*)-(−)-*N*-(*p*-toluene-sulphonyl)-1,2-diphenylethylene-diamine (TsDPEN) (4.3 mg, 12×10^{-3} mmol) in a formic acid:triethylamine mixture (5/2 molar) (2 mL) was stirred for 20 min at 28 °C. Then 3-(acetylamino)-but-3-en-2-one **4** (0.300 g, 2.4 mmol) was added and the reaction mixture was stirred for 2 days at

28 °C, filtered through a plug of silica gel and washed with a 20% solution of methanol in ethyl acetate (2×10 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product, which was purified by flash chromatography (0→10% v/v methanol/ethyl acetate) to afford a mixture of compounds described below (overall yield 61%).

3.3.1. 3-(Acetylamino)-butan-2-one 14. Yellow oil (0.079 g, 25%); ν_{max} (film) 3293, 1721 (CO), 1652 (NHCO), 1540, 1374, 1146 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.41 (1H, br s, N*H*), 4.66–4.57 (1H, m, C*H*), 2.23 (3H, s, COCH_3), 2.03 (3H, s, NHCOCH_3), 1.38 (3H, d, J=7.1 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 207.3, 170.2, 55.1, 27.0, 23.5, 18.0; *m/z* (CI) 147 ($[M+NH_4]^+$, 8%), 130 ($[M+H]^+$, 100), 88 (8), 86 ($[M-Ac]^+$, 9), 44 (31), 35 (25); HRMS (CI, NH_3): $[M+H]^+$, found 130.0865. $C_6H_{12}O_2N$ requires 130.0868.

3.3.2. 3-(Acetylamino)-butan-2-ol 15. Yellow oil (0.103 g, 33%); ν_{max} (film) 3308, 2978, 1652 (NHCO), 1557, 1455, 1374, 1301, 1142 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) (1:1 mixture of diastereomers) 6.14 (1H, br s, N*H*), 6.10 (1H, br s, N*H*), 4.04–3.90 (1H, m, C*H*), 3.90–3.81 (2H, m, 2×C*H*), 3.78–3.68 (1H, m, C*H*), 2.89 (2H, br s, 2×O*H*), 2.01 (3H, s, CH_3), 2.00 (3H, s, CH_3), 1.18 (6H, d, J=6.2 Hz, 2×CH_3), 1.17 (3H, d, J=7.0 Hz, CH_3), 1.11 (3H, d, J=7.0 Hz, CH_3); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) (1:1 mixture of diastereomers) 171.2, 171.1, 71.0, 70.5, 51.1, 51.0, 23.75, 23.7, 20.9, 19.1, 18.3, 14.6; *m/z* (CI) 132 ($[M+H]^+$, 100%), 114 ($[M-H_2O]^+$, 16), 87 (7), 44 (14), 35 (22); HRMS (CI, NH_3): $[M+H]^+$, found 132.1022. $C_6H_{14}O_2N$ requires 132.1024).

3.4. Reduction of α,β-unsaturated ketone 3c with catalyst (*R*,*R*)-C

A mixture of (pentamethycyclopentadienyl) rhodium(III) chloride dimer (1.4 mg, 2.2×10^{-3} mmol) and *R*,*R*)-(−)-*N*-(*p*-toluenesulphonyl)-1,2-diphenylethylene-diamine (TsDPEN) (1.6 mg, 4.4×10^{-3} mmol) in a formic acid–triethylamine mixture (5/2 molar) (1 mL) was stirred for 20 min at rt. Then, 2-(methoxycarbonylamino)-cyclohex-2-en-1-one **3c** (0.150 g, 0.88 mmol) was added and the reaction mixture was stirred at rt for 9 days. The reaction mixture was filtered through a plug of silica gel and washed with ethyl acetate (2×10 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product, which was purified by flash chromatography (0→50% v/v ethyl acetate/hexane) to afford a mixture of products described below (overall yield 67%).

3.4.1. (±)-2-(Methoxycarbonylamino)-cyclohexan-1-one 9. White crystals (0.030 g, 20%). Mp 54–56 °C. The product was confirmed to be racemic by chiral HPLC analysis (chiralcel OD column, hexane:ethanol=90:10, 0.5 mL/min), isomer 14.2 min, isomer 19.4 min. ν_{max} (Nujol) 1738, 1720, 1318, 1270, 1051 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.68 (1H, br s, N*H*), 4.30–4.22 (1H, m, C*H*NH), 3.67 (3H, s, CH_3), 2.65–2.46 (2H, m, COC*H*H, C*H*HCHNH), 2.46–2.31 (1H, m, COCH*H*), 2.20–2.08 (1H, m, $COCH_2CHH$), 1.95–1.56 (3H, m, $COCH_2CHHCH_2$), 1.50–1.39 (1H, m, CH*H*CHNH); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 208.6, 157.7, 59.8, 52.5, 41.4, 36.2, 28.3, 24.4; *m/z* (CI) 189 ($[M+NH_4]^+$, 8%), 172 ($[M+H]^+$, 100), 157 ($[MH-Me]^+$, 7), 140 ($[M-OMe]^+$, 11), 127 (10), 114 (19); HRMS (CI, NH_3): $[M+H]^+$, found 172.0975. $C_8H_{14}O_3N$ requires 172.0974).

3.4.2. (*R*)-(+)-2-(Methoxycarbonylamino)-cyclohex-2-en-1-ol 8c. Colourless oil (0.011 g, 7%); $[\alpha]_D^{11}$ +33.4 (*c* 0.2, EtOH). The product was determined to be of 92% ee from the reduction using (*S*,*S*)-(+)-*N*-(*p*-toluenesulphonyl)-1,2-diphenylethylene-diamine by chiral HPLC analysis chiralcel OD column, hexane:ethanol=90:10, 0.5 mL/min), *R* isomer 16.9 min, *S* isomer 31.8 min. The ^1H NMR spectrum is identical to the one previously described.

3.4.3. (−)-*cis*-(2-Hydroxy-cyclohexyl)-carbamic acid methyl ester 10. Colourless crystals (0.040 g, 26%). Mp 81–85 °C; $[\alpha]_D^{26}$ −20.1 (*c* 0.8, EtOH); ν_{max} ($CDCl_3$) 3436, 3013, 2939, 2862, 1698, 1519 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.09 (1H, br s, N*H*), 3.98–3.92 (1H, m, C*H*OH), 3.67 (4H, br s, C*H*NH, CH_3), 2.01 (1H, br s, O*H*), 1.80–1.69 (1H, m, CH(OH)C*H*H), 1.69–1.46 (5H, m, CH(OH)CH*H*C*H*HC*H*H, CH_2CHNH), 1.46–1.30 (2H, m, $CH(OH)CH_2CHHCHH$); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 157.3, 68.4, 52.9, 52.4, 32.0, 27.75, 24.1, 20.1; *m/z* (CI) 174 ($[M+H]^+$, 29%), 159 ($[MH-Me]^+$, 8), 142 ($[M-OMe]^+$, 100), 98 ($[M-NH_2CO_2Me]^+$, 14), 35 (34); HRMS (CI, NH_3): $[M+H]^+$, found 174.1130. $C_8H_{16}O_3N$ requires 174.1130. The enantiomers could not be separated by HPLC analysis or by chiral shift reagent ([Eu(hfc)$_3$]).

3.4.4. *trans*-(2-Hydroxy-cyclohexyl)-carbamic acid methyl ester 10. White crystals (0.020 g, 13%). Mp 111–113 °C (lit.,[26] 111–112 °C); ν_{max} ($CHCl_3$) 3436, 2933, 2860, 1707, 1519 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.78 (1H, br s, N*H*), 3.69 (3H, s, CH_3), 3.40–3.24 (2H, m, C*H*OH, C*H*NH), 3.00 (1H, br s, O*H*), 2.07–1.97 (2H, m, CH(OH)C*H*H, C*H*HCHNH), 1.76–1.67 (2H, m, $CH(OH)CH_2CHHCHH$), 1.41–1.09 (4H, m, CH(OH)CH*H*CH*H*CH*H*CH*H*); δ_C (75.5 MHz; $CDCl_3$; Me_4Si) 164.7, 75.4, 57.4, 52.7, 34.5, 32.2, 25.0, 24.4; *m/z* (CI) 174 ($[M+H]^+$, 76%), 159 ($[MH-Me]^+$, 33), 142 ($[M-OMe]^+$, 100), 98 ($[M-NH_2CO_2Me]^+$, 16), 56 (6), 35 (14); HRMS (CI, NH_3): $[M+H]^+$, found 174.1130. $C_8H_{16}O_3N$ requires 174.1130. The enantiomers could not be separated by HPLC analysis or by chiral shift reagent ([Eu(hfc)$_3$]).

3.5. Reduction of α,β-unsaturated ketone 4 with catalyst (*R*,*R*)-C

A mixture of (pentamethycyclopentadienyl) rhodium(III) chloride dimer (3.6 mg, 5.9×10^{-3} mmol) and (*R*,*R*)-(−)-*N*-(*p*-toluenesulphonyl)-1,2-diphenylethylene-diamine (4.3 mg, 12×10^{-3} mmol) in a formic acid:triethylamine mixture (5:2 molar) (2 mL) was stirred for 20 min at rt. Then 3-(acetylamino)-but-3-en-2-one **4** (0.300 g, 2.4 mmol) was added and the reaction mixture was stirred at rt for 2 days, filtered through a plug of silica gel and washed with a 20% solution of methanol in ethyl acetate (2×10 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product, which was purified by flash chromatography (0→10% v/v

methanol/ethyl acetate) to afford 3-(acetylamino)-butan-2-one **14** (0.212 g, 71%). ^{1}H NMR spectrum is identical to the one previously described.

3.6. General procedure for the α tosylation of ketones

Hydroxytosyloxyiodobenzene (3 g) was added to a stirred solution of ketone (0.9 g) in acetonitrile (60 mL). The reaction mixture was stirred under reflux for 2 h, cooled to rt and then concentrated in vacuo. Ethanol (2 mL) was added and the mixture was left overnight in a fridge. The suspension was then filtered and the solid washed with cold ethanol to give white crystals. Ethanol (1 mL) was added to the filtrate and the solution was cooled to 2 °C overnight. The suspension was filtered, washed with cold ethanol and the crystals combined with the first batch to afford the product.

3.6.1. α-Tosyloxy-*p*-methoxyacetophenone 23. Pale red solid (3.1 g, 74%). Mp 118–120 °C; ν_{max} (KBr) 3414, 1686 (C=O), 1602, 1360, 1249, 1172 cm^{-1}; δ_H (300 MHz; $CDCl_3$, Me_4Si) 2.4 (3H, s, tosyl Me), 3.9 (3H, s, methoxy Me), 5.2 (2H, s, CH_2), 6.9 (2H, d, J=9.0 Hz, ArH), 7.3 (2H, d, J=7.8 Hz, Tosyl ArH), 7.8 (2H, d, J=8.9 Hz, ArH), 7.8 (2H, d, J=8.3 Hz, tosyl ArH); δ_c (75.5 MHz; $CDCl_3$; Me_4Si) 22.0 (q), 56.0 (q), 70.2 (t), 114.5 (d), 128.6 (d), 130.3 (d), 130.8 (d); *m/z* (EI) 135 (100%, M^+-OTs); *m/z* (CI) 338 (100%, $M^{+\cdot}$ NH_4), 151 (98%, $M^{+\cdot}$ NH_4-OTs); HRMS (EI): M^+, found 320.0711. $C_{16}H_{16}O_5S$ requires 320.0718.

3.6.2. α-Tosyloxy-*p*-nitroacetophenone 24. Pale yellow crystalline solid (2.4 g, 59%). Mp 136–138 °C. [Found: C, 53.61; H, 3.85; N, 4.04. $C_{15}H_{13}O_6NS$ requires C, 53.73; H, 3.91; N, 4.18%); ν_{max} (KBr) 3406, 1710, 1525, 1361, 1172 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.5 (3H, s, Me), 5.3 (2H, s, CH_2), 7.3 (2H, d, J=8.5 Hz, tosyl ArH), 7.8 (2H, d, J=8.6 Hz, tosyl ArH), 8.1 (2H, d, J=8.7 Hz, ArH), 8.4 (2H, d, J=8.6 Hz, ArH); δ_c (75.5 MHz; $CDCl_3$; Me_4Si); 22.1 (q), 70.4 (t), 124.5 (d), 128.5 (d), 129.7 (d), 130.4 (d); *m/z* (EI) 335 (10%), 289 (11), 257 (8), 150 (100), 120 (98), 91 (72), 65 (40).

3.7. General procedure for asymmetric transfer hydrogenation of tosyloxyketones using rhodium

Pentamethylcyclopentadiene rhodium chloride dimer (6.2 mg, 0.01 mmol) and (1*R*,2*R*)-TsDPEN (7.3 mg, 0.02 mmol) were stirred in a formic acid:triethylamine mixture (2 mL, 5:2 molar ratio) in a flame dried Schlenk under a nitrogen atmosphere for 20 min. Ketone (4 mmol) was added and the reaction was stirred at rt until the substrate had been consumed as monitored by TLC (typically 12–48 h). The reaction mixture was then filtered through a plug of silica and washed with ethyl acetate (2×50 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product. This was purified by flash column chromatography (5–20% v/v ethyl acetate/hexane) to give the product.

3.8. General procedure for asymmetric transfer hydrogenation of tosyloxyketones using ruthenium

(*p*-Cymene)ruthenium chloride dimer (6.2 mg, 0.01 mmol) and (*R*,*R*)-TsDPEN (7.3 mg, 0.02 mmol) were stirred in a formic acid:triethylamine mixture (2 mL, 5:2 molar ratio) in a flame dried Schlenk under a nitrogen atmosphere at 28 °C for 20 min. Ketone (4 mmol) was added and the reaction was stirred at 28 °C until the substrate had disappeared by TLC (typically 48 h). The reaction mixture was then filtered through a plug of silica and washed with ethyl acetate (2× 50 mL). The organic fractions were collected, combined and concentrated in vacuo to give the crude product, which was purified by flash column chromatography (5–20% ethyl acetate in hexane) to give the product.

3.8.1. (*R*)-2-Tosyloxy-1-(*p*-methoxyphenyl)ethanol 21b. White crystalline solid (0.38 g, 59.1%). $[\alpha]_D^{20}$ −18 (*c* 0.742, $CHCl_3$); ν_{max} (KBr) 3490, 1700 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si) 2.4 (3H, s, Me), 3.1 (1H, br s, OH), 3.8 (3H, s, OMe), 4.1 (2H, m, CH_2), 4.9 (1H, dd, J=3.8, 4.5 Hz, CHOH), 6.8 (2H, d, J=6.6 Hz, ArH), 7.2 (2H, d, J=8.6 Hz, ArH), 7.3 (2H, d, J=8.3 Hz, tosyl ArH), 7.7 (2H, d, J=8.3 Hz, tosyl ArH); δ_c (75.5 MHz; $CDCl_3$; Me_4Si), 22.0 (d), 55.7 (q), 71.8 (q), 74.8 (t), 114.3 (d), 127.9 (d), 128.3 (d), 130.3 (d), 130.8 (s), 133.0 (s), 145.4 (s), 160.0 (s); *m/z* (CI) 322.0874 ($C_{16}H_{18}O_5S$ requires 322.0874), 340 (79%), 305 (83), 151 (79); (EI) 322 (13%), 305 (100); chiral HPLC; (7.5% ethanol/hexane; 0.5 mL/min), R_t 60.5, 67.6 min, 15% ee. A racemic standard was prepared by sodium borohydride reduction of **23**.

3.8.2. (*R*)-4-(4-Methoxyphenyl)-[1,3]-dioxalan-2-one 22b. White crystalline solid, (0.11 g, 28%). Mp 60–62 °C. [Found: C, 61.46; H, 5.21. $C_{10}H_{10}O_4$ requires C, 61.85; H, 5.19]; $[\alpha]_D^{20}$ −6.25 (*c* 0.942, $CHCl_3$); ν_{max} (KBr) 3413, 1783, 1615, 1252, 1174, 1047 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si), 3.8 (3H, s, Me), 4.3 (1H, t, J=8.3 Hz, CHHCHO), 4.7 (1H, t, J=8.3 Hz, CHHCHO), 5.6 (1H, t, J=8.1 Hz, CH_2CHO), 7.0 (2H, d, J=8.7 Hz, ArH), 7.3 (2H, d, J=8.9 Hz, ArH); δ_c (75.5 MHz; $CDCl_3$; Me_4Si), 55.8 (d), 71.5 (t), 78.6 (d), 115.0 (d), 127.8 (s), 128.3 (d), 161.1 (s); *m/z* (EI) 194 (63%), 121 (100), 91 (27), 77 (17); (CI) 212 (33%), 195 (25%), 135 (63), 35 (100). A racemic standard was prepared by sodium borohydride reduction of **24**.

3.8.3. (*R*)-2-Tosyloxy-1-(*p*-nitrophenyl)ethanol 21c. Yellow crystalline solid. Mp 163–166 °C. [Found; C, 53.39; H, 4.43; N, 4.18. $C_{15}H_{15}O_6NS$ requires C, 53.26; H, 4.47; N, 4.14%]; ν_{max} (KBr) 3505, 1603, 1515, 1346, 1170 cm^{-1}; δ_H (300 MHz; $CDCl_3$; Me_4Si), 3.3 (1H, s, Me) 4.1 (1H, d, J=4.4 Hz, CH_2), 4.9 (1H, q, J=4.7 Hz, CHOH), 6.1 (1H, d, J=4.7 Hz, OH), 7.4 (2H, d, J=7.9 Hz, tosyl ArH), 7.5 (2H, d, J=8.7 Hz, ArH), 7.6 (2H, d, J=8.3 Hz, tosyl ArH), 8.1 (2H, d, J=7.2 Hz, ArH); δ_c (75.5 MHz; $CDCl_3$; Me_4Si), 21.4 (q), 69.4 (d), 74.2 (t), 123.5 (d), 127.9 (d), 128.0 (d), 130.4 (d), 145.2 (s), 147.2 (s), 148.7 (s); *m/z* (CI) 355 (73%), 153 (56), 136 (100), 120 (62); (EI) 307 (19%), 106 (100), 91 (52); via rhodium catalysis: (0.53 g, 78%); $[\alpha]_D^{20}$ −32 (*c* 0.811, EtOAc); chiral HPLC; (7.5% ethanol/hexane; 0.5 mL/min), R_t 77, 85 min, 51% ee via ruthenium catalysis: (0.37 g, 55%); $[\alpha]_D^{20}$ −35.5 (*c* 0.42,

$CHCl_3$); chiral HPLC; (7.5% ethanol/hexane; 0.5 mL/min), R_t 77, 86 min, 85% ee.

3.9. Dioxolan-2-one hydrolysis to diol

Sodium hydroxide (10 mL, 2 M) was added to the crude reaction mixture (approx. 4 mmol) dissolved in diethyl ether (10 mL) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was extracted with ethyl acetate (3×25 mL) and the organic fractions were collected, combined, washed with brine (10 mL), dried (Na_2SO_4) and concentrated in vacuo to give diol 5.

3.9.1. (*S*)-1-(4-Methoxyphenyl)ethane-1,2-diol. (Enantiomeric standard); α-AD mix (1.4 g) was dissolved in ^{t}butyl alcohol (5 mL) and water (5 mL) at 0 °C. *p*-Methoxystyrene (0.14 g, 0.1 mmol) was added, and the reaction was stirred for 21 h. Sodium sulphate (1.5 g) was added and the reaction stirred for 10 min, the reaction mixture was extracted with dichloromethane (2×10 mL), and the solution evaporated under reduced pressure to give a white solid. This was purified by recrystallisation from ethyl acetate to give a white crystalline solid (0.09 g, 52%). ν_{max} (KBr) 3402, 3232, 1609, 1513, 1244, 1025 cm^{-1}; δ_H (300 MHz; CD_3CN, Me_4Si); 3.5 (2H, m, CH_2), 3.7 (3H, s, OMe), 4.6 (1H, m, CH), 6.9 (2H, d, J=8.6 Hz, ArH), 7.3 (2H, d, J=8.6 Hz, ArH); δ_c (75.5 MHz, CD_3OD, Me_4Si), 53.0 (d), 67.5 (t), 74.4 (q), 113.4 (d), 127.4 (d), 134.0 (s), 159.5 (s); *m/z* (EI) 168.0771 ($C_9H_{12}O_3$ requires 168.0786), 151 (39%), 137 (100), 121 (15), 109 (32), 94 (25), 77 (27); chiral HPLC; (10% IPA/hexane; 0.5 mL/min), R_t 37 min, >99% ee.

3.9.2. (*R*)-1-(4-Methoxyphenyl)ethane-1,2-diol. White solid, (5.7 mg, 51%). δ_H (300 MHZ, $CDCl_3$, Me_4Si); 2.1 (1H, br s, OH), 2.5 (1H, br s, OH), 3.6 (2H, m, CH_2), 3.7 (3H, s, OMe), 4.7 (1H, m, CH), 6.9 (2H, d, J=8.6 Hz, ArH), (2H, d, J=8.7 Hz, ArH); chiral HPLC; (10% IPA/hexane; 0.5 mL/min), R_t 32, 34 min, >52% ee.

3.9.3. (±)-2-Tosyloxy-1-(*p*-nitrophenyl)ethanol 21c. White/yellow crystalline solid (0.07 g, 52%). δ_H (300 MHz, DMSO-d_6, Me_4Si), 3.3 (3H, s, Me), 4.1 (2H, d, J=5.3 Hz, CH_2), 4.9 (1H, q, J=4.7 Hz, CHOH), 6.1 (1H, d, J=4.7 Hz, OH), 7.3 (2H, d, J=8.1 Hz, tosyl ArH), 7.5 (2H, d, J=8.7 Hz, ArH), 7.6 (2H, d, J=8.3 Hz, tosyl ArH), 8.1 (2H, d, J=8.9 Hz, ArH); chiral HPLC; (7.5% ethanol/hexane; 0.5 mL/min), R_t 76, 85 min (racemic standard).

3.9.4. 3-Phenyl-1,2-dihydronaphthalene.[33] Magnesium shavings (0.68 g, 2.81×10^{-2} M) were stirred in tetrahydrofuran (20 mL) and iodine (trace amount) was added. Bromobenzene (2.75 mL, 26.1 mmol) was added dropwise, and the reaction stirred for 20 min. 2-Tetralone (2.71 mL, 20.1 mmol) was added, and the reaction stirred at rt for 21 h, diluted with diethylether (100 mL) and washed with hydrochloric acid (0.5 M, aq, 50 mL). The organic extracts were dried over magnesium sulphate and evaporated to yield a yellow oil (3.46 g). This was dissolved in toluene (50 mL), *p*-toluenesulphonic acid (0.86 g, 4.52 mmol) was added, and the reaction refluxed for 3.5 h. The reaction was cooled to rt and washed with water (20 mL). The solution was dried over magnesium sulphate, and evaporated under reduced pressure to yield a brown oil (3.39 g). The crude product was purified by column chromatography on silica (2% ethyl acetate/hexane) to yield a pale yellow solid (1.25 g, 29%). Mp 50–55 °C; ν_{max} (neat) 3027, 2891, 2831, 2362, 1948, 1595, 1494, 1450, 1337, 1211, 1155, 1110, 1076, 1030, 937, 891, 747, 719, 688 cm^{-1}; δ_H (400 MHz, $CDCl_3$, Me_4Si); 2.72 (2H, t, J=6.4 Hz, CH_2CH_2CPh), 2.92 (2H, t, J=6.4 Hz, CH_2CPh), 6.83 (1H, s, C*H*), 7.13 (4H, m, Ar*H*), 7.22–7.36 (3H, m, Ar*H*), 7.52 (1H, m, Ar*H*); δ_c (100.5 MHz, $CDCl_3$, Me_4Si); 26.8 (t), 28.7 (t), 124.9 (d), 125.6 (d), 127.1 (d), 127.5 (d), 127.7 (d), 127.8 (d), 129.0 (d), 135.3 (s), 137.2 (s), 139.1 (s), 141.6 (s); *m/z* 206 (100%), 191 (15), 178 912), 152 (8), 128 (36), 115 (14), 91 (36); HRMS (EI): M^+, found 206.1105. $C_{16}H_{14}$ requires 206.1095).

3.9.5. 1-Cyclohexyl-3,4-dihydro-1*H*-naphthalen-2-one 27. Magnesium shavings (0.79 g, 32.8 mmol) were stirred in tetrahydrofuran (30 mL) and iodine (trace amount) was added. Cyclohexyl bromide (3.8 mL, 30.7 mmol) was added dropwise. The reaction was stirred at rt for 1.5 h. 1-Tetralone (2.8 mL, 20.5 mmol) was added slowly, stirred at rt for 29 h, then water (10 mL) was added. The reaction was extracted with diethyl ether (2×30 mL), and washed with hydrochloric acid (~1 M, 20 mL). The combined organic extracts were dried over magnesium sulphate and evaporated under reduced pressure to yield a yellow oil (3.40 g). The product was dissolved in toluene (80 mL), and *p*-toluenesulphonic acid (1.75 g, 9.21 mmol) was added. A Dean-Stark trap was fitted, and the reaction refluxed for 3 h. The reaction was cooled to rt and washed with water (50 mL), backwashed with toluene (2×20), dried over magnesium sulphate and evaporated under reduced pressure to yield a black oil (2.96 g). The product was purified by column chromatography on silica (1% ethyl acetate/hexane) to yield 4-cyclohexyl-1,2-dihydronaphthalene as a yellow oil (0.68 g, 16%), which was processed forward crude. *m*CPBA (0.54 g, 3.15 mmol) and sodium hydrogen carbonate (0.29 g, mmol) were stirred in dichloromethane:water (1:1, 24 mL) for 30 min. 4-Cyclohexyl-1,2-dihydronaphthalene (0.66 g, 3.15 mmol) was added, and the reaction stirred at rt for 4 h, washed with water (50 mL), and back extracted with dichloromethane (40 mL). The combined organic extracts were dried over magnesium sulphate, and evaporated to yield a black oil. (0.75 g). The oil was dissolved in toluene (20 mL), zinc iodide (0.29 g, 0.918 mmol) was added, and the reaction refluxed for 4 h. It was then cooled to rt and washed with water (30 mL) and back washed with toluene (20 mL), dried over magnesium sulphate and evaporated under reduced pressure to yield a brown oil. The product was purified by column chromatography on silica (10% ethyl acetate/hexane) to yield a yellow oil (0.098 g, 13%); ν_{max} (neat) 3063, 3019, 2920, 2849, 2666, 1707, 1485, 1447, 1365, 125, 1150, 1008, 744 cm^{-1}; δ_H (400 MHz, $CDCl_3$, Me_4Si); 0.94 (1H, m, Cy*H*), 1.14 (4H, m, Cy*H*), 1.47 (1H, m, Cy*H*), 1.58–1.76 (4H, m, Cy*H*), 1.81–1.90 (1H, m, Cy*H*), 2.44 (1H, ddd, J=7.0, 11.8, 18.3 Hz, C*H*HCH_2CO), 2.67 (1H, ddd, J=3.1, 6.3, 18.3 Hz, CH*H*CH_2CO), 2.88 (1H, ddd, J=2.3, 7.0, 15.8 Hz, C*H*HCO), 3.12 (1H, d, J=8.3 Hz, C*H*Cy), 3.31 (1H, ddd, J=6.3, 11.8, 18.3 Hz, CH*H*CO), 7.02–7.26 (4H, m, Ar*H*); δ_c (100.5 MHz, $CDCl_3$, Me_4Si); 26.4 (t), 26.7 (t), 27.9 (t), 31.4 (t), 32.1 (t), 37.6 (t), 40.9 (d), 62.4 (d), 126.7 (d), 127.3 (d), 128.4 (d), 130.5 (d), 136.9 (s), 137.0 (s), 217.2 (s); *m/z*

228 (3%), 146 (100), 128 911), 115 (18), 91 (5); HRMS (EI): M^+, found 228.1501. $C_{16}H_{20}O$ requires 228.1514).

3.9.6. 2-Phenyl-3,4-dihydro-2*H*-naphthalen-1-one 28. *m*CPBA (1.06 g, 6.18 mmol) and sodium hydrogen carbonate (0.63 g, 7.41 mmol) were stirred in dichloromethane:water (1:1, 40 mL) for 40 min. 3-Phenyl-1,2-dihydronaphthalene (1.27 g, 6.18 mmol) in dichloromethane:water (1:1, 20 mL) was added, and the reaction stirred at rt for 3.5 h. The organic layer was separated and the aqueous layer back extracted with dichloromethane (30 mL), dried over magnesium sulphate and evaporated to yield a brown solid (1.47 g). The solid was dissolved in toluene (40 mL), and zinc iodide (0.63 g, 1.98 mmol) was added. The reaction was refluxed for 2.5 h, washed with water (30 mL) and back extracted with toluene (20 mL), dried over magnesium sulphate, and evaporated under reduced pressure to yield a brown oil. The oil was purified by column chromatography on silica (4% ethyl acetate/hexane) to yield a yellow solid. Note the ketone is in the enol form in $CDCl_3$ solution, (0.50 g, 37%). Mp 72–74 °C. [Found: C, 86.47; H, 6.35. $C_{16}H_{14}O$ requires C, 86.45; H, 6.35]; ν_{max} (neat) 3060, 3027, 2958, 2889, 2361, 2340, 1943, 1673, 1596, 1450, 1311, 1218, 1006, 896, 757, 695 cm^{-1}; δ_H (400 MHz, $CDCl_3$, Me_4Si); 2.45 (2H, m, CH_2CH_2CHAr), 3.08 (2H, m, CH_2CHAr), 3.80 (1H, dd, $J=6.2$, 6.3 Hz, C*H*Ar), 7.19 (1H, d, $J=5.8$ Hz, Ar*H*), 7.26–7.36 (6H, m, Ar*H*), 7.50 (1H, m, Ar*H*), 8.10 (1H, d, $J=5.8$ Hz, Ar*H*); δ_c (100.5 MHz, $CDCl_3$, Me_4Si); 29.2 (t), 31.6 (t), 127.2 (d), 127.3 (d), 128.2 (d), 128.8 (d), 128.9 (d), 130.0 (d), 133.3 (s), 133.8 (d), 140.2 (s), 144.5 (s), 146.8 (s), 198.6 (s); *m*/*z* (EI+), 222 (80%), 194 (28), 165 (7), 131 (40), 118 (100), 90 (50), 77 (14).

3.9.7. (1*R*,2*S*) 1-Cyclohexyl-1,2,3,4-tetrahydronaphthalen-2-ol 31. Dichloro-*p*-cymene ruthenium dimer (1.6 mg, 2.61×10^{-3} mmol) and (*S*,*S*)-TsDPEN (1.9 mg, 5.22×10^{-3} mmol) were stirred in formic acid:triethylamine (5:2, 0.3 mL) at 28 °C for 40 min. 1-Cyclohexyl-3,4-dihydro-1*H*-naphthalen-2-one **27** (0.0641 g, 0.261 mmol) was added, and the reaction stirred at 28 °C for 140 h. The mixture was filtered through a pad of silica and washed through with ethyl acetate (20 mL), and evaporated under reduced pressure to yield a brown oil (0.0609 g). The product was purified by column chromatography on silica (10% ethyl acetate/hexane) to yield a brown oil (0.0193 g, 30%); $[\alpha]_D^{24}$ −116.67 ($c=0.98$, $CHCl_3$); ν_{max} (neat) 3274, 2919, 2846, 2359, 2342, 1487, 1445, 1048, 765, 735 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si); 0.71–0.85 (1H, m, aliphatic C*H*), 0.95–1.38 (5H, m, aliphatic C*H*), 1.55–1.93 (8H, m, 7× aliphatic C*H* + O*H*), 2.60 (1H, t, $J=4.1$ Hz, aliphatic C*H*), 2.76 (1H, m, aliphatic C*H*), 2.85–2.95 (1H, m, aliphatic C*H*), 4.18 (1H, m, C*H*OH), 6.52–7.22 (4H, m, Ar*H*); δ_c (300 MHz, $CDCl_3$, Me_4Si); 26.9 (t), 27.3 (t), 27.3 (t), 27.7 (t), 28.9 (t), 33.2 (t), 34.1 (t), 37.6 (d), 50.3 (d), 125.7 (d), 126.4 (d), 128.5 (d), 128.8 (d), 136.8 (s), 137.8 (s); *m*/*z* (EI) 230 (0.9%), 147 (10), 130 (100), 117 (15), 91 (13), 83 (11); HRMS (EI). M^+, 230.1672. $C_{16}H_{22}O$ requires 230.1671). Chiral HPLC; (1% IPA/hexane; 1.0 mL/min), R_t 17, 14 min, 80% ee. A racemic standard was prepared by sodium borohydride reduction of **27**.

3.9.8. (1*S*,2*S*) 2-Phenyl-1,2,3,4-tetrahydronaphthalen-1-ol 32. Dichloro-*p*-cymene ruthenium dimer (1.0 mg, 1.70×10^{-3} mmol) and (*S*,*S*) TsDPEN (1.2 mg, 3.40×10^{-3} mmol) was stirred in formic acid:triethylamine (5:2, 0.40 mL) at 28 °C for 20 min. 2-Phenyl-3,4-dihydro-2*H*-naphthalen-1-one **28** (0.0378 g, 0.170 mmol) was added and the reaction stirred at 28 °C for 77 h. The reaction was filtered through a plug of silica and washed through with ethyl acetate (40 mL), evaporated under reduced pressure to yield a brown oil (0.0423 g), then purified by column chromatography on silica (5% ethyl acetate/hexane) to yield a colourless solid (0.033 g, 87%). Mp 76–78 °C; $[\alpha]_D^{24}$ −186.90 ($c=1.16$, $CHCl_3$); ν_{max} (neat) 3260, 3022, 2360, 2341, 1601, 1488, 1450, 1430, 1096, 1074, 1008, 958, 758, 736, 696 cm^{-1}; δ_H (400 MHz, $CDCl_3$, Me_4Si); 1.58 (1H, d, $J=2.8$ Hz, O*H*), 1.96 (1H, m, C*H*HCH$_2$CAr), 2.44 (1H, ddd, $J=4.1$, 4.3, 5.5 Hz, CH*H*CH$_2$CAr), 2.92 (1H, m, C*H*HCAr), 3.02 (1H, m, CH*H*CAr), 3.10 (1H, m, C*H*Ar), 4.79 (1H, m, C*H*OH), 7.18–7.40 (9H, m, Ar*H*); δ_c (100.5 MHz, $CDCl_3$, Me_4Si); 21.9 (t), 30.1 (t), 46.4 (d), 71.7 (d), 126.6 (d), 127.2 (d), 128.5 (d), 128.6 (d), 129.1 (d), 129.5 (d), 130.4 (d), 137.1 (s), 138.0 (s), 143.0 (s); *m*/*z* (EI) 224 (15%), 206 (49), 120 (100), 91 (40); HRMS (EI): M^+, found 224.1199. $C_{16}H_{16}O$ requires 224.1201. Chiral HPLC; (5% IPA/hexane; 0.5 mL/min), R_t 13, 19 min, >98% ee. A racemic standard was prepared by sodium borohydride reduction of **28**.

3.9.9. (1*S*,2*S*) 2-Phenylcyclohexanol 33. Dichloro-*p*-cymene ruthenium dimer (1.8 mg, 2.87×10^{-3} mmol) and (*S*,*S*) TsDPEN (2.1 mg, 5.74×10^{-3} mmol) were stirred in formic acid:triethylamine (5:2, 1 mL) at 28 °C for 1 h. 2-Phenylcyclohexane **29** (0.20 g, 1.148 mmol) was added and the reaction stirred at 28 °C for 186 h. The reaction was filtered through a plug of silica, and washed through with ethyl acetate (30 mL), then evaporated under reduced pressure to yield a red solid (0.188 g, 72%). Mp 25–26 °C; $[\alpha]_D^{24}$ +213.37 ($c=0.95$ MeOH); ν_{max} (neat) 3558, 3439, 3024, 2927, 2858, 2365, 1941, 1600, 1496, 1445, 1227, 1182, 1114, 1049, 964, 744, 696 cm^{-1}; δ_H (300 MHz, $CDCl_3$, Me_4Si); 1.20–2.01 (9H, m, 4×CH_2 + O*H*), 2.75 (1H, dt, $J=3.0$, 12.8 Hz, C*H*Ar), 4.02 (1H, m, C*H*OH), 7.20–7.37 (5H, m, Ar*H*); δ_c (75.5 MHz, $CDCl_3$, Me_4Si); 20.0 (t), 24.7 (t), 26.6 (t), 33.3 (t), 48.4 (d), 71.0 (d), 126.9 (d), 128.2 (d), 128.9 (d), 144.4 (s); *m*/*z* (EI), 176 (100%), 130 (47), 117 (35), 104 (35), 91 (63), 69 (27); HRMS (EI): M^+, found 176.1199. $C_{12}H_{16}O$ requires 176.1201. 98% ee determined with 25% europium *tris*[3(hepafluropropylhydroxymethylene)-(+)-camphorate]. A racemic standard was prepared by sodium borohydride reduction of **29**.

Acknowledgements

We thank the EPSRC for a research studentship (J.H.) and EPSRC/GlaxoSmithKline pharmaceuticals for a CASE studentship (J.A.K.). Professor D. Games and Dr. B. Stein of the EPSRC National Mass Spectroscopic service (Swansea) are thanked for HRMS analysis of certain compounds. We also acknowledge the generous loan of ruthenium and rhodium salts by Johnson-Matthey limited and the use of the EPSRC's Chemical Database Service at Daresbury.[34]

References and notes

1. (a) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045. (b) Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 97. (c) Zassinovich, G.; Mestroni, G.; Gladiali, S. *Chem. Rev.* **1992**, *92*, 1051.
2. (a) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S.-I.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233. (b) Hashiguchi, S.; Fujii, A.; Takehara, J.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 7562. (c) Fujii, A.; Hashiguchi, S.; Uematsu, N.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 2521. (d) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916. (e) Haack, K. J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 285. (f) Murata, K.; Ikariya, T.; Noyori, R. *J. Org. Chem.* **1999**, *64*, 2186. (g) Yamakawa, M.; Yamada, I.; Noyori, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 2818. (h) Hamada, T.; Torii, T.; Izawa, K.; Noyori, R.; Ikariya, T. *Org. Lett.* **2002**, *4*, 4373. (i) Everaere, K.; Mortreux, A.; Carpentier, J.-F. *Adv. Synth. Catal.* **2003**, *345*, 67.
3. (a) Palmer, M.; Walsgrove, T.; Wills, M. *J. Org. Chem.* **1997**, *62*, 5226. (b) Nordin, S. J. M.; Roth, P.; Tarnai, T.; Alonso, D. A.; Brandt, P.; Andersson, P. G. *Chem. Eur. J.* **2001**, *7*, 1431. (c) Everaere, K.; Mortreux, A.; Bulliard, M.; Brussee, J.; van der Gen, A.; Nowogrocki, G.; Carpentier, J. F. *Eur. J. Org. Chem.* **2001**, 275. (d) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (e) Petra, D. G. I.; Reek, J. N. H.; Kamer, P. C. J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Commun.* **2000**, 683. (f) Mashima, K.; Abe, T.; Tani, K. *Chem. Lett.* **1998**, 1199. (g) Roth, P.; Anderson, P. G.; Somfai, P. *Chem. Commun.* **2002**, 1752. (h) Hannedouche, J.; Clarkson, G.; Wills, M. *J. Am. Chem. Soc.* **2004**, *126*, 986.
4. To our knowledge, only a few examples of highly enantioselective reduction of alkyl/alkyl ketones have been reported and these are using chiral bidentate phosphinooxazoline ligands: (a) Nishibayashi, Y.; Takei, I.; Uemura, S.; Hidai, M. *Organometallics* **1999**, *18*, 2291. (b) Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163. (c) Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215.
5. (a) Watanabe, M.; Murata, K.; Ikariya, T. *J. Org. Chem.* **2002**, *67*, 1712. (b) Koike, T.; Murata, K.; Ikariya, T. *Org. Lett.* **2000**, *2*, 3833. (c) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119. (d) Eustache, F.; Dalko, P. I.; Cossy, J. *Org. Lett.* **2002**, *4*, 1263. (e) Mohar, B.; Valleix, A.; Desmurs, J. R.; Felemez, M.; Wagner, A.; Mioskowski, C. *Chem. Commun.* **2001**, 2572. (f) Okano, K.; Murata, K.; Ikariya, T. *Tetrahedron Lett.* **2000**, *41*, 9277. (g) Kenny, J. A.; Palmer, M. J.; Smith, A. R. C.; Walsgrove, T.; Wills, M. *Synlett* **1999**, 1615. (h) Cross, D. J.; Kenny, J. A.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron: Asymmetry* **2001**, *12*, 1801. (i) Kawamoto, A.; Wills, M. *Tetrahedron: Asymmetry* **2000**, *11*, 3257. (j) Kawamoto, A. M.; Wills, M. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1916. (k) Alcock, N. W.; Mann, I.; Peach, P.; Wills, M. *Tetrahedron: Asymmetry* **2002**, *13*, 2485.
6. (a) Wills, M.; Hannedouche, J. *Curr. Opin. Drug Discov. Dev.* **2002**, *5*, 881. (b) Yamashita, H.; Ohtani, T.; Morita, S.; Otsubo, K.; Kan, K.; Matsubara, J.; Kitano, K.; Kawano, Y.; Uchida, M.; Tabusa, F. *Heterocycles* **2002**, *56*, 123. (c) Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M.; Miyagi, M.; Takehara, J.; Okano, K. *J. Org. Chem.* **2000**, *65*, 432. (d) Miyagi, M.; Takehara, J.; Collet, S.; Okano, K. *Org. Process Res. Dev.* **2000**, *4*, 346.
7. (a) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738. (b) Katho, A.; Carmona, D.; Viguri, F.; Remacha, C. D.; Kovacs, J.; Joo, F.; Oro, L. A. *J. Organomet. Chem.* **2000**, *594*, 299. (c) Hennig, M.; Puntener, K.; Scalone, M. *Tetrahedron: Asymmetry* **2000**, *11*, 1849. (d) Bianchini, C.; Glendenning, L.; Zanobini, F.; Farnetti, E.; Graziani, M.; Nagy, E. *J. Mol. Catal.* **1998**, *132*, 13. (e) Hannedouche, J.; Kenny, J. A.; Walsgrove, T.; Wills, M. *Synlett* **2002**, 263.
8. (a) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624. (b) Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3667. (c) Yamano, Y.; Watanabe, Y.; Watanabe, N.; Ito, M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2833. (d) Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 733. (e) Marshall, J. A.; Bourbeau, M. P. *Org. Lett.* **2003**, *5*, 3197.
9. Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumura, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1997**, *36*, 288.
10. Strictly, catalysts **A–C** are catalyst precursors. The true catalytic species are formed by HCl elimination.
11. Chidambaram, N.; Chandrasekaran, S. *J. Org. Chem.* **1987**, *52*, 5048.
12. Ponaras, A. A.; Younus Meah, M. *Tetrahedron Lett.* **1986**, *27*, 4953.
13. Magnus, P.; Lacour, J.; Coldham, I.; Mugrage, B.; Bauta, B. W. *Tetrahedron* **1995**, *51*, 11087.
14. Magnus, P.; Barth, L. *Tetrahedron* **1995**, *51*, 11075.
15. Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455.
16. Cossy, J.; Bouzbouz, S. *Tetrahedron Lett.* **1996**, *37*, 5091.
17. (a) Procedure adapted from: Driguez, H.; Vermes, J. P.; Lessard, J. *Can. J. Chem.* **1978**, *56*, 119. (b) Caron, G.; Lessard, J. *Tetrahedron* **1993**, *49*, 8039.
18. Bachand, C.; Driguez, H.; Paton, J. M.; Touchard, D.; Lessard, J. *J. Org. Chem.* **1974**, *39*, 3136.
19. Shishido, K.; Hiroya, K.; Ueno, Y.; Fukumoto, K. *J. Chem. Soc., Perkin Trans. 1* **1986**, 829.
20. Gemal, A. L.; Luche, J.-L. *J. Am. Chem. Soc.* **1981**, *103*, 5454.
21. Bäckvall, J.-E.; Andreasson, U. *Tetrahedron Lett.* **1993**, *34*, 5459.
22. Aelterman, W.; De Kimpe, N.; Kulinkovich, O. *Bull. Soc. Chim. Belg.* **1997**, *106*, 703.
23. Effenberger, F.; Beisswenger, T.; Rainer, A. *Chem. Ber.* **1985**, *118*, 4869.
24. Bianchini, C.; Peruzzini, M.; Farnetti, E.; Kaspar, J.; Graziani, M. *J. Organomet. Chem.* **1995**, *488*, 91.
25. Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236.
26. Baranov, S. V.; Mochalin, V. B. *Chem. Heterocyl. Compd. (Engl. Transl.)* **1981**, *8*, 779.
27. House, H. O.; Giese, R. W.; Kronberger, K.; Kaplan, J. P.; Simeone, J. F. *J. Am. Chem. Soc.* **1970**, *92*, 2800.
28. Dickinson, J. M.; Murphy, J. A.; Patterson, C. W.; Wooster, N. F. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1179.
29. Lee, D.; Huh, E. A.; Kim, M.-J.; Jung, H. M.; Koh, J. H.; Park, J. *Org. Lett.* **2000**, *2*, 2377.
30. Watanabe, M.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2218.
31. Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13525.
32. P. Peach, PhD Thesis, University of Warwick, 2003.
33. Lamberts, J. J. M.; Cuppen, T. J. H. M.; Laarhoven, W. H. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1819.
34. Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 746.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1877–1885

A glycal approach towards an efficient and stereodivergent synthesis of polyhydroxypyrrolidines☆

Vipin Kumar and Namakkal G. Ramesh*

Department of Chemistry, Indian Institute of Technology-Delhi, Hauz Khas, New Delhi 110016, India

Received 15 July 2005; revised 2 November 2005; accepted 17 November 2005

Available online 13 December 2005

Dedicated to Professor K. K. Balasubramanian on the occasion of his 66th birthday

Abstract—A stereo-defined synthesis of two diastereomers of polyhydroxypyrrolidines from 3,4,6-tri-*O*-benzyl-D-glucal **4** involving a cleavage–recyclization strategy is reported. Hemiacetal **7** obtained from glucal **4**, upon reduction with $LiAlH_4$ afforded diol **8**. Selective acetylation of **8** to **11**, followed by Mitsunobu cyclization yielded the diversely protected polyhydroxypyrrolidine **12**. Oxidation of **11** and subsequent stereoselective reduction led to **20**, the C-5 epimer of **11**, which upon Mitsunobu cyclization gave polyhydroxypyrrolidine **21**. Selective deprotection of the acetyl groups of **12** and **21** were carried out using Na_2CO_3 in MeOH. Polyhydroxypyrrolidines **12** and **21** upon heating with an excess of Mg in MeOH underwent simultaneous *N*-detosylation and deacetylation to afford amino alcohols **15** and **24**, respectively, in quantitative yield. Catalytic hydrogenation of **15** and **24** provided quantitatively the polyhydroxypyrrolidines **2** and **3**, respectively.

1. Introduction

Naturally occurring 3,4-dihydroxy-2,5-bis(hydroxymethyl)-pyrrolidine (DMDP) **1** (Fig. 1) and its analogues constitute a realm of important functional molecules that have drawn considerable attention by virtue of their potent and varied biological activities. These compounds are known to be selective inhibitors of glycosidases, and hence are expected to have potential chemotherapeutic utilities such as antidiabetic, anticancer and anti-HIV properties.[2] DMDP **1** is a strong inhibitor of α- and β-glucosidases but shows weak inhibition against α-fucosidase.[3b,4b,d] Contrastingly, polyhydroxypyrrolidine **2** shows mild inhibitory action against α- and β-glucosidases but is a strong inhibitor of α-fucosidase.[3b] Compound **3**, a C-5 epimer of DMDP, exhibits a broad spectrum of inhibition against α- and β-glucosidases and α-mannosidase. Significantly, while compound **3** is a selective inhibitor of α-galcatosidase (and not β-galactosidase), naturally occurring DMDP **1** is totally inactive against galactosidases.[4b,d] This varied biological significance has provided a great impetus worldwide for the synthesis of DMDP and its analogues.[3–7]

Several carbohydrate-based[3,5] as well as a few chemoenzymatic[4] and asymmetric[6] syntheses of DMDP analogues **2** and **3** have been reported. However, a more general approach towards various diastereomers of polyhydroxypyrrolidines, especially a stereodivergent route proceeding through a common intermediate, still remains a challenging task. The well-defined multichiral architecture of carbohydrates as well as their structural resemblance to aza sugars provides unique advantages of a 'chiral pool' strategy over others. Among the carbohydrate based approaches, D-mannitol has been the choice of chiral synthon by several groups, for the synthesis of **2**.[3a,b,d–h] Surprisingly, glycals have hardly been used in the synthesis of polyhydroxypyrrolidines, despite their ready availability. Herein we report an efficient stereodivergent synthesis of two diastereomers of polyhydroxypyrrolidines, **2** and **3**, from tri-*O*-benzyl-D-glucal **4** in seven and nine steps, respectively, in high yields.

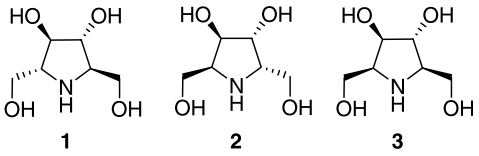


Figure 1.

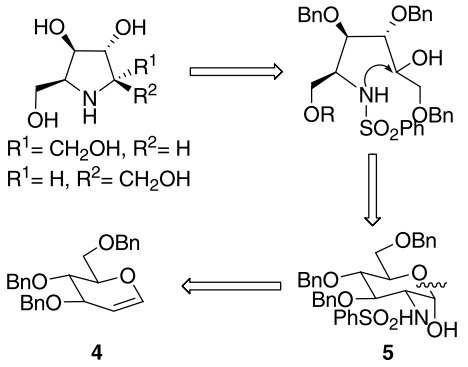
☆ See Ref.1

Keywords: Azasugars; Glycosidase inhibitors; Polyhydroxypyrrolidines; Glycals; Mitsunobu cyclization.
* Corresponding author. Tel.: +91 11 26596584; fax: +91 11 26581102/26582037; e-mail: ramesh@chemistry.iitd.ac.in

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.037

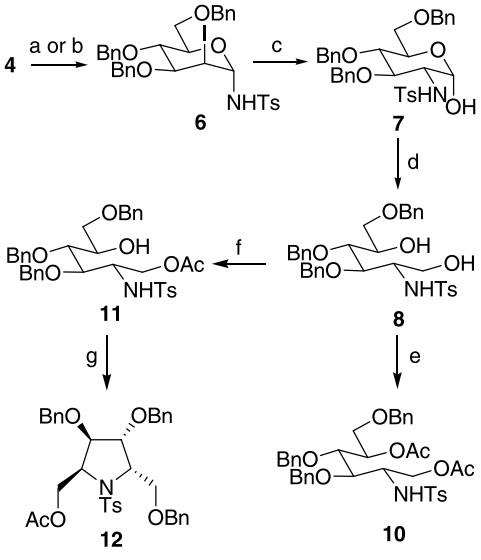
2. Results and discussion

Danishefsky et al. have earlier reported a two step synthesis of 3,4,6-tri-*O*-benzyl-2-deoxy-2-sulfonamido-α-D-glucopyranose **5** from tri-*O*-benzyl-D-glucal **4**.[8] However, the synthetic utility of this compound has not been explored much. It occurred to us that the hemiacetal **5** would be an ideal substrate for a stereo-defined synthesis of polyhydroxypyrrolidines via the cleavage of O–C_1 bond followed by ring closure through the nitrogen (Scheme 1).



Scheme 1.

Thus, iodonium di-*sym*-collidine perchlorate-promoted stereoselective iodosulfonamidation of 3,4,6-tri-*O*-benzyl-D-glucal **4** with *p*-toluenesulfonamide afforded 3,4,6-tri-*O*-benzyl-2-deoxy-2-iodo-1-deoxy-1-(*p*-toluenesulfonamido)-α-D-mannopyranose **6** in 78% yield (Scheme 2).[8] Subsequently, we have found that *N*-iodosuccinimide (NIS) is a convenient alternative to iodonium di-*sym*-collidine perchlorate in the above reaction; iodo compound **6** was obtained in an isolated yield of 90%. Exposure of **6** to Et_3N in aq THF provided the required material, namely, 3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-α-D-glucopyranose **7** in 83% yield.[8] The next step in our synthetic sequence was the reduction of the hemiacetal **7** to the corresponding diol **8**. Even though structurally similar compounds have been readily reduced using $NaBH_4$,[5a,9] surprisingly compound **7** was robust to reduction with $NaBH_4$ under various conditions (entries 1–3; Table 1). Other reagents such as $NaBH_4/CeCl_3\cdot 7H_2O$, Bu_4NBH_4, $LiAlH_4$ also failed to reduce **7** at room temperature (entries 4–7; Table 1). The reason for the reluctance to reduction, under mild conditions, may presumably be due to an initial formation of a very highly stable complex such as **9** (Fig. 2). After extensive experimentation, reduction of **7** to **8** was successfully accomplished in quantitative yield by heating **7** with 3 equiv of $LiAlH_4$ in THF at reflux (entry 9, Table 1).[10] Acetylation of **8** with excess Ac_2O in the presence of a catalytic amount of DMAP afforded the diacetate **10** in 65% yield. However, selective protection of the primary hydroxyl group of **8** is an essential requisite in our synthetic approach to polyhydroxypyrrolidine **12**. This was conveniently achieved by using 0.9 equiv of Ac_2O at −15 °C in the presence of a catalytic amount of DMAP. Monoacetate **11** was isolated in 66% along with 16% of unreacted diol **8**, which could be readily separated and re-used. The mono acetylation thus avoids the need for expensive TBDMSCl or trityl chloride that are commonly used for the selective protection of primary hydroxyl group. Intramolecular cyclization of **11** proceeded smoothly under Mitsunobu conditions, with complete inversion of configuration at C-5, to afford **12** in 88% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) I(*sym*-collidine)$_2$ClO$_4$ (1.6 equiv), *p*-toluenesulfonamide (1.27 equiv), molecular sieves 4 Å, CH_2Cl_2, 0 °C, 0.5 h, 78%; (b) NIS (1.1 equiv), *p*-toluenesulfonamide (1.1 equiv), molecular sieves 4 Å, CH_2Cl_2, 0 °C, 0.5 h, 90%; (c) Et_3N (2 equiv), THF–H_2O (5/2), rt 4 h, 83%; (d) $LiAlH_4$ (3 equiv), THF, reflux, 10 h 100%; (e) Ac_2O (4 equiv), cat. DMAP, pyridine, rt, 2 h, 65%; (f) Ac_2O (0.9 equiv), cat. DMAP, pyridine, −15 °C, 2.25 h, **11**=66%, **8**=16%; (g) Ph_3P (1.3 equiv), DEAD (1.5 equiv), THF, 0 °C, 15 min, 88%.

Table 1. Reduction of hemiacetal (**7**) under various conditions

Entry	Reagent	Condition	Conversion of **7** (%)
1	$NaBH_4$/MeOH	10 equiv, room temperature, 30 min	0
2	$NaBH_4$/MeOH–THF	1.5 equiv, room temperature, 4 h	0
3	$NaBH_4$/MeOH–THF	10 equiv, room temperature, 16 h	0
4	$NaBH_4/CeCl_3\cdot 7H_2O$	10 equiv, room temperature, 17 h	0
5	Bu_4NBH_4/THF	1.1 equiv, room temperature, 12 h	0
6	$LiAlH_4$/THF	1.1 equiv, room temperature, 10 h	0
7	$LiAlH_4$/THF	2 equiv, room temperature, 6.5 h	0
8	$LiAlH_4$/THF	3 equiv, reflux, 5 h	60
9	$LiAlH_4$/THF	3 equiv, reflux, 10 h	100[a]

[a] Yield is also 100% (see experimental details).

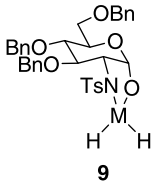
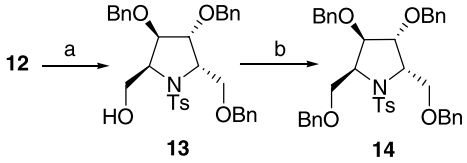


Figure 2.

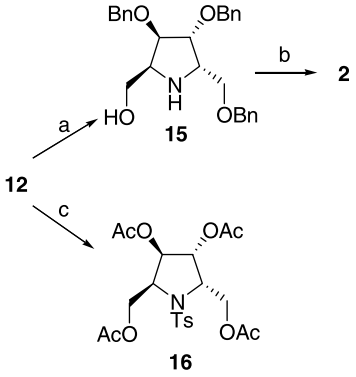
The stereochemistry at C-5 of **12** was confirmed by a two-step transformation into a C_2-symmetric tetra-*O*-benzyl derivative **14**. Deacetylation of **12** (Na_2CO_3 in MeOH, 93%)

to **13** followed by benzylation using NaH and benzyl chloride afforded **14** in 60% yield whose ^{13}C NMR spectrum displayed signals corresponding to only half the number of carbon atoms (Scheme 3).



Scheme 3. Reagents and conditions: (a) Na_2CO_3 (3 equiv), MeOH, rt, 12 h, 93%; (b) NaH (1.2 equiv), BnCl (1.2 equiv), DMF, rt, 6 h, 60%.

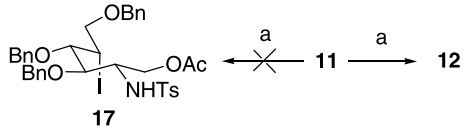
One-step global deprotection of **12** to **2** was attempted using Na/liquid NH_3. Even though the reaction was successful, isolation of the water-soluble **2** from the reaction mixture was tedious and time-consuming. Hence, a two-step procedure was followed. Simultaneous *N*-detosylation and deacetylation of **12** were carried out by heating with 20 equiv of Mg in MeOH for 1 h at reflux. Catalytic hydrogenation of the resulting amino alcohol **15** over Pd/C in ethanol afforded the polyhydroxypyrrolidine **2** in quantitative yield (over two steps) (Scheme 4). The specific rotation $\{[\alpha]_D^{28}$ −12 (*c* 0.20, H_2O)} and spectral data (^1H and ^{13}C NMR) of the polyhydroxypyrrolidine obtained were consistent with the literature values for the free base **2** reported by Dureault et al.[3f] Different data were reported by Dureault et al. $\{[\alpha]_D$ −13 (*c* 1, H_2O); ^1H NMR (D_2O) δ 4.37 (2H, d), 3.87–4.10 (6H, m); ^{13}C NMR (D_2O) δ 77.2, 65.4, 60.0.}[3f] and by Zou et al. $\{[\alpha]_D$ +9.6 (*c* 0.57, H_2O); ^1H NMR (D_2O) δ 3.76 (2H, d), 3.43 (2H, dd), 3.36 (2H, dd), 3.02 (2H, dt); ^{13}C NMR (D_2O) δ 79.93, 64.41, 63.33.}[3d] for free base **2**. More confusingly, the data reported by Dureault et al. for free base **2**[3f] and by Zou et al. for its HCl salt[3d] were identical. It should be pointed out that in all the earlier literature reports, invariably acidic reagents and/or resins have been used in the final deprotection step to obtain the polyhydroxypyrrolidine **2**. In our case, the reactions and work-up (especially the deprotecting steps) have been carried out under completely neutral conditions. The formation of HCl salt is thus extremely unlikely and that the data reported in this manuscript may unambiguously provide the correct one for the free base **2**.



Scheme 4. Reagents and conditions: (a) Mg (20 equiv), MeOH, reflux, 1 h, 100%; (b) H_2, 5% Pd–C, 30 °C, 13 h, 100%; (c) 32% HBr in AcOH, EtOAc, rt, 72 h, 51%.

It is worth mentioning here that among the various reagents available for *N*-detosylation,[11-13] Mg in MeOH[12] was best suited in our case. Though a few scattered reports are available,[12] only one example has been so far reported for *N*-detosylation of an unactivated sulfonamide using Mg in MeOH and that too under sonication.[12b] In our case, *N*-detosylation occurred smoothly even without sonication. On the other hand, exposure of **12** to 32% HBr in AcOH, did not bring about the expected *N*-detosylation, but interestingly took a different course to afford the tetra acetyl derivative **16** (Scheme 4).[13] The formation of **16** may be visualized by initial debenzylation of the hydroxyl groups followed by their acetylation under the reaction conditions.

Our next attempt was the synthesis of **3** (C-5 epimer of **2**), which requires the inversion of configuration at C-5 of **11**. It was envisaged that iodination of **11** to **17** followed by an intramolecular S_N2 displacement of the iodine by the nitrogen would lead to **21**. However, when **11** was treated with triphenylphosphine/I_2/imidazole (Garegg's reagent), **17** was not formed. Instead, a facile intramolecular cyclization occurred to afford **12** in 60% yield, with the spectral data and specific rotation identical to those obtained from Mitsunobu cyclization (Scheme 5). Garegg's reagent has found wide applications in the halogenation of alcohols, dehydration, didehydoxylation, epoxide formation, reduction of nitro group to nitrile[14] etc. We are not aware of this reagent combination being used for such an intramolecular cyclization. This protocol thus provides a synthetic alternative to Mitsunobu cyclization in the present case.



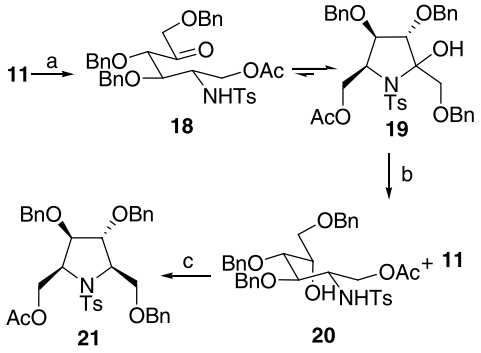
Scheme 5. Reagents and conditions: (a) PPh_3 (4 equiv), I_2 (3 equiv), imidazole (4 equiv), toluene, reflux, 45 min, 60%.

In order to epimerize the C-5 centre of **11**, an oxidation–reduction route was followed. Oxidation of **11** with PDC proceeded smoothly to afford the carbonyl compound **18**, which was found to exist preferentially in its cyclic form **19**, as evident from the absence of ketone C=O signal in its ^{13}C NMR spectrum and appearance of a quaternary carbon signal at δ 88.97 (due to C-5 carbon). Selective reduction of **19** to **20** was then attempted with $NaBH_4$ at room temperature. The outcome of the initial reaction was not very encouraging, with the epimeric alcohols **11** and **20** obtained in equal proportions (entry 1, Table 2). In order to achieve stereoselective reduction of **19** to **20**, various reagent combinations were tried under different conditions, but most of them either provided **11** and **20** in equal proportions or preferably **11** (entries 2–4, Table 2). However, with $NaBH_4/CeCl_3\cdot 7H_2O$, at −78 °C, stereoselective reduction in favour of **20** could be realized in a ratio of 4:1 (entry 6, Table 2). The epimeric alcohols **11** and **20** could be readily separated by column chromatography. Mitsunobu cyclization of **20** provided protected polyhydroxypyrrolidine **21** in 70% yield (Scheme 6). The stereochemistry at C-5 of **21** was confirmed as before by converting it to the tetra-*O*-benzyl derivative **23** whose ^{13}C NMR spectrum displayed signals corresponding to same number of carbon atoms (Scheme 7).

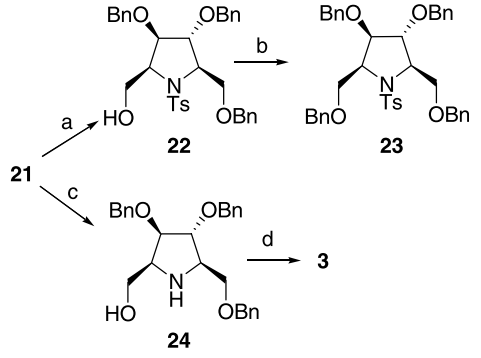
Table 2. Stereoselective reduction of **19** under various conditions

Entry	Reagent	Condition	Ratio[a] **11**:**20**
1	$NaBH_4/CH_2Cl_2$–MeOH	1 equiv, room temperature, 30 min	50:50
2	Bu_4NBH_4/CH_2Cl_2	1.2 equiv, room temperature, 15 min	60:40
3	Bu_4NBH_4/CH_2Cl_2	1.2 equiv, 0 °C, 30 min	60:40
4	$NaBH_4/CH_2Cl_2$–MeOH	1 equiv, −25 °C, 1 h	50:50
5	$NaBH_4/CeCl_3\cdot 7H_2O$ MeOH	1 equiv, 0 °C, 20 min	35:65
6	$NaBH_4/CeCl_3\cdot 7H_2O$ MeOH	3.6 equiv, −78 °C, 5 h	20:80[b]

[a] Diastereomeric ratio was determined using NMR spectra.
[b] Isolated yield of **11**=16%; **20**=60%.



Scheme 6. Reagents and conditions: (a) PDC (6 equiv), CH_2Cl_2, reflux, 8 h, 83%; (b) $NaBH_4$ (3.6 equiv), $CeCl_3\cdot 7H_2O$ (1.2 equiv), MeOH, −78 °C, 5 h, **20**=60%, **11**=16%; (c) Ph_3P (1.3 equiv), DEAD (1.5 equiv), THF, 0 °C, 15 min, 70%.



Scheme 7. Reagents and conditions: (a) Na_2CO_3 (6 equiv), CH_2Cl_2–MeOH, rt, 51 h, 90%; (b) NaH (1.2 equiv), BnCl (1.2 equiv), DMF, rt, 6 h, 60%; (c) Mg (20 equiv), MeOH, reflux, 1 h, 100%; (d) H_2, 5% Pd–C, 30 °C, 12 h, 100%.

Finally, the parent polyhydroxypyrrolidine **3** was obtained in two steps from **21** as before in quantitative yield. The spectral data and optical rotation {$[\alpha]_D^{28}$ +22.7 (*c* 0.14, H_2O)} of **3** were consistent with the literature values {$[\alpha]_D^{23}$ +25.7 (*c* 4.00, H_2O),[4d] $[\alpha]_D^{20}$ +25.1 (*c* 1.5, H_2O)[5b]} for the free base.

3. Conclusion

In conclusion, we have developed a simple and stereo-divergent route to two diastereomers of polyhydroxypyrrolidines from readily available 3,4,6-tri-*O*-benzyl-D-glucal **4**. The salient feature of our methodology is that stereo-defined two diastereomers of polyhydroxypyrrolidines could be obtained in high yields from a common intermediate, which is not the case in most of the carbohydrate based approaches reported so far. The diverse protection of **12** and **21** assumes synthetic significance and provides a handle for selective deprotection, which may find applications in the synthesis of other complex natural products. Extension of this methodology to other glycals would make this a much more general approach to these classes of compounds. During the course of our synthesis, we have demonstrated that Garegg's protocol provides a synthetic alternative to Mitsunobu cyclization in ideal cases. We have also shown that Mg in MeOH is a very convenient and simple reagent for *N*-detosylation of even unactivated sulfonamides, which may provide a synthetically useful protocol in organic chemistry.

4. Experimental

4.1. General

All solvents were purified using standard procedures. Thin-layer chromatography (TLC) was performed on Merck precoated silica gel aluminium plates. Flash column chromatography was performed on 230–400 mesh silica gel. Optical rotations were recorded on an Autopol II and Autopol V (Rudolph Research Flanders, New Jersey) instrument. All the rotations were measured at 589 nm (sodium D′ line). Melting points of the compounds are uncorrected. IR spectra were taken within the range 4000–400 cm^{-1} as KBr pellets on a Nicolet (Madison, USA) FT-IR spectrophotometer (Model Protege 460). All the ^1H and ^{13}C NMR spectra were recorded on 300 MHz Bruker Spectrospin DPX FT NMR. Chemical shifts are reported as δ values (ppm) relative to internal standard Me_4Si. Elemental analyses were performed on a Perkin Elmer 2400 series II analyzer. Mass spectra were recorded using Waters Micro Mass Q-TOF instrument.

4.1.1. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-iodo-1-deoxy-1-(*p*-toluenesulfonamido)-α-D-mannopyranose (6).

Procedure A: using I(sym-collidine)$_2$ClO$_4$. To a suspension of tri-*O*-benzyl glucal **4** (4.91 g, 11.80 mmol), *p*-toluenesulfonamide (2.56 g, 14.98 mmol) and powdered 4 Å molecular sieves (4.91 g) in dry CH_2Cl_2 (20 mL) was added I(*sym*-collidine)$_2$$ClO_4$[15] (8.85 g, 18.88 mmol) under a N_2 atmosphere and stirred at 0 °C. When the reaction was complete (TLC, 30 min), the solid was filtered and the filtrate was diluted with ether (300 mL). The combined organic layer was washed with saturated $Na_2S_2O_3$ (200 mL), $CuSO_4$ (200 mL), NaCl (2×200 mL), dried over sodium sulfate and concentrated. Flash chromatography (5:1 hexane/ethyl acetate) of the resulting residue provided **6** (6.56 g, 78%) as a white solid.

Procedure B: using NIS. To a suspension of tri-*O*-benzyl glucal **4** (3.33 g, 8.00 mmol), *p*-toluenesulfonamide (1.50 g, 8.80 mmol) and powdered 4 Å molecular sieves (3.50 g) in dry CH_2Cl_2 (15 mL) was added NIS (1.98 g, 8.80 mmol) under a N_2 atmosphere and stirred at 0 °C. When the reaction was complete (TLC, 30 min), the solid was filtered and the filtrate was diluted with CH_2Cl_2 (300 mL). The combined organic layer was washed with saturated

$Na_2S_2O_3$ (200 mL), water (200 mL), dried over sodium sulfate and concentrated. Flash chromatography (5:1, hexane/ethyl acetate) of the resulting residue provided **6** (5.14 g, 90%) as a white solid, mp 120–122 °C; [Found: C, 57.38; H, 5.10; N, 1.78. $C_{34}H_{36}O_6NSI$ requires C, 57.22; H, 5.05; N, 1.96%]; $[\alpha]_D^{28}$ −21.2 (*c* 0.99, $CHCl_3$); ν_{max}(KBr) 3254, 3030, 2863, 1496, 1453, 1432, 1358, 1325, 1157, 1103, 1041, 1027, 697 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, J=8.2 Hz, SO_2Ar), 7.33–7.25 (13H, m, *Ph*), 7.16–7.11 (4H, m, SO_2Ar, *Ph*), 5.58 (2H, br s, N*H*, H-1), 4.66 (2H, t, J=10.8 Hz, CH_2Ph), 4.56–4.52 (2H, m, CH_2Ph), 4.46–4.35 (3H, m), 3.82 (1H, t, J=7.6 Hz), 3.54–3.44 (2H, m), 3.14–3.07 (2H, m), 2.33 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 143.7, 138.1, 137.8, 137.3, 129.5, 128.2, 128.0, 127.7, 127.5, 127.2, 83.5, 77.1, 74.8, 74.6, 73.2, 73.0, 71.2, 67.5, 31.3, 21.4.

4.1.2. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-α-D-glucopyranose (7). To a stirred solution of **6** (4.06 g, 5.69 mmol) in THF (60 mL) and H_2O (24 mL) at room temperature was added triethylamine (1.58 mL, 11.38 mmol). After 4 h, saturated NaCl solution (250 mL) was added and the resulting mixture was extracted with ether (4×100 mL). The combined organic layer was dried over sodium sulfate and concentrated to give a white solid, which on recrystallization (THF/hexane) provided pure **7** (2.85 g, 83%) as a white solid, mp 178 °C (decomp.); [Found: C, 67.76; H, 6.28; N, 1.87. $C_{34}H_{37}O_7NS$ requires C, 67.66; H, 6.13; N, 2.32%]; $[\alpha]_D^{28}$ +23.8 (*c* 0.79, THF); ν_{max}(KBr) 3284, 3031, 2912, 1451, 1327, 1160, 1140, 1072, 1048, 1028, 700 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, J=8.2 Hz, SO_2Ar), 7.30–7.08 (17H, m, SO_2Ar, *Ph*), 5.01 (1H, br s, H-1), 4.88 (1H, d, J=9.1 Hz, N*H* exchangeable with D_2O), 4.74–4.67 (3H, m), 4.57–4.41 (3H, m), 3.96 (1H, d, J=9.1 Hz), 3.70–3.42 (5H, m), 2.88 (1H, br s, O*H* exchangeable with D_2O), 2.35 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 142.7, 138.2, 138.0, 137.7, 129.3, 128.1, 127.9, 127.8, 127.5, 127.1, 126.7, 91.5, 79.8, 78.3, 75.1, 74.6, 73.2, 69.6, 68.8, 57.8, 21.3; HRMS (ESI): $[M+Na]^+$, found 626.2225. $C_{34}H_{37}O_7NSNa$ requires 626.2188.

4.1.3. 3,4,6-Tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-D-glucitol (8). In a flame dried 250 mL three-necked round bottomed flask **7** (5.96 g, 9.88 mmol) was dissolved in dry THF (90 mL) under a N_2 atmosphere. To this, LAH (1.13 g, 29.64 mmol) was added and the reaction was heated at reflux for 10 h. The reaction mixture was then quenched with 2 M HCl (250 mL) and extracted with $CHCl_3$ (4×100 mL). The combined organic layer was dried over sodium sulfate and concentrated to yield **8** (5.98 g, quantitative) as colourless gummy liquid. The compound was pure enough (NMR) and does not require further purification; $[\alpha]_D^{28}$ −3.0 (*c* 1.95, THF); ν_{max}(KBr) 3397, 3030, 2922, 1453, 1328, 1157, 1097, 737, 698; δ_H (300 MHz, $CDCl_3$) 7.71 (2H, d, J=7.7 Hz, SO_2Ar), 7.33–7.20 (17H, m, SO_2Ar, *Ph*), 5.31 (1H, d, J=8.0 Hz, N*H* exchangeable with D_2O), 4.72 (1H, d, J=11.2 Hz), 4.62 (1H, d, J=11.2 Hz), 4.54–4.46 (4H, m, 2×CH_2Ph), 3.83–3.74 (2H, m), 3.64–3.57 (m, 3H), 3.49–3.46 (2H, m), 3.32–3.24 (1H, m), 2.68 (1H, d, J=5.6 Hz, O*H* exchangeable with D_2O), 2.36 (3H, s, *Me*), 2.17 (1H, dd, J=4.4, 3.0 Hz, O*H* exchangeable with D_2O); δ_C (75 MHz, $CDCl_3$) 143.1, 137.8, 137.6, 129.4, 128.2, 127.7, 126.8, 78.4, 78.2, 74.6, 73.8, 73.1, 71.0, 70.8, 62.2, 55.5, 21.2; HRMS (ESI): $[M+Na]^+$, found 628.2336. $C_{34}H_{39}O_7NSNa$ requires 628.2345.

4.1.4. 1,5-Di-*O*-acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-D-glucitol (10). To a stirred solution of **8** (0.51 g, 0.84 mmol) in pyridine (1 mL) was added DMAP (0.015 g, 0.126 mmol) and acetic anhydride (0.32 mL, 3.37 mmol). The reaction mixture was allowed to stir for 2 h at room temperature, quenched with 100 mL of 10% HCl and extracted with ethyl acetate (3×50 mL). The combined organic layer was then washed with brine (100 mL), dried over sodium sulfate and concentrated. Flash chromatography (6:1 hexane/ethyl acetate) of resulting residue provided **10** (0.38 g, 65%) as colourless gummy liquid; $[\alpha]_D^{28}$ +2.8 (*c* 2.01, $CHCl_3$); ν_{max}(KBr) 3431, 3030, 2925, 1740, 1631, 1366, 1231, 1162, 1092, 1048, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.71 (2H, d, J=7.9 Hz, SO_2Ar), 7.31–7.20 (17H, m, SO_2Ar, *Ph*), 5.19 (1H, d, J=4.5 Hz, H-1), 5.06 (1H, d, J=8.5 Hz, N*H* exchangeable with D_2O), 4.76 (1H, d, J=11 Hz), 4.67 (1H, d, J=11.2 Hz), 4.51 (3H, m), 4.44 (1H, d, J=11 Hz), 3.85–3.73 (6H, m), 3.55 (1H, dd, J=10.2, 5.4 Hz), 2.37 (3H, s, $SO_2C_6H_4Me$), 2.03 (3H, s, CHOCO*Me*), 1.72 (3H, s, CH_2OCOMe); δ_C (75 MHz, $CDCl_3$) 170.1, 169.8, 143.0, 137.8, 137.6, 137.2, 129.4, 128.1, 127.6, 127.4, 126.8, 77.9, 76.5, 74.7, 74.2, 72.8, 72.4, 67.8, 63.1, 53.1, 21.2, 20.8, 20.2; HRMS (ESI): $[M+Na]^+$, found: 712.2516. $C_{38}H_{43}O_9NSNa$ requires 712.2556.

4.1.5. 1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-D-glucitol (11). To a stirred solution of **8** (1.74 g, 2.87 mmol) in pyridine (3 mL) was added DMAP (0.035 g, 0.287 mmol). After the reaction mixture was cooled to −15 °C, acetic anhydride (0.24 mL, 2.58 mmol) dissolved in pyridine (2 mL) was added dropwise during the course of 1.25 h. After complete addition, the reaction mixture was stirred for an additional 1 h at −15 °C, then quenched with 10% HCl (200 mL) and extracted with ethyl acetate (4×75 mL). The combined organic layer was washed with brine (3×100 mL), dried over sodium sulfate and concentrated. Flash chromatography (5:1 hexane/ethyl acetate) of the resulting residue provided **11** (1.23 g, 66%) as colourless gummy liquid along with unreacted **8** (0.28 g, 16%). Compound **11**. $[\alpha]_D^{28}$ +6.2 (*c* 1.10, $CHCl_3$); ν_{max} (KBr) 3442, 3030, 2921, 2856, 2361, 1739, 1631, 1227, 1158, 1097, 766, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, J=8.1 Hz, SO_2Ar), 7.34–7.19 (17H, m, SO_2Ar, *Ph*), 5.15 (1H, d, J=7.4 Hz, N*H* exchangeable with D_2O), 4.76 (1H, d, J=11.2 Hz), 4.68 (1H, d, J=11.2 Hz), 4.56–4.45 (4H, m, 2×CH_2Ph), 3.97 (1H, dd, J=12.6, 3.6 Hz), 3.93–3.88 (2H, m), 3.83–3.80 (1H, m), 3.76 (1H, d, J=7.2 Hz), 3.66 (1H, t, J=6.9 Hz), 3.59 (1H, dd, J=9.5, 3.6 Hz), 3.48 (1H, dd, J=9.5, 5.0 Hz), 2.59 (1H, d, J=5.9 Hz, O*H* exchangeable with D_2O), 2.37 (3H, s, $SO_2C_6H_4Me$), 1.75 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 170.4, 143.1, 137.8, 137.6, 137.3, 129.4, 128.2, 127.7, 126.8, 78.1, 74.5, 74.1, 73.1, 71.2, 70.6, 63.4, 53.3, 21.2, 20.3; HRMS (ESI): MH^+, found: 648.2623. $C_{36}H_{42}O_8NS$ requires 648.2631.

4.1.6. (2*S*,3*R*,4*R*,5*S*)-2-(Acetoxymethyl)-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (12). *Procedure A: using Mitsunobu conditions*. In a flame dried 100 mL three-necked round bottomed flask was taken **11** (2.21 g, 3.42 mmol) and dissolved in dry

THF (15 mL) under a N_2 atmosphere. PPh_3 (1.16 g, 4.45 mmol) was then added and the reaction mixture was cooled to 0 °C. DEAD (0.81 mL, 5.13 mmol) was injected into the reaction mixture dropwise. After the reaction was over (15 min, as indicated by TLC), the reaction was stopped and the solvent was evaporated. Flash chromatography (6:1 hexane/ethyl acetate) of resulting residue provided **12** (1.89 g, 88%) as colourless gummy liquid.

Procedure B: using Garegg's reagent. A mixture of **11** (0.200 g, 0.309 mmol), PPh_3 (0.324 g, 1.236 mmol), imidazole (0.840 g, 1.236 mmol) and iodine (0.235 g, 0.927 mmol) in toluene (5 mL) was stirred under reflux at a bath temperature of 120 °C for 45 min, after which the reaction mixture was cooled to room temperature. Saturated $NaHCO_3$ solution (10 mL) was added and the mixture was stirred for 5 min. Compound was extracted with chloroform (3×75 mL), and washed with saturated $Na_2S_2O_3$ solution (100 mL). The combined organic layer was dried over sodium sulfate and concentrated. Flash chromatography (6:1 hexane/ethyl acetate) of the resulting residue provided **12** (0.116 g, 60%) as colourless gummy liquid; $[\alpha]_D^{28}$ −21.4 (*c* 1.26, $CHCl_3$); ν_{max}(KBr) 2925, 2854, 1740, 1454, 1243, 1219, 1155, 1128, 764, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, d, *J*=8.1 Hz, SO_2Ar), 7.28–7.17 (15H, m, *Ph*), 7.11–7.08 (2H, m, SO_2Ar), 4.61–4.55 (3H, m), 4.53 (1H, d, *J*=11.7 Hz), 4.47 (1H, d, *J*=8.4 Hz), 4.37 (1H, dd, *J*=11.8, 3.9 Hz), 4.30 (1H, d, *J*=11.8 Hz), 4.23–4.18 (3H, m), 4.00–3.94 (2H, m), 3.87 (1H, dd, *J*=9.9, 3.9 Hz), 3.64 (1H, d, *J*=9.9 Hz), 2.33 (3H, s, $SO_2C_6H_4Me$), 1.71 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 169.9, 143.0, 138.2, 137.7, 129.3, 128.3, 128.0, 127.6, 127.5, 127.1, 126.9, 80.2, 80.0, 73.3, 72.9, 66.8, 61.4, 58.2, 56.8, 21.3, 20.6; HRMS (ESI): MH^+, found: 630.2552. $C_{36}H_{40}O_7NS$ requires 630.2525.

4.1.7. (2*S*,3*R*,4*R*,5*S*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-2-(hydroxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (13). To a stirred solution of **12** (0.050 g, 0.079 mmol) in MeOH (1 mL) at room temperature was added Na_2CO_3 (0.025 g, 0.237 mmol). After completion of the reaction (12 h, as indicated by TLC), the solid was filtered and MeOH was evaporated to obtain **13** (0.043 g, 93%) as colourless viscous liquid. The compound was pure enough (NMR) and does not require further purification; $[\alpha]_D^{28}$ −26.6 (*c* 0.70, $CHCl_3$); ν_{max}(KBr) 3351, 3258, 2924, 1616, 1333, 1160, 1110, 758, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J*=7.9 Hz, SO_2Ar), 7.30–7.18 (15H, m, *Ph*), 7.01 (2H, d, *J*=3.8 Hz, SO_2Ar), 4.70–4.50 (5H, m), 4.30–4.10 (4H, m), 3.99 (1H, d, *J*=10 Hz), 3.85–3.77 (3H, m), 3.57 (1H, d, *J*=10 Hz), 2.69 (1H, br s, O*H* exchangeable with D_2O), 2.32 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 143.2, 138.0, 137.7, 137.5, 137.0, 129.3, 128.3, 127.9, 127.6, 127.3, 127.1, 126.8, 81.3, 81.2, 73.3, 73.1, 72.6, 66.2, 61.0, 59.8, 58.2, 21.3; HRMS (ESI): $[M+Na]^+$, found: 610.2220. $C_{34}H_{37}O_6NSNa$ requires 610.2239.

4.1.8. (2*S*,3*R*,4*R*,5*S*)-3,4-Di-*O*-benzyl-2,5-bis(benzyloxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (14). To a solution of **13** (0.050 g, 0.085 mmol) in DMF (1 mL) at 0 °C was added NaH (0.004 g as 60% in mineral oil; 0.102 mmol) and benzyl chloride (0.012 mL, 0.102 mmol). Reaction mixture was then brought to room temperature and allowed to stir for 6 h. The reaction mixture was then quenched with water (10 mL) and extracted with ethyl acetate (3×50 mL). The combined organic layer was then washed with brine (100 mL), dried over sodium sulfate and concentrated. Flash chromatography (8:1 hexane/ethyl acetate) of resulting residue provided **14** (0.034 g, 60%) as colourless gummy liquid; $[\alpha]_D^{28}$ −27.9 (*c* 0.42, $CHCl_3$); ν_{max}(KBr) 3030, 2925, 2870, 2360, 1769, 1722, 1604, 1454, 1367, 1207, 1102, 1027, 738, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.68 (2H, d, *J*=7.9 Hz, SO_2Ar), 7.38–7.12 (22H, m, *Ph*), 4.63 (2H, d, *J*=11.9 Hz), 4.55 (2H, d, *J*=11.9 Hz), 4.46–4.45 (2H, m), 4.32 (2H, d, *J*=11.9 Hz), 4.26 (2H, d, *J*=11.9 Hz), 3.94 (2H, br s), 3.86 (2H, dd, *J*=9.8, 3.8 Hz), 3.63 (2H, d, *J*=9.8 Hz), 2.28 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 142.7, 138.4, 138.2, 129.1, 128.7, 128.2, 128.0, 127.4, 127.1, 126.3, 80.7, 73.1, 72.9, 67.1, 58.4, 21.3; HRMS (ESI): $[M+Na]^+$, found: 700.2701. $C_{41}H_{43}O_6NSNa$ requires 700.2709.

4.1.9. (2*S*,3*R*,4*R*,5*S*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-2-(hydroxymethyl)pyrrolidine (15). In a flame dried 50 mL three-necked round bottomed flask was taken activated Mg turnings (0.252 g, 10.50 mmol) and further flame dried under a N_2 atmosphere. Compound **12** (0.330 g, 0.525 mmol) dissolved in dry MeOH (7 mL) was transferred into the reaction flask and heated at reflux for 1 h. After this time, MeOH was evaporated, water (400 mL) was added to the reaction mixture and stirred for 15 min. Compound was then extracted with chloroform (4×100 mL), dried over sodium sulfate and concentrated to obtain **15** (0.227 g, 100%) as colourless gummy liquid. The compound was pure enough (NMR) and does not require further purification; $[\alpha]_D^{28}$ −6.1 (*c* 0.79, THF); ν_{max}(KBr) 3397, 3030, 2924, 2871, 1769, 1722, 1605, 1454, 1377, 1103, 1028, 738, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33–7.23 (15H, m, *Ph*), 4.59–4.53 (5H, m), 4.39 (1H, d, *J*=11.8 Hz), 4.06 (2H, d, *J*=4.1 Hz), 3.78 (1H, dd, *J*=11.8, 4.5 Hz), 3.71–3.55 (4H, m), 3.48 (1H, dd, *J*=9.3, 4.5 Hz), 1.90 (2H, br s, N*H*, O*H* exchangeable with D_2O); δ_C (75 MHz, $CDCl_3$) 137.9, 137.4, 137.1, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.7, 127.6, 81.8, 80.8, 73.3, 72.4, 72.3, 67.3, 61.0, 60.0, 59.1; HRMS (ESI): MH^+, found: 434.2332. $C_{27}H_{32}O_4N$ requires 434.2331.

4.1.10. (2*S*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (2). Five percentage palladium on charcoal (0.270 g) was taken up in a 50 mL three-necked round bottomed flask. Compound **15** (0.090 g, 0.208 mmol) dissolved in ethanol (4 mL) was added to the reaction flask. H_2 gas was then bubbled slowly into reaction mixture for 13 h at 30 °C, after which time the reaction mixture was filtered and ethanol was evaporated. Recrystallization of the resulting residue (MeOH/ethyl acetate) yielded **2** (0.034 g, 100%) as a white solid; $[\alpha]_D^{28}$ −12 (*c* 0.20, H_2O); δ_H (300 MHz, D_2O) 4.22 (2H, br s), 3.95–3.74 (6H, m); δ_C (75 MHz, D_2O) 78.3, 66.4, 61.1.

4.1.11. (2*S*,3*R*,4*R*,5*S*)-3,4-Di-*O*-(acetyl)-2,5-bis(acetoxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (16). To a stirred, 0 °C cooled, 32% HBr in AcOH (5 mL), **12** (0.200 g, 0.318 mmol) dissolved in ethyl acetate (2 mL) was added in four portions over a period of 2 h. Then reaction mixture was allowed to stir for 72 h at room temperature, after which

time it was cooled to 0 °C, quenched with saturated $NaHCO_3$ solution (10 mL) and extracted with chloroform (4×50 mL). The combined organic layer was washed with water, dried over sodium sulfate and concentrated. Flash chromatography (3:1 hexane/ethyl acetate) of the resulting residue provided **16** (0.079 g, 51%) as colourless gummy liquid; $[\alpha]_D^{28}$ −5.7 (*c* 0.34, $CHCl_3$); ν_{max}(KBr) 2924, 2361, 1745, 1643, 1371, 1223, 1158, 1100, 1055, 771 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J*=7.7 Hz, SO_2Ar), 7.30 (2H, d, *J*=7.7 Hz, SO_2Ar), 5.42 (2H, d, *J*=4.2 Hz, H-2, H-5), 4.36 (4H, m, 2×CH_2OCOMe), 4.17 (2H, d, *J*=11.5 Hz, H-3, H-4), 2.43 (3H, s, $SO_2C_6H_4Me$), 2.07 (6H, s, 2×CHOCO*Me*), 1.88 (6H, s, 2×CH_2OCO*Me*); δ_C (75 MHz, $CDCl_3$) 170.2, 169.7, 143.8, 136.8, 129.7, 127.0, 72.5, 60.5, 55.9, 21.4, 20.5; HRMS (ESI): MH^+, found: 486.1432. $C_{21}H_{28}O_{10}NS$ requires 486.1434.

4.1.12. Oxidation of 11 to 19 using PDC. To a flame dried 100 mL three-necked round bottomed flask, was added **11** (0.70 g, 1.08 mmol) dissolved in dry dichloromethane (15 mL) under a N_2 atmosphere. To this, PDC (2.44 g, 6.48 mmol) was added and the reaction mixture heated at 45°C for 8 h, after which time the residue was filtered through a G-4 sintered filter and washed with more dichloromethane (100 mL). The organic layer was washed with 10% HCl (2×75 mL) and saturated $NaHCO_3$ (100 mL). The organic layer was dried over sodium sulfate and concentrated. Flash chromatography (6:1 hexane/ethyl acetate) of resulting residue provided **19** (0.58 g, 83%) as colourless gummy liquid; $[\alpha]_D^{28}$ −18.7 (*c* 1.48, $CHCl_3$); ν_{max}(KBr) 3445, 3030, 2923, 2856, 2361, 1740, 1455, 1347, 1242, 1159, 1091, 738, 699, 666 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.82 (2H, d, *J*=7.5 Hz, SO_2Ar), 7.31–7.20 (17H, m, SO_2Ar, *Ph*), 4.71–4.47 (6H, m, 3×CH_2Ph), 4.30–4.16 (4H, m), 3.90–3.76 (4H, m), 2.40 (3H, s, $SO_2C_6H_4Me$), 1.84 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 170.1, 143.2, 137.7, 137.0, 129.5, 129.0, 128.2, 128.0, 127.9, 127.6, 127.4, 127.1, 126.9, 88.9, 82.0, 79.5, 73.7, 73.4, 73.1, 63.0, 56.0, 21.3, 20.6; HRMS (ESI): $[M+Na]^+$, found: 668.2306. $C_{36}H_{39}O_8NSNa$ requires 668.2294.

4.1.13. 1-*O*-Acetyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-(*p*-toluenesulfonamido)-L-iditol (20). To a −78 °C cooled solution of **19** (0.97 g, 1.50 mmol) in MeOH (3 mL) was added $CeCl_3 \cdot 7H_2O$ (0.67 g, 1.80 mmol) and the mixture allowed to stir for 1 h. After 1 h, $NaBH_4$ (0.205 g, 5.40 mmol) was added in portions over a period of 4.5 h. The reaction was stirred for an additional 30 min, at −78 °C. It was then brought to room temperature, MeOH was evaporated and saturated NH_4Cl (100 mL) was added to quench the reaction. The solution was extracted with chloroform (3×75 mL). The combined organic layer was washed with brine (200 mL), dried over sodium sulfate and concentrated. Flash chromatography (5:1 hexane/ethyl acetate) of resulting residue provided **20** (0.584 g, 60%) as white crystalline solid along with **11** (0.155 g, 16%). Compound **20**, mp 104 °C; $[\alpha]_D^{28}$ −2.8 (*c* 0.35, THF); ν_{max}(KBr) 3443, 2922, 2853, 2359, 1728, 1638, 1452, 1332, 1159, 1091, 768, 699 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.73 (2H, d, *J*=7.9 Hz, SO_2Ar), 7.33–7.21 (17H, m, SO_2Ar, *Ph*), 5.09 (1H, d, *J*=9.1 Hz, N*H* exchangeable with D_2O), 4.83 (1H, d, *J*=10.8 Hz), 4.76 (1H, d, *J*=10.8 Hz), 4.51–4.43 (4H, m), 3.94–3.73 (5H, m), 3.62 (1H, d, *J*=8.6 Hz), 3.47 (1H, t, *J*=8.6 Hz), 3.24 (1H, dd, *J*=9.3, 4.0 Hz), 2.37 (4H, s, $SO_2C_6H_4Me$, O*H*), 1.82 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 170.3, 143.3, 138.2, 137.7, 137.6, 132.1, 131.9, 129.6, 128.3, 128.2, 127.9, 127.8, 126.9, 78.9, 77.2, 75.3, 75.0, 73.2, 71.6, 69.3, 63.3, 52.4, 21.4, 20.4; HRMS (ESI): MH^+, found: 648.2650. $C_{36}H_{42}O_8NS$ requires 648.2631.

4.1.14. (2*S*,3*R*,4*R*,5*R*)-2-(Acetoxymethyl)-3,4-di-*O*-benzyl-5-(benzyloxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (21). Following a similar procedure as for compound **12**, 1.14 g (1.77 mmol) of **20** provided **21** (0.77 g, 70%) as white crystalline solid, mp 84 °C; $[\alpha]_D^{28}$ −4.2 (*c* 1.42, THF); ν_{max}(KBr) 3028, 2907, 1744, 1455, 1348, 1216, 1161, 1080, 1031, 739, 667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.72 (2H, d, *J*=7.8 Hz, SO_2Ar), 7.29–7.18 (15H, m, *Ph*), 7.00 (2H, m, SO_2Ar), 4.60–4.53 (2H, m, CH_2Ph), 4.47 (1H, d, *J*=11.9 Hz), 4.41–4.31 (3H, m), 4.24 (2H, m), 4.04 (1H, m), 3.88–3.84 (1H, dd, *J*=12.5, 5.8 Hz), 3.78–3.71 (3H, m), 3.68–3.64 (1H, m), 2.34 (3H, s, $SO_2C_6H_4Me$), 1.96 (3H, s, CO*Me*); δ_C (75 MHz, $CDCl_3$) 170.4, 143.7, 138.0, 137.4, 136.9, 133.3, 129.5, 128.3, 128.1, 127.8, 127.5, 127.3, 81.1, 79.9, 73.2, 72.1, 71.0, 70.5, 64.1, 62.3, 59.7, 21.4, 20.7; HRMS (ESI): MH^+, found: 630.2532. $C_{36}H_{40}O_7NS$ requires 630.2525.

4.1.15. (2*S*,3*R*,4*R*,5*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-2-(hydroxymethyl)-*N*-(*p*-toluenesulfonamido)-pyrrolidine (22). To a stirred solution of **21** (0.070 g, 0.11 mmol) in dichloromethane (1 mL), was added MeOH (1 mL) and Na_2CO_3 (0.070 g, 0.67 mmol) at room temperature. After completion of the reaction (51 h, TLC), the reaction mixture was filtered and MeOH was evaporated to obtain **22** (0.059 g, 90%) as colourless viscous liquid. The compound was pure enough (NMR) and does not require further purification; $[\alpha]_D^{28}$ −11.1 (*c* 0.67, $CHCl_3$); ν_{max}(KBr) 3464, 3030, 2924, 2870, 2359, 1733, 1496, 1454, 1343, 1216, 1162, 1089, 1045, 1028, 751, 698, 669 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.66 (2H, d, *J*=7.7 Hz, SO_2Ar), 7.33–7.18 (15H, m, *Ph*), 7.05 (2H, br s, SO_2Ar), 4.53–4.25 (7H, m), 3.88–3.82 (3H, m), 3.70–3.59 (4H, m), 3.27 (1H, br s, O*H* exchangeable with D_2O), 2.36 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 143.8, 137.6, 136.9, 133.5, 129.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.7, 82.3, 80.1, 73.4, 72.4, 71.8, 70.0, 63.5, 62.8, 62.6, 21.5; HRMS (ESI): $[M+Na]^+$, found: 610.2249. $C_{34}H_{37}O_6NSNa$ requires 610.2239.

4.1.16. (2*R*,3*R*,4*R*,5*S*)-3,4-Di-*O*-benzyl-2,5-(benzyloxymethyl)-*N*-(*p*-toluenesulfonamido)pyrrolidine (23). Following a similar procedure as for compound **14**, 0.050 g (0.085 mmol) of **22** provided **23** (0.034 g, 60%) as colourless gummy liquid; $[\alpha]_D^{28}$ −3.8 (*c* 0.26, $CHCl_3$); ν_{max}(KBr) 3030, 2361, 2335, 1737, 1646, 1454, 1350, 1162, 1090, 737, 697, 667 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (2H, d, *J*=7.5 Hz, SO_2Ar), 7.29–7.24 (18H, m, *Ph*), 7.15 (2H, m, *Ph*), 6.94 (2H, d, *J*=4.2 Hz, SO_2Ar), 4.53–4.39 (6H, m), 4.15 (2H, s), 4.04 (1H, dd, *J*=4.9, 3.2 Hz), 4.00 (1H, s), 3.89–3.72 (6H, m), 2.29 (3H, s, *Me*); δ_C (75 MHz, $CDCl_3$) 143.5, 138.2, 137.6, 133.3, 129.4, 128.2, 127.9, 127.6, 127.1, 81.6, 80.5, 73.4, 73.2, 72.6, 71.0, 70.7, 68.7, 64.5, 61.6, 21.4; HRMS (ESI): $[M+Na]^+$, found: 700.2695. $C_{41}H_{43}O_6NSNa$ requires 700.2709.

4.1.17. (2*S*,3*R*,4*R*,5*R*)-3,4-Di-*O*-benzyl-5-(benzyloxymethyl)-2-(hydroxymethyl)pyrrolidine (24). Following a similar procedure as for compound **15**, 0.316 g (0.502 mmol) of **21** provided **24** (0.217 g, quantitative) as colourless gummy liquid; $[\alpha]_D^{28}$ +11.3 (*c* 0.53, $CHCl_3$); ν_{max}(KBr) 3380, 3030, 2922, 2857, 1649, 1453, 1364, 1251, 1095, 912, 743, 698 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.31–7.24 (15H, m, *Ph*), 4.58–4.49 (5H, m), 4.41 (1H, d, *J*=11.6 Hz), 4.06 (1H, dd, *J*=5.1, 2.0 Hz), 3.92 (1H, dd, *J*=4.6, 2.0 Hz), 3.87 (1H, dd, *J*=11.8, 4.4 Hz), 3.78 (1H, dd, *J*=11.6, 4.4 Hz), 3.61–3.57 (2H, m), 3.35 (2H, t, *J*=4.9 Hz), 2.36 (2H, br s, N*H*, O*H* exchangeable with D_2O); δ_C (75 MHz, $CDCl_3$) 138.0, 137.5, 128.3, 127.6, 86.2, 84.6, 73.1, 71.9, 71.5, 70.7, 63.1, 61.5, 60.9; HRMS (ESI): MH^+, found: 434.2368. $C_{27}H_{32}O_4N$ requires 434.2331. Spectral data of **24** were consistent with the literature values reported by Wong et al.[5i]

4.1.18. (2*R*,3*R*,4*R*,5*S*)-3,4-Dihydroxy-2,5-bis(hydroxymethyl)pyrrolidine (3). Following a similar procedure as for compound **2**, 0.252 g (0.582 mmol) of **24** using 1.512 g of 5% palladium on charcoal for 12 h at 30 °C provided 0.094 g of **3** (quantitative); $[\alpha]_D^{28}$ +22.7 (*c* 0.14, H_2O); δ_H (300 MHz, D_2O) 4.17 (1H, br t), 3.99 (1H, br t), 3.92–3.71 (5H, m), 3.50 (1H, quintet, *J*=4.0 Hz,); δ_C (75 MHz, D_2O): 78.4, 77.0, 69.1, 65.4, 61.7, 59.3; δ_C (75 MHz, MeOH-d_4): δ 76.2, 74.8, 66.7, 62.1, 59.6, 57.1.

Acknowledgements

We are grateful to the Department of Science and Technology, New Delhi for financial support (SP/S1/G-19/2000). V.K. thanks the Council of Scientific and Industrial Research, New Delhi for a research fellowship.

References and notes

1. Part of this work was presented at the IUPAC International Conference on Biodiversity and Natural products, Chemistry and Medical Applications, (ICOB-4 and ISCNP-24), New Delhi, India, January 26–31, 2004. Abstract no. P-166.
2. For recent reviews on biological activity, see: (a) Asano, N. *Glycobiology* **2003**, *13*, 93R–104R. (b) Nishimura, Y. *Curr. Top. Med. Chem.* **2003**, *3*, 575–591. (c) Wrodnigg, T. M. *Monatsh. Chem.* **2002**, *133*, 393–426.
3. (a) Esposito, A.; Falorni, M.; Taddei, M. *Tetrahedron Lett.* **1998**, *39*, 6543–6546. (b) Le Merrer, Y.; Poitout, L.; Depezay, J. C.; Dosbaa, I.; Geoffroy, S.; Foglietti, M.-J. *Bioorg. Med. Chem.* **1997**, *5*, 519–533. (c) Poitout, L.; Le Merrer, Y.; Depezay, J. C. *Tetrahedron Lett.* **1996**, *37*, 1609–1612. (d) Zou, W.; Szarek, W. A. *Carbohydr. Res.* **1993**, *242*, 311–314. (e) Masaki, Y.; Oda, H.; Kazuta, K.; Usui, A.; Itoh, A.; Xu, F. *Tetrahedron Lett.* **1992**, *33*, 5089–5092. (f) Dureault, A.; Portal, M.; Depezay, J. C. *Synlett* **1991**, 225–226. (g) Shing, T. K. M. *Tetrahedron* **1988**, *44*, 7261–7264. (h) Shing, T. K. M. *J. Chem. Soc., Chem. Commun.* **1987**, 262–263. (i) Martin, M.-T.; Morin, C. *Heterocycles* **1986**, *24*, 901–902. (j) Morin, C. *Tetrahedron Lett.* **1984**, *25*, 3205–3206.
4. (a) Dax, K.; Peinsipp, R.; Stutz, A. E. *Tetrahedron Lett.* **1997**, *38*, 225–226. (b) Takayama, S.; Martin, R.; Wu, J.; Laslo, K.; Siuzdak, G.; Wong, C.-H. *J. Am. Chem. Soc.* **1997**, *119*, 8146–8151. (c) Legler, G.; Korth, A.; Berger, A.; Ekhart, C.; Gradnig, G.; Stutz, A. E. *Carbohydr. Res.* **1993**, *250*, 67–77. (d) Liu, K. K.-C.; Kajimoto, T.; Chen, L.; Zhong, Z.; Ichikawa, Y.; Wong, C. H. *J. Org. Chem.* **1991**, *56*, 6280–6289.
5. (a) Liu, J.; Numa, M. M. D.; Liu, H.; Huang, S.-J.; Sears, P.; Shikhman, A. R.; Wong, C.-H. *J. Org. Chem.* **2004**, *69*, 6273–6283. (b) Dondoni, A.; Giovannini, P. P.; Perrone, D. *J. Org. Chem.* **2002**, *67*, 7203–7214. (c) Cubero, I. I.; Lopez-Espinosa, M. T. P.; Diaz, R. R.; Montalban, F. F. *Carbohydr. Res.* **2001**, *330*, 401–408. (d) McCort, I.; Fort, S.; Dureault, A.; Depezay, J. C. *Bioorg. Med. Chem.* **2000**, *8*, 135–143. (e) Dondoni, A.; Perrone, D. *Tetrahedron Lett.* **1999**, *40*, 9375–9378. (f) Lee, S. G.; Yoon, Y. J.; Shin, S. C.; Lee, B. Y.; Cho, S. D.; Kim, S. K.; Lee, J. H. *Heterocycles* **1997**, *45*, 701–706. (g) Lee, R. E.; Smith, M. D.; Nash, R. J.; Griffiths, R. C.; McNeil, M.; Grewal, R. K.; Yan, W.; Besra, G. S.; Brennan, P. J.; Fleet, G. W. J. *Tetrahedron Lett.* **1997**, *38*, 6733–6736. (h) Park, K. H. *Heterocycles* **1995**, *41*, 1715–1719. (i) Wong, C.-H.; Provencher, L.; Porco, J. A., Jr.,; Jung, S.-H.; Wang, Y. F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492–1501. (j) Baxter, E. W.; Reitz, A. B. *J. Org. Chem.* **1994**, *59*, 3175–3185. (k) Reitz, A. B.; Baxter, E. W. *Tetrahedron Lett.* **1990**, *31*, 6777–6780. (l) McCort, I.; Dureault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 7717–7720.
6. (a) Singh, S.; Han, H. *Tetrahedron Lett.* **2004**, *45*, 6349–6352. (b) Singh, S.; Chikkanna, D.; Singh, O. V.; Han, H. *Synlett* **2003**, 1279–1282.
7. (a) Moreno-Vargas, A. J.; Robina, I.; Petricci, E.; Vogel, P. *J. Org. Chem.* **2004**, *69*, 4487–4491. (b) Yu, C.-Yi.; Asano, N.; Ikeda, K.; Wang, M.-X.; Butters, T. D.; Wormald, M. R.; Dwek, R. A.; Winters, A. L.; Nash, R. J.; Fleet, G. W. J. *Chem. Commun.* **2004**, 1936–1937. (c) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901–903. (d) Chikkanna, D.; Han, H. *Synlett* **2004**, 2311–2314. (e) Garcia, A. L. L.; Correia, C. R. D. *Tetrahedron Lett.* **2003**, *44*, 1553–1557 and references cited therein. (f) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999–1002.
8. Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 5811–5819.
9. (a) de Gracia, I. S.; Dietrich, H.; Bobo, S.; Chiara, J. L. *J. Org. Chem.* **1998**, *63*, 5883–5889. (b) Rohde, J. M.; Parquette, J. R. *Tetrahedron Lett.* **1998**, *39*, 9161–9164. (c) Gallo-Rodriguez, C.; Varela, O.; de Lederkremer, R. M. *J. Org. Chem.* **1996**, *61*, 1886–1889. (d) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776–2786.
10. For an alternative approach to **8** (–NHAc, $–NBn_2$, –NHBoc) from D-glucosamine see: Chiara, J. L.; de Gracia, I. S.; Bastida, A. *Chem. Commun.* **2003**, 1874–1875.
11. (a) Enders, D.; Gries, J.; Kim, Z.-S. *Eur. J. Org. Chem.* **2004**, *21*, 4471–4482. (b) Haskins, C. M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 599–601. (c) Kuriyama, M.; Soeta, T.; Hao, X.; Chen, Q.; Tomioka, K. *J. Am. Chem. Soc.* **2004**, *126*, 8128–8129. (d) Wellner, E.; Sandin, H.; Paakkonen, L. *Synthesis* **2003**, *2*, 223–226. (e) Isabel, B. M.; Luis, S. V.; Miravet, J. F.; Querol, M.; Diaz, P.; Garcia-Espana, E.; Ramirez, J. A. *Chem. Commun.* **1999**, 649–650. (f) Jordis, U.; Sauter, F.; Siddiqi, S. M.; Kuenburg, B.; Bhattacharya, K. *Synthesis* **1990**, 925–930.

12. (a) Nadir, U. K.; Krishna, R. V. *J. Heterocycl. Chem.* **2004**, *41*, 737–739. (b) Jonsson, S. Y.; Lofstrom, C. M. G.; Backvall, J.-E. *J. Org. Chem.* **2000**, *65*, 8454–8457. (c) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017–1018. (d) Yokoyama, Y.; Matsumoto, T.; Murakami, Y. *J. Org. Chem.* **1995**, *60*, 1486–1487.
13. For some examples of *N*-detosylation using HBr–AcOH see: (a) Zhang, Z.; Mikkola, S.; Loennberg, H. *Org. Biomol. Chem.* **2003**, *1*, 854–858. (b) Lescop, C.; Mevellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187–4193.
14. (a) Kaliappan, K. P.; Nandurdikar, R. S. *Chem. Commun.* **2004**, 2506–2507. (b) Olsen, C. A.; Witt, M.; Jaroszewski, J. W.; Franzyk, H. *Org. Lett.* **2004**, *6*, 1935–1938. (c) Luzzio, F. A.; Duveau, D. Y. *Tetrahedron: Asymmetry* **2002**, *13*, 1173–1180. (d) Mereyala, H. B.; Goud, P. M.; Gadikota, R. R.; Reddy, K. R. *J. Carbohydr. Chem.* **2000**, *19*, 1211–1222. (e) Dorta, R. L.; Rodriguez, M. S.; Salazar, J. A.; Suarez, E. *Tetrahedron Lett.* **1997**, *38*, 4675–4678. (f) Myers, A. G.; Hammond, M.; Wu, Y.; Xiang, J.-N.; Harrington, P. M.; Kuo, E. Y. *J. Am. Chem. Soc.* **1996**, *118*, 10006–10007. (g) Luzzio, F. A.; Menes, M. E. *J. Org. Chem.* **1994**, *59*, 7267–7272. (h) Garegg, P. J.; Johansson, R.; Ortega, C.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1982**, 681–683. (i) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2866–2869. (j) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978–980.
15. Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2190–2198.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
ELSEVIER
Tetrahedron 62 (2006) 1886–1894

New axially dissymmetric ligand recoverable with fluorous solvent

Masaaki Omote, Yuji Nishimura, Kazuyuki Sato, Akira Ando and Itsumaro Kumadaki*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata 573-0101, Japan

Received 19 October 2005; revised 4 November 2005; accepted 9 November 2005

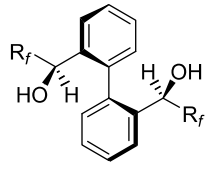
Available online 20 December 2005

Abstract—Axially dissymmetric ligands with perfluoroalkyl groups, (*R*a)-2,2′-bis[(*R*)-1-hydroxy-1*H*-perfluorooctyl]biphenyl [(*R*a)-(*R*)$_2$-**1c**] and its enantiomer, have been synthesized successfully by the coupling reaction of the corresponding aryl bromide using Ni(COD)$_2$. These ligands showed much higher asymmetric induction in the reaction of various aldehydes with diethylzinc than the trifluoromethyl (**1a**) or pentafluoroethyl (**1b**) analogues. Furthermore, **1c** was recovered quantitatively by extraction with a fluorous solvent from the reaction mixture due to its high fluorine content. The recovered ligand **1c** was pure enough to be reused without purification. The efficiency of **1c** as the chiral ligand was not decreased at all even after seven times recycling.

1. Introduction

The search for easily recoverable and efficient chiral ligand for asymmetric synthesis is of major interest in modern chemistry from ecological and environmental points of view. One of the most interesting advances in this field is based on a selective recovery of highly fluorinated compounds with perfluorocarbons, called fluorous solvents.[2] Since the first report by Horváth and Rábai,[3] the fluorous recovering technique has aroused a growing scientific and industrial interest due to the simple procedure and use of a chemically inert and low toxic fluorous solvent. The fluorous recovering technique can be classified into two categories, liquid–liquid partition[4] and solid separation using fluorine-capped silica-gel.[5] The former is an economical and simple procedure but introduction of long perfluoroalkyl chains into target materials is essential for the efficient partition. On the other hand, the latter can be applied to the recovery of partly fluorinated molecules, but it is necessary to use a very expensive fluorine-capped silica-gel. There are many reports on recoverable chiral ligands by liquid–liquid fluorous technique involving recoverable analogues of BINAP,[6] BINOL,[7] BOX,[8] salen[9] and chiral phase-transfer catalyst[10] tethered with long perfluoroalkyl chains. These ligands have the perfluoroalkyl chains far from the active centers, and their activities are not improved by the introduction of perfluoroalkyl chains. These analogues exhibit their efficient recoverabilities. However, there are few reports on their recycling, since they are too labile toward oxygen and moisture to be recycled, or likely to be deactivated by racemization.

In our previous study, axially dissymmetric ligands with short perfluoroalkyl (R_f) groups, (*R*a)-2,2′-bis[(*R*)-2,2,2-trifluoro-1-hydroxyethyl]biphenyl [(*R*a)-(*R*)$_2$-**1a**], (*R*a)-2,2′-bis[(*R*)-1-hydroxy-1*H*-perfluoropropyl]biphenyl [(*R*a)-(*R*)$_2$-**1b**], and their enantiomers have been synthesized as chiral ligands for Lewis metals (Fig. 1).[11] The symbols (*R*a) and (*S*a) represents the axial chirality. Titanium complex prepared from **1a** or **1b** and Ti(OiPr)$_4$ catalyzed asymmetric addition reaction of diethylzinc to benzaldehyde much better than the BINOL–Ti(OiPr)$_4$ complex, and **1b** showed higher asymmetric induction than **1a**. These suggested that the electron-withdrawing R_f groups increased the Lewis acidity of the titanium complex and that the bulkier perfluoroalkyl groups might show the higher asymmetric induction. Based on this observation, we designed a perfluoroheptyl analogue (**1c**) whose fluorine content is 60%. We expected that large R_f groups and high fluorine content of **1c** would make it not only an excellent asymmetric inducer but also a recoverable ligand with a fluorous solvent. In our preliminary reports,[1] the synthesis of **1c** and its application were presented. In this paper, we would like to discuss in details a modified synthesis of **1c**, its applicability for asymmetric addition of diethylzinc to



R_f = CF_3: (*R*a)-(*R*)$_2$-**1a**
R_f = C_2F_5: (*R*a)-(*R*)$_2$-**1b**
R_f = C_7F_{15}: (*R*a)-(*R*)$_2$-**1c**

Figure 1. Structures of **1a** to **1c**.

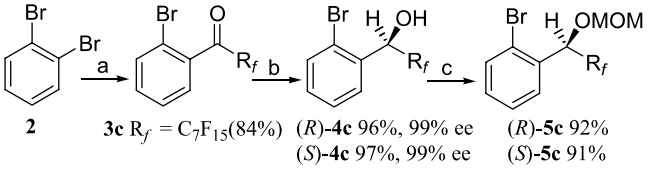
Keywords: Axial dissymmetry; Chiral ligand; Fluorine; Fluorous solvent; Recoverable; Reusable.
* Corresponding author. Tel.: +81 72 866 3140; fax: +81 72 850 7020; e-mail: kumadaki@pharm.setsunan.ac.jp

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.11.063

various aldehydes, and its high reusability on recycling using a fluorous solvent.

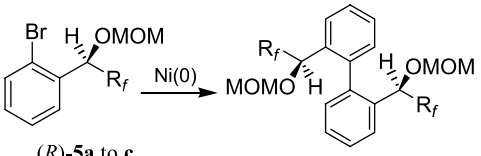
2. Results and discussion

The key step for the synthesis of the ligands (**1a** and **1b**) was the Ullmann type coupling reaction of the corresponding aryl bromides using copper powder. The chiral substrate (**5c**) for this coupling reaction was prepared according to the same procedure as the previous route as shown Scheme 1. Thus, enantioselective reduction of **3c**[12] with catecholborane in the presence of CBS catalyst[13] gave **4c** quantitatively in a high ee. Interestingly, while (*S*)-**4a** was obtained with (*R*)-CBS catalyst, (*R*)-**4c** was obtained with the same (*R*) catalyst.[14] This suggested that the order of steric bulkiness is $C_7F_{15} \gg C_6H_5 \gg C_2F_5 > CF_3$. The reduction of heptafluoropropyl analogue with the (*R*)-CBS catalyst gave the (*S*) product only in 60% ee, which means that the bulkiness of C_3F_7 is comparable to that of C_6H_5 on this reduction. After protection of the hydroxyl groups, (*R*)-**5c** was used for the next coupling reaction. The enantiomer (*S*)-**5c** was also prepared efficiently by the same sequence.



Scheme 1. Reagents and conditions: (a) (i) *n*-BuLi, THF–Et_2O, −110 °C, (ii) RfCOOEt; (b) catecholborane, THF, (*R*)- or (*S*)-2-methyl-5,5-diphenyl-3-4-propano-1,3,2-oxazaborolidine, −78 to −30 °C; (c) NaH, MOMCl, THF.

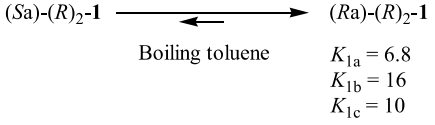
The coupling reaction of **5c** using copper powder hardly proceeded probably due to the steric repulsion between the large C_7F_{15} groups. To solve this problem, tetrakis(triphenylphosphine)nickel(0) or bis(1,5-cyclooctadiene)nickel(0)[15] [$Ni(COD)_2$], were examined in the place of the active copper powder, since they were reported to have high reactivity on oxidative addition to aryl bromide[16] (see Eq. 1).



(1)

Results of the coupling reaction are summarized in Table 1. The reaction of (*R*)-**5c** with $Ni(COD)_2$ in DMF at 60 °C gave 59% of (*R*a)-(*R*)$_2$-**6c** and 12% of the axial isomer (*S*a)-(*R*)$_2$-**6c** after separation by a column chromatography (entry 1). The latter was easily converted to (*R*a)-(*R*)$_2$-**1c** after hydrolysis as mentioned later. This means that the total yield of **6c** is more than 70%. When NMP was used as a solvent, the total yield was decreased to 30% (entry 2). Raising the reaction temperature did not improve the yield of the coupling reaction (entry 3). When $Ni(PPh_3)_4$ was used, the total yield of **6c** was decreased to 6%, and a fairly large amount of **5c** was recovered. This suggested that the low reactivity might be due to a low oxidative additivity of this nickel complex to aryl bromide. The enantiomer (*S*)-**5c** was also coupled efficiently by the same manner to give **6c** in total 68% yield, 57% of (*S*a)-(*S*)$_2$-**6c** and 11% of the axial isomer (*R*a)-(*S*)$_2$-**6c** (entry 5). This coupling reaction using $Ni(COD)_2$ in DMF gave much higher yields of **6a** or **6b** than the former method[11] (entries 6 and 7).

Deprotection of (*R*a)-(*R*)$_2$-**6a–c** with TFA gave the desired ligands (*R*a)-(*R*)$_2$-**1a–c** quantitatively. The axial isomers (*S*a)-(*R*)$_2$-**6a–c** were also deprotected quantitatively to (*S*a)-(*R*)$_2$-**1a–c**. The (*S*a)-(*R*)$_2$-ligands could be converted to the corresponding (*R*a)-(*R*)$_2$-ligands by thermal equilibration followed by separation. Namely, refluxing a solution of each (*S*a)-(*R*)$_2$-ligand in toluene gave an equilibrium mixture, where the corresponding (*R*a)-(*R*)$_2$-ligand predominated. The efficiency of the conversion depended on each equilibrium constant (*K*) shown in Eq. 2. The equilibrium mixture was separated by silica-gel column chromatography to give a large amount of the desired (*R*a)-(*R*)$_2$-ligand and a small amount of (*S*a)-(*R*)$_2$-ligand. The large *K* values of **1b** and **1c** facilitated the conversion of (*S*a)-(*R*)$_2$-**1b** or (*S*a)-(*R*)$_2$-**1c** to the corresponding (*R*a)-(*R*)$_2$-isomers over 90% by only one equilibration followed by separation. Compound (*S*a)-(*R*)$_2$-**1a** was also converted into (*R*a)-(*R*)$_2$-**1a** in 93% yield by twice equilibration and separation. Compound (*S*a)-(*S*)$_2$-**1c** was obtained similarly.



(2)

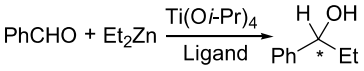
Ability of **1c** as an asymmetric inducer was evaluated by the reaction of diethylzinc with benzaldehyde in the presence of a stoichiometric amount of $Ti(OiPr)_4$

Table 1. Ni(0) mediated coupling reaction

Entry	Substrate	Catalyst	Product Yield (%)[a]			
1	(*R*)-**5c**	$Ni(COD)_2$	(*R*a)-(*R*)$_2$-**6c**	59	(*S*a)-(*R*)$_2$-**6c**	12
2[b]		$Ni(COD)_2$		25		5
3[c]		$Ni(COD)_2$		55		10
4		$Ni(PPh_3)_4$		5		1
5	(*S*)-**5c**	$Ni(COD)_2$	(*S*a)-(*S*)$_2$-**6c**	57	(*R*a)-(*S*)$_2$-**6c**	11
6	(*R*)-**5a**	$Ni(COD)_2$	(*R*a)-(*R*)$_2$-**6a**	56	(*S*a)-(*R*)$_2$-**6a**	36
7	(*R*)-**5b**	$Ni(COD)_2$	(*R*a)-(*R*)$_2$-**6b**	69	(*S*a)-(*R*)$_2$-**6b**	11

[a] Isolated yield.
[b] NMP was employed as a solvent.
[c] Reaction was carried out at 120 °C.

(see Eq. 3).[17,18]



(3)

The results are summarized with the results of **1a** and **1b** in Table 2. The trifluoromethyl analogue **1a** showed a good asymmetric induction, as reported before:[11a] the product was obtained in 85% ee using 5 mol% of **1a**. The pentafluoroethyl analogue **1b** with bulkier pentafluoroethyl groups showed higher asymmetric induction: ee of the product increased to 91% with the same amount of **1b** as **1a**. The highest asymmetric induction was achieved by the perfluoroheptyl analogue **1c**. A 5 mol% of **1c** catalyzed the reaction efficiently to give the product of 97% ee. Increasing the amount of **1c** to 8 mol% resulted in a further improvement of the ee. Only 1 mol% of (*Sa*)-(*S*)$_2$-**1c** gave the (*R*)-product in 88% ee. These results suggest that the asymmetric induction depends significantly on the size of perfluoroalkyl moieties of the ligands. The larger perfluoroalkyl groups give the better asymmetric induction. It was reported that 20 mol% of BINOL showed 85% ee in the same reaction. This means that **1c** is more than twenty times effective than BINOL.

Table 2. Asymmetric induction by **la** to **lc**

Ligand	Mol%	Yield (%)[a]	ee (%)[b]	Config.[c]
(*Sa*)-(*S*)$_2$-**1a**	2	95	81	*R*
(*Ra*)-(*R*)$_2$-**1a**	2	97	82	*S*
	3	92	81	*S*
	5	94	85	*S*
	10	97	85	*S*
(*Ra*)-(*R*)$_2$-**1b**	1	97	63	*S*
	2.5	99	90	*S*
	5	96	91	*S*
	10	99	93	*S*
(*Sa*)-(*S*)$_2$-**1c**	1	92	88	*R*
	3	93	94	*R*
	5	97	96	*R*
(*Ra*)-(*R*)$_2$-**1c**	5	96	97	*S*
	8	91	98	*S*
(*Sa*)-BINOL	20	97	85	*S*

[a] Isolated yield.
[b] ee was determined by chiral GLC analysis.
[c] Determined by sign of optical rotation.

To investigate scope of applicability of **1c**, the same asymmetric reaction of other aromatic and aliphatic aldehydes was examined. The results are summarized in Table 3. Electron-withdrawing and donating substituents had no significant effects on the asymmetric induction (entries 1 and 2). The reaction could be applied to the synthesis of labile chiral allyl alcohol as shown in entry 3. A large aromatic aldehyde, 1-naphthaldehyde, also reacted, while ee of the product was slightly decreased (entry 4). This ligand was less effective for the reactions of aliphatic aldehydes as shown in entries 5 and 6. These results suggest that titanium complex of **1c** is an effective chiral catalyst for the reaction of diethylzinc with aromatic aldehydes including conjugated ones.

To apply the fluorous extraction methodology to a compound, its partition between a fluorous solvent and a common organic solvent is very important. We expected that the high fluorine content of **1c** would make its partition high enough to be recovered by the fluorous phase separation technique. Partition of **1c** between perfluorohexane (FC-72) and some organic solvents was investigated as follows. To a mixture of FC-72 and an organic solvent (2 mL each), 50 mg of **1c** was added. The mixture was shaken vigorously enough to establish the partition. Both layers were separated on ice-cooling, and the amount of **1c** dissolved in each solvent was determined by weighing each residue after evaporation of the solvent. The results are summarized in Table 4. The highest partition to FC-72 was observed, when hexane was used. This may be due to the fact that two hydroxyl groups of **1c** lower the solubility in nonpolar hexane. Dichloromethane was also found to be a good solvent for this fluorous phase separation technique. Other solvents, chloroform or ether, did not show sufficient partition for fluorous extraction. This moderate partition of **1c** in FC-72 is attributed to rather low content of fluorine (60%) for fluorous extraction. This content is believed to be the border whether the fluorous phase separation can be used or not. While the introduction of more fluorine to **1c** might increase the solubility in a fluorous solvent, it would lower the solubility in a common organic solvent. The solubility in a common solvent, in which a reaction is carried out, is crucial for a reaction to proceed. Thus, we expected that 60% of fluorine content of **1c** would have not only its recoverability by a fluorous solvent but also good solubility in various solvents. To estimate the recoverability of **1c**, combination of FC-72 and dichloromethane was chosen as the solvent system for extraction, since dichloromethane would extract common organic materials better than hexane.

Table 3. Asymmetric ethylation of other aldehydes (R-CHO)

Entry	R	Ligand	Yield (%)	ee (%)	Config.[a]
1	*p*-Cl–C$_6$H$_4$	(*Sa*)-(*S*)-**1c**	96	95[b]	*R*
2	*p*-Me–C$_6$H$_4$	(*Sa*)-(*S*)-**1c**	94	95[b]	*R*
3	C$_6$H$_5$–CH=CH	(*Sa*)-(*S*)-**1c**	97	96[c]	*R*
4	1-Napthyl	(*Sa*)-(*S*)-**1c**	98	93[c]	*R*
5	C$_6$H$_5$–CH$_2$CH$_2$CHO	(*Ra*)-(*R*)-**1c**	73	80[b]	*S*
6	*n*-C$_7$H$_{15}$	(*Ra*)-(*R*)-**1c**	89	82[d]	*S*

[a] Determined by comparing the optical rotation with the literature data. For entries 1– and 5: Watanabe, M.; Araki, S.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2218. For entry 4: Dai, W.-M.; Zhu, H.-J.; Hao X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315. For entry 6: Nakano, H.; Kumagai, N.; Matsuzaki, H.; Kabuto, C.; Hongo, H. *Tetrahedron Asymmetry* **1997**, *8*, 1391.
[b] ee was determined by chiral GLC analysis.
[c] ee was determined by chiral HPLC analysis.
[d] ee was determined by chiral HPLC analysis after derivatization to benzoyl ester.

Table 4. Partition of **1c**: FC-72/solvent

Solvent	mL	Amount (mg)
FC-72/hexane	2/2	37/13
	2/1	47/3
FC-72/dichloromethane	2/2	30/20
	2/1	42/7
FC-72/toluene	2/2	26/23
	2/1	35/15
FC-72/chloroform	2/2	20/29
	2/1	32/17
FC-72/diethyl ether	2/2	13/37
	2/1	23/26

The procedure for recovering **1c** from the reaction of diethylzinc with benzaldehyde is as follows: the titanium complex of the catalyst was prepared by warming a solution of **1c** (34 mg, 0.036 mmol) and $Ti(OiPr)_4$ (0.86 mmol) in toluene (0.3 mL) at 50 °C for 30 min. The solution was cooled to −78 °C and a solution of diethylzinc in hexane (0.86 mmol) was added to the solution. To this solution, a solution of benzaldehyde (0.72 mmol) in toluene (0.3 mL) was added over 30 min. The temperature was raised to −30 °C gradually and the reaction was followed by TLC. After the completion of the reaction (within 5 h), the reaction mixture was quenched with 2 mL of 10% aqueous HCl. Dichloromethane (1 mL) and FC-72 (2 mL) were added to the mixture for extraction. The mixture was shaken vigorously to complete the partition. After separation of FC-72 phase containing **1c**, another FC-72 (2 mL) was added to the remaining mixture for the next extraction. Extraction with FC-72 (2 mL each) was performed three times to recover almost all of **1c**. Evaporation of combined FC-72 layer under reduced pressure gave **1c** in a recovery of 97% with an excellent purity of 98%. After the recovery of **1c** from the reaction mixture, the product was extracted by dichloromethane in three portions (1 mL×1+2 mL×2). The yield and ee of the product were measured after evaporation of the combined dichloromethane layers followed by separation with silica-gel column chromatography.

By the simple procedure shown above, almost perfect recovery of **1c** was attained in high purity. This high purity seemed to enable **1c** to be recycled. For the effective recycling of the ligand, its chemical stability during several times recycling must be ensured. The chemical stability of **1c** was estimated by subjecting it to a recycling procedure, as shown by a flow chart in Figure 2. After the reaction using 5 mol% of **1c** (34 mg, 0.036 mmol), **1c** was partitioned into FC-72 as in the above procedure. Three times extraction was necessary for almost all extraction of **1c**. The combined FC-72 layer containing **1c** was evaporated to give **1c** quantitatively and high purity as shown above. The activity of recovered **1c** was evaluated as follows. The amounts of all other reagents and compounds

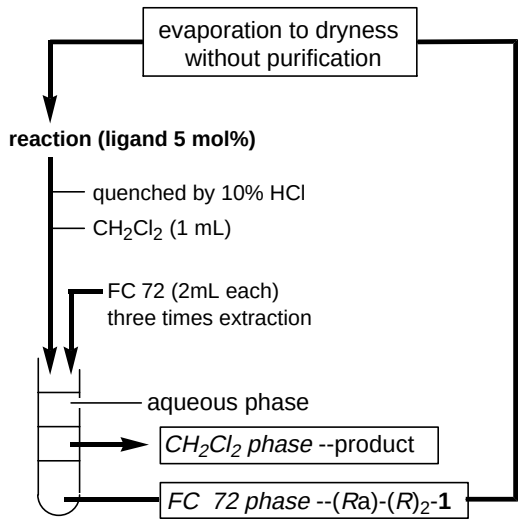


Figure 2. Recycled use of **1c**.

Table 5. Recycled use of **1c**

	Product		**1c**
Cycle	Yield (%)[a]	ee (%)[b]	Recovery (%)
—	97	97	97
1	99	97	98
2	95	97	97
3	92	97	97
4	98	98	98
5	95	97	97
6	97	97	99
7	97	97	97

[a] Isolated yields.
[b] Ee were determined by chiral GLC analysis.

were adjusted based on the amount of recovered **1c** for the ratio to be constant (5 mol%) in every recycled use. The results of recycling experiments are shown in Table 5. The efficiency of **1c** did not decrease at all even after seven times recycling. This is well demonstrated by the fact that the product from every cycle has high and constant ee and yield. This means that the purity of recovered **1c** is pure enough to be used for the next reaction without purification.

In conclusion, we have succeeded in the synthesis of new axially dissymmetric ligands, (*R*a)-$(R)_2$-**1c** and (*S*a)-$(S)_2$-**1c** by coupling reaction of **5c** using $Ni(COD)_2$ in DMF. The undesired axial diastereomer, (*S*a)-$(R)_2$-**1c**, was converted efficiently into the desired ligand (*R*a)-$(R)_2$-**1c** by the thermal equilibration and separation. This methodology could be used for less bulky analogue to give better results than the conventional Ullmann reaction using copper powder. Compound (*R*a)-$(R)_2$-**1c** or (*S*a)-$(S)_2$-**1c** showed very high asymmetric induction in the reaction of diethylzinc with aldehydes to give up to 98% ee of the products. Furthermore, the ligand **1c** is recovered quantitatively by fluorous phase separation technique using FC-72 directly from the reaction mixture. Evaporation of the fluorous solvent under reduced pressure gives **1c** in so high purity enough to be reused in the next reaction. The activity of **1c** as an asymmetric inducer is not decreased even after seven times recycled uses. These facts show that **1c** is a very stable and recyclable ligand with high asymmetric induction. Further application of this ligand to other asymmetric syntheses is now in progress.

3. Experimental

3.1. General remarks

All reactions were carried out under argon atmosphere unless noted otherwise. Chemicals were prepared as follows: THF, ether, and toluene were distilled from Na/benzophenone; and other chemicals were used as received. ^1H and ^{13}C NMR spectra were recorded on 400 or 600 MHz spectrometers and ^{19}F NMR spectra were recorded on 60 or 600 MHz spectrometers at ambient probe temperature and referenced as follows: ^1H and ^{13}C, TMS; ^{19}F, BTF. Mass spectra were recorded on EI method. Enantiomeric excess was determined by GLC with GAMMA DEX™ 225 Capillary Column (30 m×0.25 mm×0.25 μm) or HPLC with Chiralcel OD-H (0.46ϕ×25 cm, Daicel).

3.2. Synthesis of chiral ligands

3.2.1. 1-Bromo-2-(perfluorooctanoyl)benzene (3c). A solution of *n*-butyllithium (1.54 M in hexane, 40 mL, 62.0 mmol) was added to a solution of *o*-dibromobenzene (6.8 mL, 56.4 mmol) in THF (250 mL) and Et_2O (250 mL) at −110 °C over 30 min. After stirring for 20 min, ethyl perfluorooctanoate (29.5 g, 66.7 mmol) was added to the solution at the same temperature. The mixture was stirred for 1 h, and the reaction was quenched by adding 28 mL of a cooled mixture of EtOH and concd HCl (ratio=3:1). The mixture was extracted with Et_2O and organic layer was washed with H_2O and dried over $MgSO_4$. After filtration of $MgSO_4$, the filtrate was concentrated under vacuum and the residue was separated by a silica-gel column chromatography (Et_2O/hexane, 5:95). The separated product was purified by distillation under vacuum to give **3c** (26.2 g, 84%). Compound **3c**. A colorless oil. Bp 106–109 °C/4 mmHg. ^1H NMR ($CDCl_3$) δ: 7.76–7.70 (1H, m), 7.56–7.50 (1H, m), 7.49–7.41 (2H, m). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 186.8, 135.1, 134.6, 133.7, 129.1, 127.5, 120.8, 117.5, 111.5, 111.3, 111.1, 110.6, 109.7, 108.8. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 186.8 (t, J_{C-F}=27.8 Hz), 135.1, 134.6, 133.7, 129.1 (t, J_{C-F}=3.6 Hz), 127.5, 120.8, 117.5 (qt, J_{C-F}=289.0, 33.9 Hz), 111.5 (ttt, J_{C-F}=272.0, 32.6, 32.6 Hz), 111.3 (ttt, J_{C-F}=272.0, 32.6, 32.6 Hz), 111.1 (ttt, J_{C-F}=272.0, 32.6, 32.6 Hz), 110.6 (ttt, J_{C-F}=272.0, 32.6, 32.6 Hz), 109.7 (tt, J_{C-F}=272.0, 32.6 Hz), 108.8 (tqt, J=287.0, 40.0, 32.6 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −51.7 (2F, s), −57.9 (2F, s), −58.3 (2F, s), −59.2 (2F, s), −59.9 (2F, s), −63.3 (2F, s). IR (neat) cm^{-1}: 1740, 1204, 1152. LRMS (EI) *m/z*: 552 (M^+), 533 (M^+-F), 183 ($M^+-C_7F_{15}$, base peak). HRMS Calcd for $C_{14}H_4O^{79}BrF_{15}$ (M^+): 551.921, found 551.921.

3.2.2. (*R*)-1-Bromo-2-(1-hydroxy-1*H*-perfluorooctyl)benzene ((*R*)-4c). Catecholborane (7.30 g, 65.2 mmol) was added to a solution of (*R*)-2-methyl-5,5-diphenyl-3,4-propano-1,3,2-oxazaborolidine (1.00 g, 3.61 mmol) in THF (150 mL) at room temperature and stirred for 30 min. The solution was cooled to −78 °C and a solution of **3c** (20.0 g, 36.2 mmol) in THF (50 mL) was added over 30 min. The reaction mixture was stirred for over night at −30 °C. The reaction was quenched by adding slowly 150 mL of a mixed solution of 30% H_2O_2 and 20% NaOH (1:1) and the mixture was stirred for 2 h at room temperature. The mixture was extracted with Et_2O and organic layer was washed with H_2O and dried over $MgSO_4$. After filtration of $MgSO_4$, the filtrate was concentrated under vacuum, and the residue was separated by a silica-gel column chromatography (Et_2O/hexane, 10:90) to give **4c** (19.3 g, 96%). Compound (*R*)-**4c**. Colorless crystals. Mp 43.5–44.5 °C. $[\alpha]_D^{24}$ +15.2 (*c* 0.92, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.62 (1H, d, J=7.8 Hz), 7.58 (1H, d, J=7.8 Hz), 7.36 (1H, dd, J=7.8, 7.8 Hz), 7.24 (1H, ddd, J=7.8, 7.8, 1.4 Hz), 5.89 (1H, ddd, J=19.8, 5.3, 2.5 Hz), 2.78 (1H, d, J=5.3 Hz). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 134.1, 133.2, 131.2, 130.0, 128.0, 124.3, 117.4, 115.4, 111.9, 111.4, 111.1, 110.5, 108.7, 70.4. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 134.1, 133.2, 131.2, 130.0, 128.0, 124.3, 117.4 (qt, J_{C-F}=287.9, 32.8 Hz), 115.4 (ddt, J_{C-F}=267.3, 257.6, 30.8 Hz), 111.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.4 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 111.1 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 110.5 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 108.7 (tqt, J_{C-F}=272.1, 40.1, 32.8 Hz), 70.4 (dd, J_{C-F}=29.2, 20.7 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −53.6 (1F, d, J=286.6 Hz), −58.3–−59.8 (6F, m), −60.0 (2F, dd, J=407.3, 297.4 Hz), −63.3 (2F, dd, J=411.6, 286.6 Hz), −64.1 (1F, d, J=286.6 Hz). IR (KBr) cm^{-1}: 3395, 1244, 1210, 1148, 750. LRMS (EI) *m/z*: 554 (M^+), 185 ($M^+-C_7F_{15}$, base peak). HRMS (EI) Calcd for $C_{14}H_6O^{79}BrF_{15}$ (M^+): 553.936, found 553.937.

3.2.3. (*S*)-1-Bromo-2-(1-hydroxy-1*H*-perfluorooctyl)benzene ((*S*)-4c). Colorless crystals. Mp 43.5–44.5 °C. $[\alpha]_D^{24}$ −15.0 (*c* 0.96, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.67 (1H, d, J=7.8 Hz), 7.60 (1H, d, J=7.8 Hz), 7.40 (1H, dd, J=7.8, 7.8 Hz), 7.26 (1H, ddd, J=7.8, 7.8, 1.4 Hz), 5.89 (1H, ddd, J=19.9, 5.4, 2.5 Hz), 2.72 (1H, d, J=5.4 Hz). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 134.0, 133.1, 131.1, 130.0, 128.0, 124.3, 117.3, 115.3, 111.9, 111.3, 111.0, 110.5, 108.6, 70.3. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 134.0, 133.1, 131.1, 130.0, 128.0, 124.3, 117.3 (qt, J_{C-F}=287.9, 32.8 Hz), 115.3 (ddt, J_{C-F}=267.3, 257.6, 30.8 Hz), 111.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.3 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 111.0 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 110.5 (ttt, J_{C-F}=272.1, 32.8, 32.8 Hz), 108.6 (tqt, J_{C-F}=272.1, 40.1, 32.8 Hz), 70.3 (dd, J_{C-F}=29.2, 20.7 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −53.6 (1F, d, J=284.5 Hz), −58.3–−59.8 (6F, m), −60.0 (2F, dd, J=409.5, 297.4 Hz), −63.3 (2F, dd, J=411.6, 290.1 Hz), −64.1 (1F, d, J=284.5 Hz). IR (KBr) cm^{-1}: 3395, 1242, 1210, 1150, 750. LRMS (EI) *m/z*: 554 (M^+), 185 ($M^+-C_7F_{15}$, base peak). HRMS Calcd for $C_{14}H_6O^{79}BrF_{15}$ (M^+): 553.936, found 553.935.

3.2.4. (*R*)-1-Bromo-2-(1-methoxymethoxy-1*H*-perfluorooctyl)benzene ((*R*)-5c). Compound **4c** (20.0 g, 36.0 mmol) was added slowly to the suspension of sodium hydride (1.16 g, 54 mmol, 60% dispersion in mineral oil) in THF (10 mL) under ice-cooling. To the mixture was added chloromethyl methyl ether (4.35 g, 54.0 mmol) and stirred for over night at room temperature. The reaction was quenched by adding water and then the mixture was extracted with Et_2O. The organic layer was washed with H_2O and dried over $MgSO_4$. After filtration of $MgSO_4$, the filtrate was concentrated under vacuum, and the residue was purified by a silica-gel column chromatography (Et_2O/hexane, 5:95). The product was further purified by distillation under vacuum to give **5c** (19.8 g, 92%). Compound (*R*)-**5c**. A colorless oil. Bp 123–125 °C/8 mmHg. $[\alpha]_D^{24}$ +54.5 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.65 (1H, ddd, J=7.8, 1.8, 1.8 Hz), 7.60 (1H, dd, J=8.1, 1.2 Hz), 7.39 (1H, ddd, J=7.8, 7.8, 1.2 Hz), 7.25 (1H, ddd, J=8.1, 7.8, 1.8 Hz), 5.90 (1H, dd, J=20.3, 1.5 Hz), 4.64 (1H, dd, J=7.2, 1.5 Hz), 4.52 (1H, d, J=7.2 Hz), 3.34 (3H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 133.2, 132.3, 131.2, 130.9, 127.9, 125.6, 117.5, 115.5, 111.9, 111.5, 111.1, 110.6, 108.7, 95.3, 73.2, 56.7. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 133.2, 132.3, 131.2, 130.9 (d, J_{C-F}=2.4 Hz), 127.9, 125.6, 117.5 (qt, J_{C-F}=287.9, 32.8 Hz), 115.5 (ddt, J_{C-F}=266.1, 253.9, 31.6 Hz), 111.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.5 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.1 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.6 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.7 (ttt, J_{C-F}=270.9, 38.9, 31.6 Hz), 95.3, 73.2 (dd, J_{C-F}=30.2, 19.4 Hz), 56.7. ^{19}F NMR ($CDCl_3$)

δ: −18.0 (3F, s), −53.2 (1F, d, J=286.6 Hz), −58.1–−59.9 (6F, m), −60.0 (2F, dd, J=532.3, 303.8 Hz), −61.6 (1F, d, J=286.6 Hz), −63.3 (2F, dd, J=532.3, 295.3 Hz). IR (neat) cm^{-1}: 2904, 1242, 1212, 1150, 1042, 752. LRMS (EI) *m/z*: 598 (M^+), 537 ($M^+-CH_3OCH_2O$), 229 ($M^+-C_7F_{15}$, base peak). HRMS Calcd for $C_{16}H_{10}O_2^{79}BrF_{15}$ (M^+): 597.963, found 597.962.

3.2.5. (*S*)-1-Bromo-2-(1-methoxymethoxy-1*H*-perfluorooctyl)benzene ((*S*)-5c). A colorless oil. Bp 123–125 °C/8 mmHg. $[\alpha]_D^{24}$ −54.1 (*c* 0.98, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.65 (1H, ddd, J=7.9, 1.8, 1.8 Hz), 7.60 (1H, dd, J=8.2, 1.1 Hz), 7.39 (1H, ddd, J=7.9, 7.9, 1.1 Hz), 7.26 (1H, ddd, J=8.2, 7.9, 1.8 Hz), 5.88 (1H, dd, J=20.2, 1.3 Hz), 4.64 (1H, dd, J=7.2, 1.3 Hz), 4.52 (1H, d, J=7.2 Hz), 3.34 (3H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 133.2, 132.3, 131.2, 130.8, 127.9, 125.6, 117.5, 115.5, 111.9, 111.5, 111.1, 110.6, 108.8, 95.3, 73.2, 56.7. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 133.2, 132.3, 131.2, 130.8 (d, J_{C-F}=2.4 Hz), 127.9, 125.6, 117.5 (qt, J_{C-F}=287.9, 32.8 Hz), 115.5 (ddt, J_{C-F}=266.1, 253.9, 31.6 Hz), 111.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.5 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.1 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.6 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.8 (tqt, J_{C-F}=270.9, 38.9, 31.6 Hz), 95.3, 73.2 (dd, J_{C-F}=30.2, 19.4 Hz), 56.7. ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −53.2 (1F, d, J=288.8 Hz), −58.1–−59.9 (6F, m), −60.0 (2F, dd, J=530.2, 299.6 Hz), −61.6 (1F, d, J=288.8 Hz), −63.3 (2F, dd, J=530.2, 291.0 Hz). IR (neat) cm^{-1}: 2904, 1242, 1212, 1150, 1044, 752. LRMS (EI) *m/z*: 598 (M^+), 537 ($M^+-CH_3OCH_2O$), 229 ($M^+-C_7F_{15}$, base peak). HRMS Calcd for $C_{16}H_{10}O_2^{79}BrF_{15}$ (M^+): 597.963, found 597.963.

3.2.6. Coupling reaction to 2,2′-bis(1-methoxymethoxy-1*H*-perfluorooctyl)biphenyl. A typical procedure is as follows. To a suspension of $Ni(COD)_2$ (633 mg, 2.3 mmol) in anhydrous DMF (4 mL) was added (*R*)-**5c** (2.00 g, 3.3 mmol) at room temperature and the mixture was stirred for 24 h at 60 °C. The reaction was quenched by adding aqueous HCl (5%), and the mixture was extracted with Et_2O. The organic layer was concentrated after dehydration, and the residue was separated by a silica-gel chromatography (Et_2O/hexane=5:95–20:80) to give (*R*a)-(*R*)$_2$-**6c** (1.01 g, 59%) and (*S*a)-(*R*)$_2$-**6c** (0.21 g, 12%). Compound (*R*a)-(*R*)$_2$-**6c**. Colorless crystals. Mp 108.5–110.0 °C. $[\alpha]_D^{25}$ +1.8 (*c* 1.07, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.84 (1H, d, J=7.6 Hz), 7.44 (1H, dd, J=7.6, 7.6 Hz), 7.34 (1H, d, J=7.6, 7.6 Hz), 7.12 (1H, dd, J=7.6, 6.1 Hz), 5.25 (1H, d, J=20.9 Hz), 5.08 (1H, d, J=7.0 Hz), 4.57 (1H, d, J=7.0 Hz), 3.11 (3H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 139.6, 133.1, 131.9, 129.1, 128.4, 128.0, 117.6, 115.2, 112.1, 111.5, 111.1, 110.7, 108.8, 97.4, 73.5, 56.5. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 139.6, 133.1 (d, J_{C-F}=7.3 Hz), 131.9, 129.1, 128.4, 128.0, 117.6 (qt, J_{C-F}=287.9, 32.8 Hz), 115.2 (ddt, J_{C-F}=268.5, 255.1, 31.6 Hz), 112.1, (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.5 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.1 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.7 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.8 (tqt, J_{C-F}=270.9, 38.9, 31.6 Hz), 97.4, 73.5 (dd, J_{C-F}=30.4, 19.4 Hz), 56.5. ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −48.2 (1F, d, J=284.5 Hz), −58.5–−60.1 (6F, m), −60.0 (2F, dd, J=491.4, 301.7 Hz), −62.9 (1F, d, J=284.5 Hz), −63.4 (2F, dd, J=452.6, 293.1 Hz). IR (KBr) cm^{-1}: 1242, 1209, 1150, 1044. LRMS (EI) *m/z*: 1038 (M^+), 669 ($M^+-C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088, found 1038.088. Compound (*S*a)-(*R*)$_2$-**6c**. Colorless crystals. Mp 57.0–58.0 °C. $[\alpha]_D^{25}$ +41.7 (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.85 (2H, m), 7.51–7.42 (6H, m), 5.83 (2H, d, J=21.0 Hz), 4.73 (4H, d, J=1.3 Hz), 3.30 (6H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 140.9, 131.4, 131.2, 130.2, 129.2, 128.4, 117.4, 115.0, 111.7, 111.2, 110.9, 110.4, 108.6, 94.8, 71.2, 56.0. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 140.9, 131.4, 131.2, 130.2 (d, J_{C-F}=3.6 Hz), 129.2, 128.4, 117.4 (qt, J_{C-F}=287.8, 32.6 Hz), 115.0 (ddt, J_{C-F}=268.4, 252.7, 31.6 Hz), 111.7 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.4 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.6 (tqt, J_{C-F}=270.9, 38.7, 31.6 Hz), 94.8, 71.2 (dd, J_{C-F}=31.4, 17.0 Hz), 56.0. ^{19}F NMR ($CDCl_3$) δ: −18.4 (3F, s), −49.5, (1F, d, J=288.8 Hz), −58.4–−60.0 (6F, m), −60.1 (2F, dd, J=422.4, 295.3 Hz), −63.2 (1F, d, J=288.8 Hz), −63.6 (2F, dd, J=474.1, 295.3 Hz). IR (KBr) cm^{-1}: 1246, 1210, 1152, 1046. LRMS (EI) *m/z*: 1038 (M^+), 669 ($M^+-C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088, found 1038.088. Compound (*S*a)-(*S*)$_2$-**6c**. Colorless crystals. Mp 108.5–110.0 °C. $[\alpha]_D^{25}$ −1.7 (*c* 1.05, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.83 (1H, d, J=7.6 Hz), 7.46 (1H, dd, J=7.6, 7.6 Hz), 7.34 (1H, dd, J=7.6, 7.6 Hz), 7.11 (1H, dd, J=7.6, 6.1 Hz), 5.22 (1H, d, J=20.8 Hz), 5.06 (1H, d, J=7.0 Hz), 4.58 (1H, d, J=7.0 Hz), 3.12 (3H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 139.4, 133.0, 131.7, 129.0, 128.3, 128.0, 117.4, 115.3, 111.9, 111.3, 111.0, 110.5, 108.7, 97.2, 73.3, 56.4. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 139.4, 133.0 (d, J_{C-F}=7.3 Hz), 131.7, 129.0, 128.3, 128.0, 117.4 (qt, J_{C-F}=287.9, 32.8 Hz), 115.3 (ddt, J_{C-F}=268.5, 255.1, 31.6 Hz), 111.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.3 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.0 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.5 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.7 (tqt, J_{C-F}=270.9, 38.9, 31.6 Hz), 97.2, 73.3 (dd, J_{C-F}=30.4, 19.4 Hz), 56.4. ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −48.2 (1F, d, J=284.5 Hz), −58.4–−60.2 (6F, m), −59.9 (2F, dd, J=491.4, 303.9 Hz), −62.6 (1F, d, J=286.6 Hz), −63.3 (2F, dd, J=456.9, 295.3 Hz). IR (KBr) cm^{-1}: 1242, 1210, 1150, 1044. LRMS (EI) *m/z*: 1038 (M^+), 669 ($M^+-C_7F_{15}$). HRMS Calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088, found 1038.088. Compound (*R*a)-(*S*)$_2$-**6c**. Colorless crystals. Mp 57.0–58.0 °C. $[\alpha]_D^{25}$ −41.2 (*c* 1.03, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 7.8 (2H, m), 7.51–7.42 (6H, m), 5.36 (2H, d, J=21.1 Hz), 4.73 (4H, d, J=1.9 Hz), 3.30 (6H, s). ^{13}C NMR ($CDCl_3$, $^1H^{19}F$-COM) δ: 140.9, 131.4, 131.2, 130.2, 129.2, 128.4, 117.4, 115.0, 111.7, 111.2, 110.9, 110.4, 108.6, 94.8, 71.2, 56.0. ^{13}C NMR ($CDCl_3$, ^1H-COM) δ: 140.9, 131.4, 131.2, 130.2 (d, J_{C-F}=3.6 Hz), 129.2, 128.4, 117.4 (qt, J_{C-F}=287.8, 32.6 Hz), 115.0 (ddt, J_{C-F}=268.4, 252.7, 31.6 Hz), 111.7 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.4 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.6 (tqt, J_{C-F}=270.9, 38.7, 31.6 Hz), 94.8, 71.2 (dd, J_{C-F}=31.4, 17.0 Hz), 56.0. IR (KBr) cm^{-1}: 1244, 1210, 1150, 1044. ^{19}F NMR ($CDCl_3$) δ: −18.3 (3F, s), −49.5, (1F, d, J=290.1 Hz), −58.3–−60.0 (6F, m), −60.1 (2F, dd, J=418.1, 306.0 Hz), −63.2 (1F, d, J=290.1 Hz), −63.6 (2F, dd, J=476.3, 297.4 Hz). LRMS (EI) *m/z*: 1038 (M^+), 669

($M^+ - C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{32}H_{20}O_4F_{30}$ (M^+): 1038.088, found 1038.088.

3.2.7. Deprotection of 6c to 2,2′-bis(1-hydroxy-1*H*-perfluorooctyl)biphenyl and equilibration of the axial isomers. Treatment of (*R*a)-(*R*)$_2$-**6c** (1.01 g, 0.97 mmol) by TFA (5 mL) and water (0.5 mL) at room temperature for 3 h followed by extraction with Et_2O gave (*R*a)-(*R*)$_2$-**1c** (894 mg, 0.94 mmol, 97%). Any impurities were not detected by NMR and GLC. A similar treatment of (*S*a)-(*R*)$_2$-**6c** (210 mg, 0.20 mmol) with TFA (1 mL) and water (0.1 mL) gave its axial diastereomer (*S*a)-(*R*)$_2$-**1c** (183 mg, 0.19 mmol, 95%). Compound (*S*a)-(*R*)$_2$-**1c** (183 mg) was converted to (*R*a)-(*R*)$_2$-**1c** by refluxing in toluene for 4 h. The equilibrium mixture was separated by silica-gel chromatography (Et_2O/hexane=1:9–3:7) to give (*R*a)-(*R*)$_2$-**1c** (166 mg, 91%). For further purification, (*R*a)-(*R*)$_2$-**1c** was recrystallized from toluene, dissolving the crystals under 60 °C so as to avoid the axial isomerization. Compound (*R*a)-(*R*)$_2$-**1c**. Colorless crystals. Mp 82.0–83.0 °C. $[\alpha]_D^{25}$ +13.6 (*c* 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.76 (2H, d, J=7.5 Hz), 7.53 (2H, ddd, J=7.5, 7.5, 1.5 Hz), 7.48 (2H, ddd, J=7.5, 7.5, 1.5 Hz), 7.24 (2H, d, J=7.5 Hz), 4.88 (2H, dd, J=19.1, 7.0, 7.0 Hz), 3.34 (2H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H^{19}F-COM) δ: 139.7, 132.7, 130.3, 129.6, 129.0, 127.5, 117.3, 115.7, 111.8, 111.2, 111.0, 110.2, 108.4, 67.4. ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H-COM) δ: 139.7, 132.7, 130.3, 129.6, 129.0, 127.5, 117.3 (qt, J_{C-F}=287.8, 32.6 Hz), 115.7 (ddt, J_{C-F}=266.0, 255.1, 30.2 Hz), 111.8 (ttt, J_{C-F}=293.8, 30.2, 30.2 Hz), 111.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 111.0 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.4 (tqt, J_{C-F}=270.9, 39.9, 32.6 Hz), 67.4 (dd, J_{C-F}=30.2, 20.6 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.1 (3F, s), −53.6 (1F, d, J=282.8 Hz), −58.1–−60.0 (6F, m), −60.0 (2F, dd, J=305.2, 305.2 Hz), −62.0 (1F, d, J=282.8 Hz), −63.4 (2F, dd, J=305.2, 305.2 Hz). IR (KBr) cm^{-1}: 3376, 1212, 1149. LRMS (EI) *m*/*z*: 950 (M^+), 669 ($M^+ - C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{28}H_{12}O_2F_{30}$ (M^+): 950.036, found 950.036. Compound (*S*a)-(*R*)$_2$-**1c**. Colorless crystals. Mp 99.0–100.0 °C. $[\alpha]_D^{25}$ +31.5 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.84 (2H, d, J=7.5 Hz), 7.54 (2H, ddd, J=7.5, 7.5, 1.4 Hz), 7.49 (2H, ddd, J=7.5, 7.5, 1.4 Hz), 7.33 (2H, dd, J=7.5, 1.4 Hz), 5.17 (2H, dd, J=21.3, 7.5 Hz), 2.40 (2H, d, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H^{19}F-COM) δ: 140.4, 134.3, 130.9, 129.0, 128.6, 128.2, 117.2, 116.0, 111.5, 111.1, 110.7, 110.3, 108.4, 67.0. ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H-COM) δ: 140.4, 134.3, 130.9, 129.0, 128.6, 128.2, 117.2 (qt, J_{C-F}=289.0, 33.4 Hz), 116.0 (ddt, J_{C-F}=266.0, 257.5, 31.6 Hz), 111.5 (ttt, J_{C-F}=293.8, 30.2, 30.2 Hz), 111.1 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.7 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.3 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.4 (tqt, J_{C-F}=270.9, 38.7, 31.6 Hz), 67.0 (dd, J_{C-F}=30.2, 19.3 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.2 (3F, s), −51.9 (1F, d, J=283.6 Hz), −58.1–−60.8 (8F, m), −63.2 (1F, d, J=284.5 Hz), −63.6 (2F, dd, J=303.9, 303.9 Hz). IR (KBr) cm^{-1}: 3460, 1242, 1209, 1146. LRMS (EI) *m*/*z*: 950 (M^+), 669 ($M^+ - C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{28}H_{12}O_2F_{30}$ (M^+): 950.036, found 950.036. Compound (*S*a)-(*S*)$_2$-**1c**. Colorless crystals. Mp 82.0–83.0 °C. $[\alpha]_D^{25}$ −13.9 (*c* 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.76 (2H, d, J=7.4 Hz), 7.53 (2H, ddd, J=7.4, 7.4, 1.5 Hz), 7.48 (2H, ddd, J=7.4, 7.4, 1.5 Hz), 7.24 (2H, d, J=7.4 Hz), 4.87 (2H, ddd, J=19.0, 7.0, 7.0 Hz), 3.34 (2H, d, J=7.0 Hz). ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H^{19}F-COM) δ: 139.4, 133.6, 130.5, 128.7, 128.4, 128.2, 117.2, 115.5, 111.6, 111.2, 110.9, 110.2, 108.4, 66.4. ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H-COM) δ: 139.4, 133.6, 130.5, 128.7, 128.4, 128.2, 117.2 (qt, J_{C-F}=287.8, 32.6 Hz), 115.5 (ddt, J_{C-F}=266.0, 255.1, 30.2 Hz), 111.6 (ttt, J_{C-F}=293.8, 30.2, 30.2 Hz), 111.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.9 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.2 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.4 (tqt, J_{C-F}=270.9, 39.9, 32.6 Hz), 66.4 (dd, J_{C-F}=30.2, 20.6 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.0 (3F, s), −53.6 (1F, d, J=281.9 Hz), −58.1–−60.0 (6F, m), −60.0 (2F, dd, J=310.3, 310.3 Hz), −62.0 (1F, d, J=281.9 Hz), −63.4 (2F, dd, J=310.3, 310.3 Hz). IR (KBr) cm^{-1}: 3376, 1214, 1150. LRMS (EI) *m*/*z*: 950 (M^+), 669 ($M^+ - C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{28}H_{12}O_2F_{30}$ (M^+): 950.036, found 950.035. Compound (*R*a)-(*S*)$_2$-**1c**. Colorless crystals. Mp 99.0–100.0 °C. $[\alpha]_D^{25}$ −31.9 (*c* 0.99, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 7.84 (2H, d, J=7.5 Hz), 7.53 (2H, ddd, J=7.5, 7.5, 1.4 Hz), 7.49 (2H, ddd, J=7.5, 7.5, 1.4 Hz), 7.33 (2H, dd, J=7.5, 1.4 Hz), 5.17 (2H, dd, J=21.3, 7.5 Hz), 2.38 (2H, d, J=7.5 Hz). ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H^{19}F-COM) δ: 140.3, 134.0, 130.8, 128.8, 128.7, 128.4, 117.2, 115.9, 111.5, 111.0, 110.7, 110.3, 108.4, 67.1. IR (neat) cm^{-1}: 3460, 1242, 1208, 1150. ^{13}C NMR ($CDCl_3$, DMSO-d_6, ^{1}H-COM) δ: 140.3, 134.0, 130.8, 128.8, 128.7, 128.4, 117.2 (qt, J_{C-F}=289.0, 33.4 Hz), 115.9 (ddt, J_{C-F}=266.0, 257.5, 31.6 Hz), 111.5 (ttt, J_{C-F}=293.8, 30.2, 30.2 Hz), 111.0 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.7 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 110.3 (ttt, J_{C-F}=270.9, 31.6, 31.6 Hz), 108.4 (tqt, J_{C-F}=270.9, 38.7, 31.6 Hz), 67.1 (dd, J_{C-F}=30.2, 19.3 Hz). ^{19}F NMR ($CDCl_3$) δ: −18.2 (3F, s), −51.9 (1F, d, J=283.6 Hz), −58.1–−60.8 (8F, m), −63.2 (1F, d, J=284.5 Hz), −63.6 (2F, dd, J=303.9, 303.9 Hz). IR (KBr) cm^{-1}: 3460, 1242, 1208, 1150. LRMS (EI) *m*/*z*: 950 (M^+), 669 ($M^+ - C_7F_{15}$), 563 (base peak). HRMS Calcd for $C_{28}H_{12}O_2F_{30}$ (M^+): 950.036, found 950.035.

3.3. Asymmetric reaction of diethylzinc with an aldehyde

Typical procedure is as follows. $Ti(OiPr)_4$ (254 μL, 0.86 mmol) was added to a solution of (*R*a)-(*R*)$_2$-**1c** (34 mg, 0.036 mmol) in anhydrous toluene (0.3 mL) at room temperature and the mixture was stirred for 30 min at 50 °C. To the mixture was added a solution of diethylzinc (1.0 mol/L in hexane, 0.86 mL, 0.86 mmol) at −78 °C and stirred for 30 min. Then a solution of benzaldehyde (73 μL, 0.72 mmol) in anhydrous toluene (0.3 mL) was added to the mixture at the same temperature. The mixture was allowed to warm up to −30 °C over 1 h and stirred at this temperature for another 4 h to complete the reaction. The reaction was quenched by 10% HCl, and the mixture was extracted with Et_2O. The organic layer was concentrated after dehydration, and the residue was purified by a column chromatography (Et_2O/hexane=5:95–10:90) to give (*S*)-1-phenylpropanol (95 mg, 97%).

Results of other aldehydes are shown in Table 3. All the products were identified with the samples obtained according to the references shown in the note of Table 3.

3.4. Recycling of the ligand

3.4.1. Recovery of 1c from reaction mixture. After completion of the reaction using 34 mg (0.036 mmol) of **1c**, the reaction was quenched by adding 2 mL of 10% aqueous HCl. Dichloromethane (1 mL) and FC-72 (2 mL) were added to the mixture for extraction. The mixture was shaken vigorously to complete the partition. After separation of FC-72 phase containing **1c**, another FC-72 (2 mL) was added to the remaining mixture for the next extraction. Extraction with FC-72 (2 mL each) was performed three times to recover almost all of **1c**. Evaporation of combined FC-72 layer under reduced pressure gave **1c** in a recovery of 97% with an excellent purity of 98%. After the recovery of **1c** from the reaction mixture, the product was extracted by dichloromethane in three portions (1 mL×1+2 mL×2). The yield and ee of the product were measured after evaporation of the combined dichloromethane layers followed by separation with silica-gel column chromatography.

3.4.2. Recycling procedure. The asymmetric ethyl addition and recovery of the ligand was performed as mentioned above. The ligand recovered was used in the next reaction without purification. First reaction carried out with 34.0 mg (0.036 mmol) of (*R*a)-(*R*)$_2$-**1c**, 0.86 mmol of Ti(OiPr)$_4$, 0.86 mmol of diethylzinc and 0.72 mmol of benzaldehyde to give the product in 97% yield and 97% ee with 33.0 mg of the ligand (97% recovering). The second reaction carried out with 33.0 mg of the ligand recovered, 0.84 mmol of Ti(OiPr)$_4$, 0.84 mmol of diethylzinc and 0.70 mmol of benzaldehyde to give the product in 99% yield and 97% ee with 32.3 mg (0.034 mmol) of the ligand (98% recovery). The third reaction carried out with 32.3 mg (0.034 mmol) of the ligand recovered, 0.81 mmol of Ti(OiPr)$_4$, 0.81 mmol of diethylzinc and 0.68 mmol of benzaldehyde to give the product in 95% yield and 97% ee with 31.3 mg (0.033 mmol) of the ligand (97% recovery). The fourth reaction carried out with 31.3 mg (0.033 mmol) of the ligand recovered, 0.79 mmol of Ti(OiPr)$_4$, 0.79 mmol of diethylzinc and 0.66 mmol of benzaldehyde to give the product in 92% yield and 97% ee with 30.4 mg (0.032 mmol) of the ligand (97% recovery). The fifth reaction carried out with 30.4 mg (0.032 mmol) of the ligand recovered, 0.76 mmol of Ti(OiPr)$_4$, 0.76 mmol of diethylzinc and 0.64 mmol of benzaldehyde to give the product in 98% yield and 98% ee with 29.8 mg (0.031 mmol) of the ligand (98% recovery). The sixth reaction carried out with 29.8 mg (0.031 mmol) of the ligand recovered, 0.74 mmol of Ti(OiPr)$_4$, 0.74 mmol of diethylzinc and 0.62 mmol of benzaldehyde to give the product in 95% yield and 97% ee with 28.9 mg (0.030 mmol) of the ligand (97% recovery). The seventh reaction carried out with 28.9 mg (0.030 mmol) of the ligand recovered, 0.72 mmol of Ti(OiPr)$_4$, 0.72 mmol of diethylzinc and 0.60 mmol of benzaldehyde to give the product in 97% yield and 97% ee with 28.6 mg (0.030 mmol) of the ligand (99% recovery). The eighth reaction carried out with 28.6 mg (0.030 mmol) of the ligand recovered, 0.72 mmol of Ti(OiPr)$_4$, 0.72 mmol of diethylzinc and 0.60 mmol of benzaldehyde to give the product in 97% yield and 97% ee with 27.7 mg (0.029 mmol) of the ligand (97% recovery).

References and notes

1. Preliminary communications: (a) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahdedron Lett.* **2005**, *46*, 319–322. (b) Omote, M.; Nishimura, Y.; Sato, K.; Ando, A.; Kumadaki, I. *J. Fluorine Chem.* **2005**, *127*, 407–409.
2. (a) Zhu, D. W. *Synthesis* **1993**, *10*, 953–954. (b) Meinert, H.; Geister, U. *J. Fluorine Chem.* **1994**, *68*, 221–226. (c) Chambers, R. D.; Sandford, G.; Shah, A. *Synth. Commun.* **1996**, *26*, 1861–1866. (d) Pozzi, G.; Montanari, F.; Rispens, M. T. *Synth. Commun.* **1997**, *27*, 447–452. (e) Sandford, G. *Tetrahedron* **2003**, *59*, 437–454.
3. (a) Horváth, I. T.; Rábai, J. *Science* **1994**, *266*, 72. (b) Horváth, I.; Rábai, J. U.S. Patent 5,463,082, 1995. (c) Horváth, I. T.; Kiss, G.; Cook, R. A.; Bond, J. E.; Stevens, P. A.; Rábai, J.; Mozeleski, E. J. *J. Am. Chem. Soc.* **1998**, *120*, 3133.
4. (a) Miura, T.; Inazu, T. *Tetrahedron Lett.* **2003**, *44*, 1819–1821. (b) Chen, D.; Qing, F.; Huang, V. *Org. Lett.* **2002**, *4*, 1003–1005. (c) Miura, T.; Hirose, Y.; Ohmae, M.; Inazu, T. *Org. Lett.* **2001**, *3*, 3947–3950. (d) Wolf, E.; Richter, B.; Deelman, B.; Koten, G. *J. Org. Chem.* **2000**, *65*, 5422–5427. (e) Richter, B.; Wolf, E.; Koten, G.; Deelman, B. *J. Org. Chem.* **2000**, *65*, 3885–3893.
5. (a) Matsugi, M.; Curran, D. P. *Org. Lett.* **2004**, *6*, 2717–2720. (b) Vallin, K. S. A.; Zhang, Q.; Larhed, M.; Curran, D. P.; Hallberg, A. *J. Org. Chem.* **2003**, *68*, 6639–6645. (c) Curran, D. P. *Synlett* **2001**, 1488–1496. (d) Curran, D. P.; Luo, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9069–9072. (e) Kainz, S.; Luo, Z.; Curran, D. P.; Leitner, W. *Synthesis* **1998**, 1425–1427. (f) Curran, D. P.; Hadida, S.; He, M. *J. Org. Chem.* **1997**, *62*, 6714–6715.
6. Nakamura, Y.; Takeuchi, S.; Zhang, S.; Okumura, K.; Ohgo, Y. *Tetrahedron Lett.* **2002**, *43*, 3053–3056.
7. (a) Nakamura, Y.; Takeuchi, S.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett.* **2000**, *41*, 57–60. (b) Tian, Y.; Chan, K. S. *Tetrahedron Lett.* **2000**, *41*, 8813–8816. (c) Tian, Y.; Chuan, Q.; Mak, C. W. T.; Chan, K. S. *Tetrahedron* **2002**, *58*, 3951–3961. (d) Nakamura, Y.; Takeuchi, S.; Okumura, K.; Ohgo, Y.; Curran, D. P. *Tetrahedron* **2002**, *58*, 3963–3969.
8. (a) Bayardon, J.; Sinou, D. *J. Org. Chem.* **2004**, *69*, 3121–3128. (b) Bayardon, J.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 1449–1451.
9. (a) Cavazzini, M.; Quich, S.; Pozzi, G. *Tettrahedron Lett.* **2002**, *58*, 3943–3949. (b) Maillard, D.; Pozzi, G.; Quich, S.; Sinou, D. *Tetrahedron Lett.* **2002**, *58*, 3971–3976.
10. Shirakawa, S.; Tanaka, Y.; Maruoka, K. *Org. Lett.* **2004**, *6*, 1429–1431.
11. (a) Omote, M.; Kominato, A.; Sugawara, M.; Sato, K.; Ando, A.; Kumadaki, I. *Tetrahedron Lett.* **1999**, *40*, 5583–5585. (b) Omote, M.; Hasegawa, T.; Sato, K.; Ando, A.; Kumadaki, I. *Heterocycles* **2003**, *59*, 501–504. (c) Hasegawa, T.; Omote, M.; Sato, K.; Ando, A.; Kumadaki, I. *Chem. Pharm. Bull.* **2003**, *51*, 265–267.
12. Chen, L. S.; Chen, G. J.; Tamborski, C. *J. Organomet. Chem.* **1980**, *193*, 283–292.
13. (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Omote, M.; Ando, A.; Takagi, T.; Koyama, M.; Kumadaki, I.; Shiro, M. *Heterocycles* **1998**, *47*, 65–68.
14. Absolute configurations of **4c** were determined by converting them to (*S*)-methoxyphenyl(trifluoromethyl)acetic acid esters. The α-proton of the ester from (*R*)-**4c** was observed at 6.98 ppm, while that of the ester from (*S*)-isomer at 7.07 ppm. Structure optimization by MOPAC calculation suggested that

4c has large substituents and the Mosher rule could not be simply applied. By this opimization, the former proton is near the benzene ring of MTP acid, while the latter is far from it. These results support the configurations shown in the text. The results of asymmetric synthesis using these ligands are comparable to the results of **1a**, the structure of which was determined by X'ray analysis.[10a]

15. Semmelhack, M. F. *Org. React.* **1972**, *19*, 178.
16. Semmelhack, M. F.; Helquist, P. M.; Jones, L. D. *J. Am. Chem. Soc.* **1971**, *93*, 5908–5910.
17. Mori, M.; Nakai, T. *Tetrahedron Lett.* **1997**, *38*, 6233–6236.
18. (a) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348. (b) Davis, T. J.; Balsells, J.; Carroll, P. J.; Walsh, P. J. *Org. Lett.* **2001**, *3*, 699–702.

Available online at www.sciencedirect.com
SCIENCE DIRECT
Tetrahedron
Tetrahedron 62 (2006) 1895–1903

Synthesis of original thiazoloindolo[3,2-*c*]quinoline and novel 8-*N*-substituted-11*H*-indolo[3,2-*c*]quinoline derivatives from benzotriazoles. Part I

Anne Beauchard,[a] Hadjila Chabane,[a] Sourisak Sinbandhit,[b] Pierre Guenot,[b] Valérie Thiéry[a,*] and Thierry Besson[a]

[a]*Laboratoire de Biotechnologies et Chimie Bio-organique, FRE CNRS 2766, Université de La Rochelle, Avenue Michel Crépeau, 17042 La Rochelle, France*
[b]*Centre Régional de Mesures Physiques de l'Ouest, Université de Rennes 1, 35042 Rennes, France*

Received 22 July 2005; revised 23 September 2005; accepted 29 September 2005

Available online 9 January 2006

Abstract—Synthesis of novel thiazoloindolo[3,2-*c*]quinoline and 8-substituted-11*H*-indolo[3,2-*c*]quinolines was performed via Graebe–Ullmann thermal cyclization from appropriated *N*-arylated benzotriazoles. 7*H*-4,7-Diaza-benzo[*de*]anthracene, a by-product reaction structurally closed to pyridoacridine skeleton was also identified.

1. Introduction

The thiazole ring in various natural and synthetic products has generated interest of many groups on account of its useful biological properties.[1] Thus, in our laboratory we launched a research program dealing with the preparation and pharmacological evaluation of some original thiazolo derivatives.[2] We recently reported the regiocontrolled synthesis of substituted thiazoloheterocycles (**I** and **II**) mainly related to marine or terrestrial alkaloids (e.g., dercitine, kuanoniamine and ellipticine), which exhibit interesting antitumor activity (Fig. 1).[3] Numerous indoloquinoline alkaloids have been identified from extracts of West African plant *Cryptolepis sanguinolenta*. Isocryptolepine **III** (also referred to as cryptosanguinolentine) with a indolo[3,2-*c*]quinoline (or a benzo-γ-carboline) structure is very rare in nature (Fig. 1).[4] Owing to their growing use in compounds of therapeutic importance (antibacterial, antiplasmodial, anticancer drugs),[5] the synthesis of indoloquinoline derivatives has been actively pursued in the past decade.

We focussed our studies on the synthesis of biologically active compounds in which the thiazole ring might be fused onto indolo[3,2-*c*]quinoline skeleton. Synthetic strategies have been developed for benzo-γ-carboline based on palladium-catalyzed reactions (Heck, Buchwald/Hartwig),[6] Fischer indole cyclization[7] and thermal ring transformation[8] (Graebe–Ullmann). For the synthesis of thiazoloindoloquinoline **IV**, we firstly turned our attention to the Graebe–Ullmann reaction from 4-quinolinylthiazolobenzotriazole **VII** as outlined in Scheme 1. To the best of our knowledge, the chemical behaviour of 4-quinolinyl-functionalized benzotriazole has been rarely reported; a literature survey revealed cyclization of nude benzotriazole or 5,6-dimethylbenzotriazole coupled with quinoline.[5b]

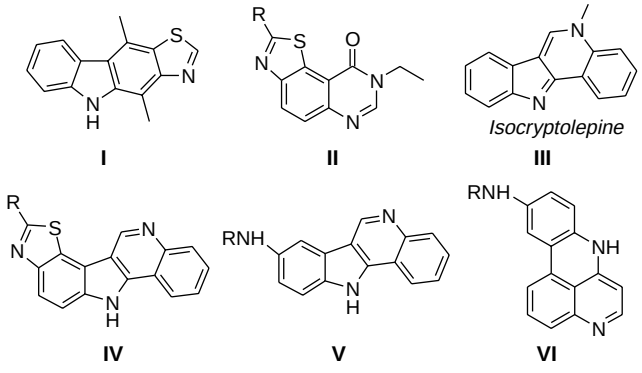
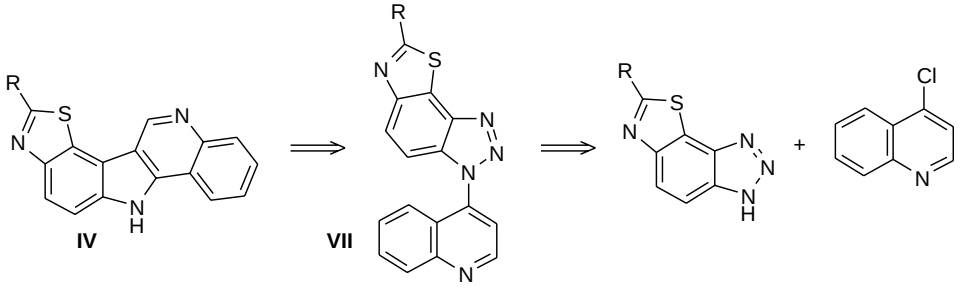


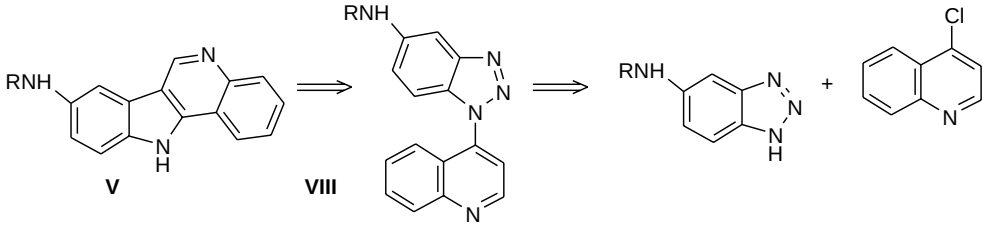
Figure 1. Structures of various potential biological heterocycles and expected skeletons studied in this paper.

Keywords: Indoloquinoline; Benzotriazoles; Fused ring systems; Graebe–Ullmann; Microwaves.
* Corresponding author. Tel.: +33 5 46 45 82 76; fax: +33 5 46 45 82 47; e-mail: vthiery@univ-lr.fr

0040–4020/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2005.09.153



Scheme 1. Retrosynthetic pathway thiazoloindoloquinoline **IV**.



Scheme 2. Retrosynthetic pathway to 8-functionalized indolo[3,2-*c*]quinoline **V**.

After several attempts to obtain 8-functionalized indolo[3,2-*c*]quinoline **V**, we decided to study the thermal cyclization of (4-quinolinyl)-5-*N*-substituted-benzotriazole **VIII** precursor (Scheme 2). The thermal cyclization of this latest provided original 8-*N*-substituted-indolo[3,2-*c*]quinoline together with unexpected 10-*N*-substituted-7*H*-4,7-diazabenzo[*de*]anthracene skeleton **VI** (Fig. 1).

In this paper, we describe the chemical transformation of substituted benzotriazolylquinoline upon thermal cyclization and the synthesis of novel substituted polyheterocyclic compounds, which have never been described until now. Reactions were performed under microwave irradiation.[9]

2. Results and discussion

2.1. Synthesis of 3*H*-thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]-triazole-7-carbonitrile precursor

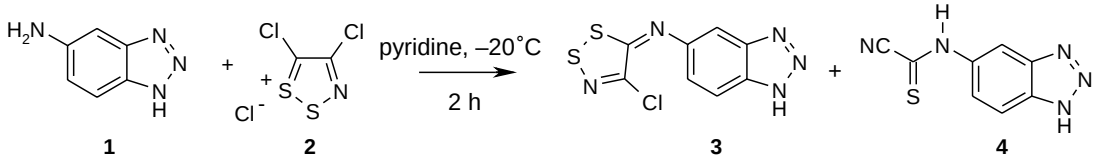
Studying the chemistry of 4,5-dichloro-1,2,3-dithiazolium chloride (Appel salt) and its derivatives, it was previously shown that 5-(*N*-arylimino)-4-chloro-5*H*-1,2,3-dithiazoles, which are stable crystalline solids, cyclized by vigorous heating to give sulphur, hydrogen chloride and 2-cyanobenzothiazoles.[10] Synthesis of rare thiazolobenzotriazole ring was then performed in two steps from the starting commercially available 5-aminobenzotriazole. Using a standard method applied to the preparation of *N*-arylimino-1,2,3-dithiazoles,[2,3] the starting amine was condensed with 4,5-dichloro-1,2,3-dithiazolium chloride in dichloromethane at room temperature, followed by addition of pyridine, to give the desired imino-1,2,3-dithiazolobenzotriazole **3** in moderate yield with cyanothioformamide **4** compound as major product. At low temperature (−20 °C), the reaction mainly yielded the attempted imine **3** (75%) (Scheme 3).

The thermolysis of the benzotriazole derivative **3** in a refluxed mixture of toluene and *N*-methylpyrrolidinone under microwave irradiation, gave the angular compound **5** in reasonable yield (68%) beside trace of decyanated counterpart **6**. No trace of linear isomer was detected. A mild procedure, which consists to heat an *ortho* bromoimine **7** in the presence of cuprous iodide in pyridine at reflux, was applied and afforded regioselectively this angular isomer **5** in good yield (73%) (Scheme 4).[2c]

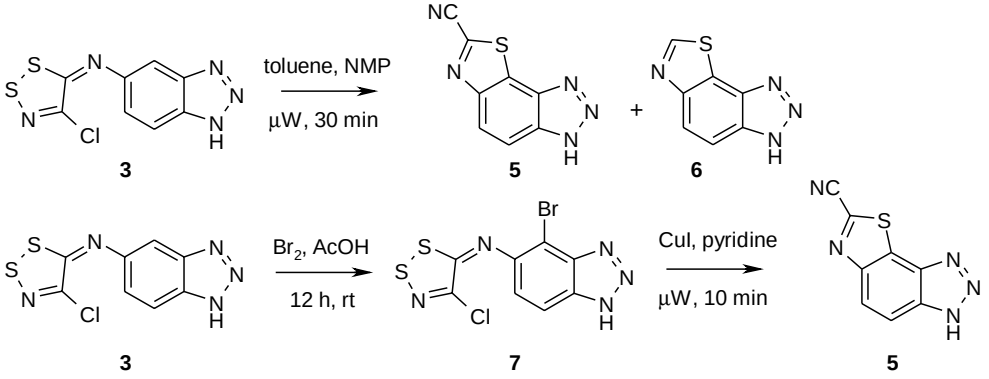
2.2. Synthesis of quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]-benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile

The preparation of quinolinylbenzotriazole by condensation of 4-chloroquinoline **8** and the corresponding benzotriazole **5** under neat conditions at high temperature led to carbonaceous mixtures. We found that microwave irradiation (160 °C, in sealed vial) of an equimolar mixture of 4-chloroquinoline and thiazolobenzotriazole in solution with a minimum of toluene afforded two condensed compounds **9** and **10** in moderate yields (33 and 44%) (Scheme 5).

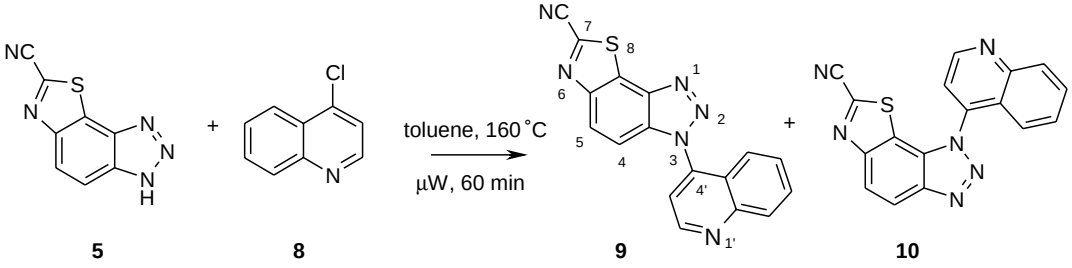
The presence of regioisomers is due to the tautomeric nature of the triazole function.[11] In literature, the alkylation of different 1,2,3-triazoles did not allow for any selective



Scheme 3. Synthesis of (1*H*-benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine **3**.



Scheme 4. Cyclization of (1*H*-benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine **3**.



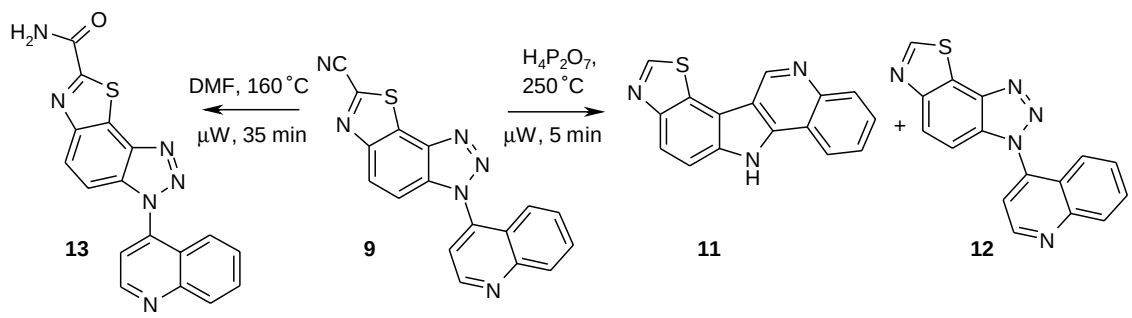
Scheme 5. Condensation of thiazolobenzotriazole with 4-chloroquinoline.

anticipation of N-alkylation of the thiazolo condensed-1,2,3-triazole. In order to establish unambiguously the structure of the different regioisomers, we envisaged an X-ray diffraction study. Unfortunately, all attempts to obtain suitable crystals failed. Because of the steric hindrance, we assumed that the isomer **9** generated arylation in position 3 of the thiazolobenzotriazole ring was the major compound. It must be noted that 2D ^{1}H–^{13}C correlation experiments and ^{1}H NMR NOESY experiments on the derivative **9** were also non-conclusive.

2.3. Thermolysis of quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]-benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile

Classic Graebe–Ullmann conditions for the elimination of nitrogen from 1-aryl-1*H*-benzo-1,2,3-triazoles involve heating the triazole derivative beyond its melting point. Inspired by Alvarez-Builla's procedure, we firstly used pyrophosphoric acid as solvent.[5b,8d] Microwave irradiation of the *N*-arylated benzotriazole **9** in a quartz glassware with pyrophosphoric acid and toluene at 250 °C for 5 min afforded a complex mixture from which thiazolo-indolo[3,2-*c*]quinoline **11** and decyanated *N*-arylbenzo-triazole **12** were isolated in, respectively, 17 and 23% yields (Scheme 6). A long exposition at high temperature was unfruitful and led to the degradation of the material and a longer reaction time at a lowest temperature (180 °C) yielded mainly to compound **12**. After several attempts with various acids, the reaction was carried out in DMF at reflux. The reaction afforded 75% of carboxamide **13**. Exposing the same benzotriazole **9** to microwave irradiation, neat in glass vial with a screw cap lid, or with few drops of acid or polar solvent (DMF, NMP, etc.) were also unsuccessful.

To the best of our knowledge, the synthesis of indolo-[3,2-*c*]quinoline fused onto 7,8-thiazole (or 8*H*-1-thia-3,6,11-triaza-cyclopenta[*d*]-benzo[*a*]fluorene) has never been reported until now.

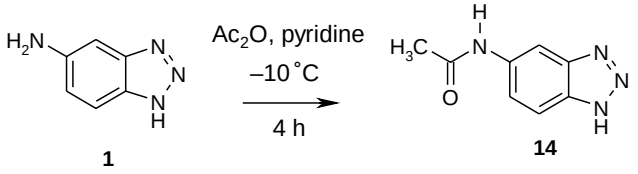


Scheme 6. Thermal cyclization of 3-*N*-aryl-thiazolobenzotriazole.

2.4. Synthesis of *N*-(quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide

The following part of our study was focused on the synthesis of original *N*-8-substituted-indolo[3,2-*c*]quinoline. According to the results obtained above, we decided to study the chemical transformation of *N*-(quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide (Scheme 2).

n-Acetylation of 5-aminobenzotriazole **1** was performed with 1 equiv of acetic anhydride in pyridine at low temperature (−10 °C) to overcome additional acetylation on triazole nitrogen and yielded 75% of acetamide **14** (Scheme 7).[12]



Scheme 7. Protection of 5-aminobenzotriazole **1**.

Using the same procedure described in Section 2.2, the acetamide **14** was subjected to the action of 4-chloroquinoline **8** under microwave irradiation. Whatever the solvent used (toluene, DMF or NMP), reaction yielded mixtures of three monoalkylated derivatives (**15**: 43%, **16**: 30% and **17**: 10%) (Scheme 8). The structures of compounds **15**–**17** were confirmed by their analytical and spectroscopic data. The isomer **17** obtained in 10% yield, was easily identified on the basis of mass spectral evidence. In agreement with the known behaviour of 2-substituted 1,2,3-triazoles to electron impact, its mass spectrum did not exhibit peaks issued from molecular ions through the initial extrusion N_2.

To unambiguously identify the regioisomers formed by arylation in position 1 and 3 on the triazole, 2D ^{1}H–^{13}C NMR (HMBC and HMQC) correlation experiments were performed on compounds **15** and **16**, but the detected ^{1}H–^{13}C correlations were not helpful for a structural determination. Unequivocal differenciation of substitution of quinoline at position N-1 or N-3 was determined by performing by ^{1}H NMR COSY, NOESY experiments on the derivative **15**, the NOE experiments showing strong effect between 7-H of triazole and 3′-H of quinoline and weaker effects between 7-H of triazole and 5′-H of quinoline (Fig. 2).

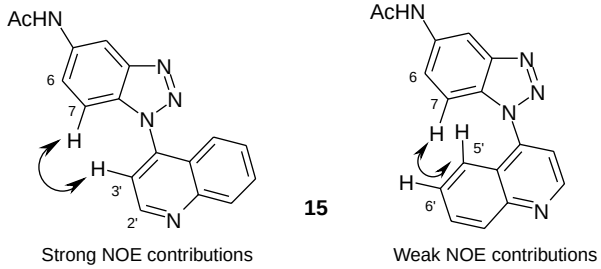


Figure 2. NOE contributions.

2.5. Thermolysis of *N*-1-quinolin-4-yl-benzotriazole 15

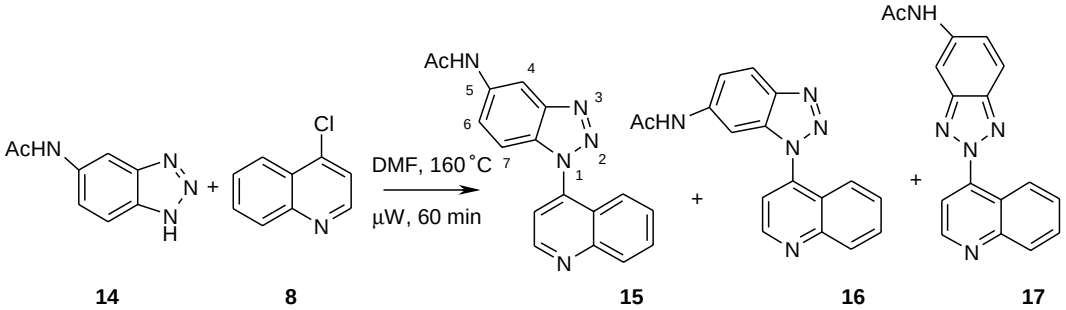
Expecting a similar chemical behaviour to that observed for benzotriazole **9**, the cyclization of *N*-protected benzotriazole **15** was also studied under microwave irradiation. Various attempts under neat conditions or in boiling neutral media (toluene or triglyme) afforded small amounts of 8-*N*-acetamidoindolo[3,2-*c*]quinoline **18** (6%) from complicated mixture. Thermolysis (in boiling pyrophosphoric acid at 250 °C) led to the complete degradation of the reactant within less than 5 min. Performed at 200 °C during 3 min, the same reaction in boiling acid appeared more efficient and yielded, respectively, 27% of deprotected 8-amino-11*H*-indolo[3,2-*c*]quinoline **19**, 8% of *N*-acetamidotetracycle **18** besides traces of non-cyclized amines **21** and **22**. Most unexpected was the isolation of a different fused ring system **20** in moderate yield 35% (Scheme 9).[5e,8f]

Furthermore, the ^{1}H NMR spectrum was different from the normal indolo[3,2-*c*]quinoline pattern showing a *H*-C6 characteristic singulet. The theoretical signal of the quinoline H-2 ($\delta=8.53$ ppm, d, $J=5.2$ Hz) and its coupling with the H-3 ($\delta=6.83$ ppm, d, $J=5.2$ Hz) still appeared. All the spectroscopic data fitted well for a fused quinolinoquinoline structure.

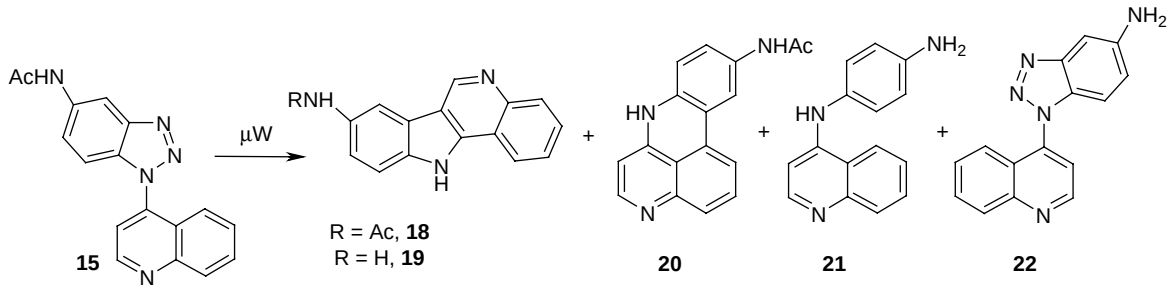
The *N*-(7*H*-4,7-diaza-benzo[*de*]anthracen-10-yl)-acetamide **20**, which is structurally closed to pyrodoacridine skeleton present in marine alkaloid can be considered as an interesting intermediate for the preparation of novel rings.[1d,e,13]

3. Conclusion

In conclusion, we showed that 4-(substituted-benzotriazolyl)quinoline might be a convenient precursor for the synthesis of the original fused ring like



Scheme 8. Condensation of acetamidobenzotriazole **14** with 4-chloroquinoline.



Scheme 9. Thermal cyclization of *N*-1-aryl-acetamidobenzotriazole.

thiazoloindolo[3,2-*c*]quinoline and quinolinoquinoline rings system, following a microwave-assisted Graebe–Ullmann cyclization.

The chemical and biological interest of thiazoloindolo[3,2-*c*]quinoline **11**, 8-amino-11*H*-indolo[3,2-*c*]quinoline derivatives **18**, **19** and quinolinoquinoline **20** mainly obtained in these experiments are under investigation. This latest new ring system was identified as a suitable starting precursor for conversion to dercitin analogs.[13]

4. Experimental

4.1. General remarks

All solvents and reagents were reagent grade and were used without purification. Melting points were determined using a Köfler melting point apparatus and are not corrected. IR spectra were recorded on a Perkin-Elmer Paragon 1000PC instrument. ^{1}H and ^{13}C NMR were recorded on a JEOL JNM LA400 (400 MHz) spectrometer (Centre Commun d'Analyses, Université de la Rochelle) and on a Brucker Avance 500 and 300 MHz (HMBC, HMQC and NOE experiments) in the Centre Régional de Mesures Physiques de l'Ouest (CRMPO); chemical shifts (δ) are reported in part per million (ppm) downfield from tetramethylsilane (TMS), which was used as internal standard. Coupling constants *J* are given in Hz. The mass spectra (HRMS) were recorded on a Varian MAT 311 spectrometer in the CRMPO, Université de Rennes. Column chromatography was performed by using Merck silica gel (70–230 mesh) at medium pressure. Light petroleum ether refers to the fraction boiling point 40–60 °C. Analytical thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 F254 aluminium backed plates.

After purification by chromatography on silica gel, compounds **3**, **4**, **5**, **7**, **9**, **10**, **12**, **15**, **16**, **17** were recrystallized in ethanol and compound **13** in DMF.

Microwave experiments were carried out at atmospheric pressure using a focused microwave reactor (CEM Discover™ or Synthewave®402 Prolabo). The instrument consists of a continuous focused microwave power output from 0–300 W. Reactions were performed in a glass vessel (CEM) and in quartz reactor vessel (Prolabo) prolonged by a condenser; it is also possible to work under dry atmosphere, in vacuo, or under pressure (0–20 bar, tubes of 10 mL, sealed with a septum) if necessary. The temperature content of a vessel is monitored using a calibrated infrared sensor mounted under the vessel.[14] All the experiments were performed using stirring option whereby the contents of a vessel are stirred by means of a rotating plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. In all experiments a target temperature was selected together with a power. The target temperature was reached with a ramp of 2 min and the chosen microwave power stayed constant to hold the mixture at this temperature. The reaction time does not include the ramp period.

4.2. Synthesis of iminodithiazoles

Under an inert atmosphere of argon, 4,5-dichloro-1,2,3-dithiazolium chloride **2** (1.71 g, 74.5 mmol) was added to a stirred solution of commercially available 5-aminobenzotriazole **1** (1.00 g, 74.5 mmol) in dichloromethane (30 mL) at −20 °C. After 45 min, pyridine (1.32 mL, 163.9 mmol) was added and the mixture stirred for 2 h. The obtained precipitate was filtered and purified by chromatography on silica gel with dichloromethane–methanol (99/1) as eluent to give the expected iminodithiazole **3** with cyanothioformamide **4**.

4.2.1. (1*H*-Benzotriazol-5-yl)-(4-chloro-[1,2,3]dithiazol-5-yliden)amine 3. Yield: 75%. Mp=195–197 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=15.70 (br s, 1H, NH), 8.04 (d, *J*=8.8 Hz, 1H, 7-H), 7.65 (s, 1H, 4-H), 7.26 (dd, *J*=8.8, 2.2 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=159.91, 148.90, 146.44, 138.32, 137.92, 119.39, 117.10, 102.19. IR=3099, 2768, 1694, 1574, 1200, 1199, 861 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_4N_5Cl_2$): calcd 268.9597; found 268.9599.

4.2.2. *N*-(1*H*-Benzotriazol-5-yl)-2-nitrilo-thioacetamide 4. Yield: 5%. Mp=130–132 °C (ethanol). ^{1}H NMR (DMSO-d_6+D_2O, 400 MHz) δ=8.79 (s, 1H, ArH), 8.02 (d, *J*=8.4 Hz, 1H, ArH), 7.67 (d, *J*=8.4 Hz, 1H, ArH). IR=3254, 2224, 1701, 1609, 1409, 1203, 995, 620 cm^{-1}. HRMS (EI) $[M-HCN]^{+}$ ($C_7H_3N_4S$): calcd 176.0156; found 176.0152.

4.3. Bromination

Under an inert atmosphere of argon, to a solution of imine **3** (0.36 g, 13.35 mmol) in dichloromethane (5 mL) was added dropwise bromine (0.08 mL, 14.68 mmol) in solution in acetic acid (3 mL). After 12 h under stirring at room temperature, the residue was treated with a saturated

solution of sodium thiosulfate Na_2SO_3 (15 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and the filtrate was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (95/5) as eluent to give the bromo derivative **7**.

4.3.1. 4-Bromo-5-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidenamino)benzotriazole 7. Yield: 87%. Mp=200–202 °C (ethanol). ^{1}H NMR (DMSO-d_6+D_2O, 400 MHz) δ=7.99 (d, J=8.8 Hz, 1H, 7-H), 7.26 (d, J=8.8 Hz, 1H, 6-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=163.55, 148.11, 146.06, 140.12, 137.07, 126.67, 118.51, 116.64. IR=3238, 2792, 1596, 1201, 1147, 857 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_3N_5^{35}Cl^{79}BrS_2$): calcd 346.8702; found 346.8703.

4.4. Cyclization

Method A. Under an inert atmosphere of argon, a solution of iminodithiazole **3** (1.0 g, 3.72 mmol) in *N*-methylpyrrolidin-2-one/toluene (5 mL, v/v) was irradiated during 30 min. The irradiation in CEM oven was programmed to maintain a constant temperature (180 °C) with a maximal power output of 150 W. After cooling, the toluene was removed under reduced pressure. The mixture was diluted with ethyl acetate (20 mL) and washed with water (3× 15 mL). The organic layer was dried ($MgSO_4$) and the filtrate was concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (90/10) as eluent to give the thiazolo derivative **5** (68%).

Method B. Under an inert atmosphere of argon, a suspension of bromo imine **7** (0.3 g, 8.6 mmol), copper iodide (0.17 g, 8.6 mmol) in pyridine (5 mL) was irradiated during 10 min. The irradiation was programmed to obtain a constant temperature (110 °C) with a maximal power output of 80 W. After cooling, the mixture was treated with a saturated solution of Na_2SO_3 (20 mL) and extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (90/10) as eluent to give the thiazolo derivative **5** (85%).

4.4.1. 3*H*-Thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]triazole-7-carbonitrile 5. Yield: 85% (obtained from method A). Mp=228–230 °C (ethanol). ^{1}H NMR (DMSO-d_6, 400 MHz) δ=16.50 (br s, 1H, NH), 8.26 (d, J=8.8 Hz, 1H, 4-H), 8.15 (d, 1H, J=8.8 Hz, 5-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=170.31, 152.2, 150.20, 135.09, 124.1, 122.79, 114.65, 113.25. IR=3111, 2830, 2239, 1712, 1694, 1407, 1197, 804 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_3N_5S$): calcd 201.0109; found 201.0108.

4.4.2. 3*H*-Thiazolo[5′,4′:3,4]benzo[1,2-*d*][1,2,3]triazole 6. Yield: trace (method A). Mp=>260 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ=16.23 (br s, 1H, NH), 9.47 (s, 1H, 7-H), 8.14 (d, J=8.8 Hz, 1H, 4-H or 5-H), 7.98 (d, 1H, J=8.8 Hz, 5-H or 4-H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ=155.21, 155.12, 152.17, 136.50, 122.37, 120.77, 113.08. IR=3436, 3073, 2925, 1412, 1315, 1189, 876 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_7H_4N_4S$): calcd 176.0156; found 176.0152.

4.5. Synthesis of quinolinylbenzotriazoles

Under an inert atmosphere of argon, a solution of an equimolar mixture of commercial 4-chloroquinoline (0.12 g, 0.73 mmol) and thiazolobenzotriazole **5** (0.14 g, 0.73 mmol) in toluene (2 mL) was heated at 160 °C in a sealed tube for 1 h. After cooling, the toluene was removed in vacuo. The mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel, with light petroleum ether–ethyl acetate (80/20) as eluent to provide 2 regioisomers **9** and **10** in, respectively, 44 and 33% yield.

4.5.1. 3-Quinolin-4-yl-1*H*-thiazolo[4′,5′:3′,4]benzo[1,2-*d*]-[1,2,3]triazole-7-carbonitrile 9. Yield: 44%. Mp=238–240 °C (ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ=9.23 (d, J=4.4 Hz, 1H, 2′-$H_{quinolin.}$), 8.38 (d, J=9.2 Hz, 1H, ArH), 8.33 (d, J=9.2 Hz, 1H, 5-H or 4-H), 7.92 (ddd, J=2.0, 6.8, 9.2 Hz, 1H, ArH), 7.69 (d, J=4.4 Hz, 1H, 3′-$H_{quinolin.}$), 7.68 (ddd, J=2.0, 6.8, 9.2 Hz, 1H, ArH), 7.66 (d, J=9.2 Hz, 1H, ArH), 7.62 (d, J=9.2 Hz, 1H, 4-H or 5-H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=151.00, 150.42 (2′-C), 150.12, 139.75, 136.24, 135.79, 133.81, 131.12 (7′-C), 130.45, 128.77, 126.71, 125.69, 122.91, 122.55, 117.72 (3′-C), 112.63, 111.09. IR=2921, 2339, 1435, 1260, 805, 760 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_8N_6S$): calcd 328.0531; found 328.0530.

4.5.2. 1-Quinolin-4-yl-1*H*-thiazolo[4′,5′:3′4]benzo[1,2-*d*]-[1,2,3]triazole-7-carbonitrile 10. Yield: 33%. Mp=252–254 °C (ethanol). ^{1}H NMR ($CDCl_3$, 400 MHz) δ=9.16 (d, J=4.9 Hz, 1H, 2′-$H_{quinolin.}$), 8.84 (d, J=8.0 Hz, 1H, 4-H or 5-H), 8.31 (d, J=8.0 Hz, 1H, 5-H or 4-H), 8.26 (d, J=9.3 Hz, 1H, ArH), 8.20 (d, J=9.3 Hz, 1H, ArH), 8.12 (d, J=4.9 Hz, 1H, 3′-$H_{quinolin.}$), 7.91 (t, J=7.2 Hz, 1H, ArH), 7.77 (t, J=7.2 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ=153.09, 150.24, 150.16, 144.73, 143.09, 139.61, 139.65, 130.55, 130.24, 128.69, 125.12, 124.54, 124.03, 120.72, 119.03, 116.17, 112.70. IR=3069, 2919, 2230, 1715, 1562, 1501, 1432, 1395, 995, 831, 774 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_8N_6S$): calcd 328.0531; found 328.0530.

4.6. Cyclization of quinolinylbenzotriazole

In a quartz reactor, a solution of the corresponding benzotriazolylquinoline **9** (0.08 g, 0.26 mmol) and $H_4P_2O_7$ (1 mL) in toluene (1 mL) placed was heated at 250 °C until the evolution of nitrogen ceased after 5 min. The reaction mixture was then triturated with water and basified with a saturated solution of $NaHCO_3$ (8 mL). The resulting precipitate was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane as eluent, to give the thiazoloindolo-[3,2-*c*]quinoline **11** and the compound **12**.

4.6.1. 8*H*-1-Thia-3,10,12-triaza-benzo[*a*]cyclopenta[*d*]-fluorene 11. Yield: 17%. Mp=>260 °C. ^{1}H NMR (CD_3OD+D_2O, 400 MHz) δ=9.47 (s, 1H, 11-$H_{quinolin.}$), 9.30 (s, 1H, 2-$H_{thiazol.}$), 8.50 (dd, J=6.8, 1.2 Hz, 1H, ArH),

8.24–8.18 (m, 2H, ArH), 7.92 (d, $J=8.8$ Hz, 1H, 4-H or 5-H), 7.82 (t, $J=7.2$ Hz, 1H, ArH), 7.75 (t, $J=7.2$ Hz, 1H, ArH). IR=2920, 1787, 1713, 1288, 611 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{16}H_9N_3S$): calcd 275.0517; found 275.0513.

4.6.2. *N*-(3-Quinolin-4-yl)-1*H*-thiazolo[5′,4′:3,4]benzo-[1,2-*d*][1,2,3]triazole 12. Yield: 23%. Mp=228–230 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.17$ (s, 1H, 7-H), 9.14 (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.91 (d, $J=8.8$ Hz, 1H, ArH), 8.29 (d, $J=8.8$ Hz, 1H, ArH), 8.14 (d, $J=9.2$ Hz, 1H, ArH), 8.12 (d, $J=4.4$ Hz, 1H, 3′-$H_{quinolin.}$), 8.08 (d, $J=9.2$ Hz, 1H, ArH), 7.87 (t, $J=7.2$ Hz, 1H, ArH), 7.75 (t, $J=7.2$ Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta=154.40$, 154.25, 148.20, 144.54, 141.09, 131.56, 129.23, 128.19, 125.80, 125.10, 121.36, 120.88, 116.87, 115.62. IR=3487, 1920, 1727, 1631, 1305, 1230, 991, 829, 760 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{16}H_9N_5S$): calcd 303.0568; found 303.0566.

4.6.3. *N*-(3-Quinolin-4-yl)-1*H*-thiazolo[5′,4′:3,4]benzo-[1,2-*d*][1,2,3]triazole-7-carboxamide 13. Yield: 75% (from DMF). Mp=>260 °C. ^1H NMR (CD_3OD+D_2O, 400 MHz) $\delta=9.15$ (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.89 (dd, $J=8.8$, 0.8 Hz, 1H, ArH), 8.29 (t, $J=8.4$ Hz, 1H, ArH), 8.19 (t, $J=8.4$ Hz, 1H, ArH), 8.14 (s, 1H, ArH), 7.88 (dd, $J=8.4$, 0.8 Hz, 1H, ArH), 7.71 (d, $J=8.4$ Hz, 1H, ArH), 7.53 (d, $J=8.4$ Hz, 1H, ArH). IR=3313, 2904, 1712, 1663, 1505, 1400, 1118, 805, 758 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{10}N_6OS$): calcd 346.0636; found 346.0639.

4.7. Acetylation

Under an inert atmosphere of argon, acetic anhydride (1.06 mL, 11.82 mmol) was added to a solution of 5-aminobenzotriazole **1** (1.50 g, 11.82 mmol) in pyridine (7 mL) at −10 °C. After 4 h, the resulting precipitate was filtered and purified by chromatography on silica gel with dichloromethane as eluent, to give acetamide **14**.

4.7.1. *N*-(1*H*-Benzotriazol-5-yl)-acetamide 14. Yield: 75%. Mp=>260 °C. ^1H NMR (DMSO-d_6, 400 MHz) $\delta=$ 15.39 (s, 1H, NH), 10.14 (s, 1H, NH), 8.23 (s, 1H, 4-H), 7.83 (d, $J=8.8$ Hz, 1H, 6-H or 7-H), 7.34 (d, $J=8.8$ Hz, 1H, 7-H or 6-H), 2.55 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) $\delta=169.54$, 149.40, 137.12, 123.98, 118.73, 109.93, 30.52, 23.69. IR=3087, 1738, 1682, 1568, 1413, 1257, 1204, 1007, 810 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_8H_8N_4O$): calcd 176.0698; found 176.0694.

4.8. Synthesis of acetamidoquinolinylbenzotriazoles

Under an inert atmosphere of argon, a solution of 4-chloroquinoline **8** (0.93 g, 5.6 mmol) and acetamidobenzotriazole **14** (1.0 g, 5.6 mmol) in DMF (2 mL) was heated at 160 °C for 1 h. After cooling, the DMF was removed under reduced pressure. The mixture was diluted with ethyl acetate (15 mL) and washed with water (2×15 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–ethyl acetate (30/70) as eluent to provide the regioisomers **15**, **16**, **17** in 43, 30 and 10% yields, respectively.

4.8.1. *N*-(1-Quinolin-4-yl-1*H*-benzotriazol-5-yl)-acetamide 15. Yield: 43% (0.72 g). Mp=>260 °C (ethanol). ^1H NMR (DMSO-d_6, 400 MHz) $\delta=10.37$ (s, 1H, NH), 9.21 (d, $J=4.5$ Hz, 1H, 2′-$H_{quinolin.}$), 8.65 (d, $J=0.9$ Hz, 1H, 4-H), 8.27 (d, 1H, $J=8.4$ Hz, 8′-H), 7.95 (d, $J=4.5$ Hz, 1H, 3′-$H_{quinolin.}$), 7.94 (td, $J=1.5$, 6.7 Hz, 7′-H), 7.79 (dd, $J=$ 1.0, 8.7 Hz, 1H, 5′-H), 7.72 (td, $J=1.0$, 6.7 Hz, 6′-H partially mixed with 6-H), 7.70 (d, 1H, 6-H), 7.63 (d, $J=$ 8.9 Hz, 1H, 7-H), 2.14 (s, 3H, $COCH_3$). ^{13}C NMR (CD_3OD, 100 MHz) $\delta=168.68$, 151.04, 149.19, 145.61, 139.46, 136.64, 130.68, 129.91, 129.51, 128.29, 123.00, 122.60, 122.33, 117.53, 110.91, 107.32, 23.96. IR=3487, 1666, 1378, 1305, 1041, 809, 757 cm^{-1}. MS (*m*/*z*) 303, 275 ($M^{+\cdot}-N_2$). HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1120.

4.8.2. *N*-(3-Quinolin-4-yl-3*H*-benzotriazol-5-yl)-acetamide 16. Yield: 30% (0.49 g). Mp=>260 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.15$ (d, $J=4.4$ Hz, 1H, 2′-$H_{quinolin.}$), 8.30 (d, 1H, $J=8.8$ Hz, ArH), 8.20 (s, 1H, ArH), 8.13 (d, 1H, $J=8.8$ Hz, ArH), 7.89–7.81 (m, 2H, ArH), 7.64–7.60 (m, 2H, $J=4.4$ Hz, 3′-$H_{quinolin.}$, ArH), 7.51 (br s, 1H, NH), 7.21 (dd, 1H, $J=2.0$, 8.8 Hz, ArH), 2.20 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) $\delta=168.54$, 150.42, 150.05, 142.71, 140.44, 138.51, 134.76, 130.73, 130.09, 128.18, 123.31, 123.09, 120.86, 118.19, 117.06, 99.94, 24.80. IR= 3243, 3069, 1696, 1555, 1496, 1261, 813 cm^{-1}. MS (*m*/*z*) 303, 275 ($M^{+\cdot}-N_2$). HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1112.

4.8.3. *N*-(2-Quinolin-4-yl-3*H*-benzotriazol-5-yl)-acetamide 17. Yield: 10% (0.17 g). Mp=226–228 °C (ethanol). ^1H NMR ($CDCl_3$, 400 MHz) $\delta=9.11$ (d, $J=4.8$ Hz, 1H, 2′-$H_{quinolin.}$), 8.88 (d, 1H, $J=8.4$ Hz, ArH), 8.48 (s, 1H, ArH), 8.26 (d, 1H, $J=8.8$ Hz, ArH), 8.07 (d, 1H, $J=4.8$ Hz, 3′-$H_{quinolin.}$), 7.97 (d, 1H, $J=8.8$ Hz, ArH), 7.85 (t, 1H, $J=$ 7.8 Hz, ArH), 7.72 (t, 1H, $J=7.8$ Hz, ArH), 7.39 (dd, 1H, $J=2.0$, 8.8 Hz, ArH), 7.37 (s, 1H, NH), 2.29 (s, 3H). IR= 3423, 2953, 1693, 1498, 1261, 668, 612 cm^{-1}. MS (*m*/*z*) 303. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_5O$): calcd 303.1120; found 303.1122.

4.9. Cyclization of acetamidoquinolinylbenzotriazole

Method A. In a sealed vial, a solution of the corresponding benzotriazolylquinoline **15** (0.10 g, 0.33 mmol) in DMF (2 mL) was heated at 250 °C during 60 min. The reaction mixture was then triturated with water (8 mL). The precipitate formed was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by recrystallization to afford the expected acetamido indolo[3,2-*c*]quinoline **18**.

4.9.1. *N*-(11*H*-Indolo[3,2-*c*]quinolin-8-yl)-acetamide 18. Yield: 6% (0.007 g). Mp=>260 °C. ^1H NMR (DMSO-d_6, 400 MHz) $\delta=12.71$ (s, 1H, NH), 10.04 (s, 1H, NH), 9.52 (s, 1H, 6-H), 8.57 (d, $J=1.0$ Hz, 1H, 7-H), 8.49 (d, 1H, $J=$ 8.0 Hz, 1-H), 8.11 (d, 1H, $J=8.0$ Hz, 4-H), 7.74 (t, 1H, $J=$ 6.8 Hz, 3-H), 7.68 (t, 1H, $J=6.8$ Hz, 2-H), 7.64 (d, 1H, $J=8.8$ Hz, 10-H), 7.56 (dd, 1H, $J=2.0$, 8.8 Hz, 9-H), 2.11 (s, 3H, CH_3). ^{13}C NMR (DMSO-d_6, 100 MHz) $\delta=24.39$, 110.89 (7-C), 112.30 (10-C), 114.74, 115.18, 119.26 (9-C),

122.51 (1-C), 123.48, 126.12 (2-C), 128.46 (3-C), 129.98 (4-C), 133.48, 135.63, 138.90, 140.66, 145.05 (6-C), 168.47. IR = 3485, 1669, 1128, 1016, 754, 514 cm^{-1}. HRMS (EI) $[M+H]^{+\cdot}$ ($C_{17}H_{14}N_3O$): calcd 276.1137; found 276.1136.

Method B. In a quartz reactor, a solution of the corresponding benzotriazolylquinoline **15** (0.18 g, 0.54 mmol) and $H_4P_2O_7$ (1 mL) in toluene (1 mL) placed was heated at 200 °C until the evolution of nitrogen ceased after 3 min. The reaction mixture was then triturated with water and basified with a saturated solution of $NaHCO_3$ (8 mL). The resulting precipitate was diluted with ethyl acetate (15 mL) and extracted. The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was purified by chromatography on silica gel, with dichloromethane–methanol (90/10) as eluent to provide 8-amino-11*H*-indolo[3,2-*c*]quinoline **19**, quinolinoquinoline **20** and amino by-products **21**.

4.9.2. 11*H*-Indolo[3,2-*c*]quinolin-8-ylamine 19. Yield: 27% (0.06 g). Mp = 180–182 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 12.28 (s, 1H, NH), 9.38 (s, 1H, 6-H), 8.44 (dd, J = 1.2, 8.0 Hz, 1H, 4-H or 1-H), 8.07 (d, J = 8.0 Hz, 1H, 1-H or 4-H), 7.68 (td, J = 1.2, 8.0 Hz, 1H, 2-H or 3-H), 7.63 (td, J = 1.2, 8.0 Hz, 1H, 3-H or 2-H), 7.41 (d, J = 8.5 Hz, 1H, 10-H), 7.38 (d, J = 2.1 Hz, 1H, 7-H), 6.86 (dd, J = 2.1, 8.5 Hz, 1H, 9-H), 5.06 (br s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 103.40 (7-C), 112.53 (10-C), 114.45, 115.61 (9-C), 117.75, 122.40 (4-C), 123.23, 125.82 (2-C), 128.01 (3-C), 129.77 (1-C), 132.13, 140.00, 143.67, 144.98 (6-C), 145.47. IR = 3341, 1632, 1566, 1509, 1341, 1240, 1176, 755 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{15}H_{11}N_3$): calcd 233.0953; found 233.0952.

4.9.3. *N*-(7*H*-4,7-Diaza-benzo[*de*]anthracen-10-yl)-acetamide 20. Yield: 35% (0.054 g). Mp = > 260 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.53 (d, J = 5.2 Hz, 1H, 5-$H_{quinolin.}$), 8.07 (d, J = 8.8 Hz, 1H, 3-H or 1-H), 7.96 (d, J = 8.8 Hz, 1H, 1-H or 3-H), 7.71 (t, J = 7.6 Hz, 1H, 2-H), 7.61 (d, J = 2.0 Hz, 1H, 11-H), 7.56–7.50 (m, 2H, 9-H, 8-H), 6.83 (d, 1H, J = 5.2 Hz, 6-$H_{quinolin.}$), 2.60 (s, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 171.24, 165.30, 150.85, 148.63, 148.25, 142.72, 135.96, 130.07, 128.48, 125.40, 121.12, 119.41, 119.21, 114.92, 111.03, 101.51, 29.70. IR = 3341, 1632, 1566, 1509, 1341, 1240, 1176, 755 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{17}H_{13}N_3O$): calcd 275.1059; found 275.1062.

4.9.4. *N*-Quinolin-4-yl-benzene-1,4-diamine 21. Yield: 5% (0.006 g). Mp = 152–154 °C. ^{1}H NMR (DMSO-d_6, 400 MHz) δ = 8.48 (d, J = 5.5 Hz, 1H, 2-$H_{quinolin.}$), 8.06 (d, J = 8.4 Hz, 1H, ArH), 7.90 (d, J = 8.4 Hz, 1H, ArH), 7.69 (td, J = 1.2, 6.4 Hz, 1H, ArH), 7.50 (td, J = 1.2, 6.4 Hz, 1H, ArH), 7.12 (dd, J = 2.4, 6.4 Hz, 2H, ArH), 6.76 (dd, J = 2.4, 6.4 Hz, 2H, ArH), 6.65 (d, J = 5.2 Hz, 1H, 3-$H_{quinolin.}$), 3.49 (s, 2H, NH_2). ^{13}C NMR (DMSO-d_6, 100 MHz) δ = 150.62, 149.40, 148.48, 144.62, 129.97, 129.74, 129.35, 126.50, 125.04, 119.39, 118.88, 116.05, 100.93. IR = 3421, 2314, 1709, 1260, 1124 cm^{-1}. HRMS (EI) $[M]^{+\cdot}$ ($C_{15}H_{13}N_3$): calcd 235.1109; found 235.1094.

Acknowledgements

We thank the Ministère de la Recherche et de l'Enseignement Supérieur for PhD grant (A.B.) and the 'Comité de Charente-Maritime de la Ligue Nationale Contre le Cancer' for financial support.

References and notes

1. (a) Wells, G.; Bradshaw, T. D.; Diana, P.; Seaton, A.; Shi, D.-F.; Westwell, A. D.; Stevens, M. F. G. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 513–515. (b) Bradshaw, T. D.; Wrigley, S.; Shi, D.-F.; Schultz, R. J.; Paull, K. D.; Stevens, M. F. G. *Br. J. Cancer* **1998**, *77*, 745–752. (c) Molinski, T. F. *Chem. Rev.* **1993**, *93*, 1825–1838. (d) Gunawardana, G. P.; Kohmoto, S.; Gunasekara, S. P.; McConnel, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *110*, 4856–4858. (e) Gunawardana, G. P.; Kohmoto, S.; Burres, N. S. *Tetrahedron Lett.* **1989**, *30*, 4359–4362.
2. (a) Lamazzi, C.; Chabane, H.; Thiéry, V.; Pierre, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Besson, T. *J. Enz. Inhib. Med. Chem.* **2002**, *17*, 397–401. (b) Frère, S.; Thiéry, V.; Bailly, C.; Besson, T. *Tetrahedron* **2003**, *59*, 773–779. (c) Chabane, H.; Pierre, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Thiéry, V.; Guillaumet, G.; Besson, T. *J. Enz. Inhib. Med. Chem.* **2004**, *19*, 567–575.
3. (a) Chabane, H.; Lamazzi, C.; Thiéry, V.; Guillaumet, G.; Besson, T. *Tetrahedron Lett.* **2002**, *43*, 2483–2486. (b) Chabane, H.; Lamazzi, C.; Thiéry, V.; Pierre, A.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Besson, T. *J. Enz. Inhib. Med. Chem.* **2003**, *18*, 167–174.
4. (a) Pousset, J.; Jossag, A.; Boch, B. *Phytochemistry* **1995**, *39*, 735–736. (b) Sharaf, M.; Schiff, P.; Tackie, A.; Phoebe, C.; Martin, G. *J. Heterocycl. Chem.* **1996**, *33*, 239–243.
5. (a) Helissey, P.; Giorgi-Renault, S.; Renault, J.; Cros, S. *Chem. Pharm. Bull.* **1989**, *37*, 675–689. (b) Molina, A.; Vaquero, J.-J.; Garcia-Navio, J.; Alvarez-Builla, J.; de Pasqual-Teresa, B.; Gago, F.; Rodrigo, M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587–5599. (c) Schmitt, P.; Nguyen, C. H.; Sun, J. S.; Grierson, D.; Bisagni, E.; Garestier, T.; Hélène, C. *Chem. Commun.* **2000**, 763–764. (d) Lamazzi, C.; Léonce, S.; Pfeiffer, B.; Renard, P.; Guillaumet, G.; Rees, C. W.; Besson, T. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2183–2185. (e) He, L.; Chang, H.-X.; Chou, T.-C.; Savaraj, N.; Cheng, C. C. *Eur. J. Med. Chem.* **2003**, *38*, 101–107. (f) Onyeibor, O.; Croft, S. L.; Dodson, H.; Feiz-Haddad, M.; Kendrick, H.; Millington, N.; Paparini, S.; Philipps, R.; Seville, S.; Shnyder, S.; Taramelli, D.; Wright, C. *J. Med. Chem.* **2005**, *48*, 2701–2709.
6. (a) Timari, G.; Sooos, T.; Hajos, G. *Synlett* **1997**, 1067–1068. (b) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40*, 1055–1091. (c) Hajos, G.; Riedl, Z.; Timari, G.; Matyus, P.; Maes, B.; Lemière, G. *Molecules* **2003**, *8*, 480–487. (d) Mouaddib, A.; Joseph, B.; Hasnaoui, A.; Mérour, J. Y. *Synthesis* **2000**, 549–556. (e) Hostyn, S.; Maes, B.; Pieters, L.; Lemière, G.; Matyus, P.; Hajos, G.; Dommisse, R. *Tetrahedron* **2005**, *61*, 1571–1577.
7. (a) Koo, J. *J. Org. Chem.* **1963**, *28*, 1134–1135. (b) Dhanabal, T.; Sangeetha, R.; Mohan, P. *Tetrahedron Lett.* **2005**, *46*, 4509–4510.

8. (a) Fresneda, P. M.; Molina, P.; Delgado, S. *Tetrahedron* **2001**, *57*, 6197–6202. (b) Molina, P.; Fresneda, P.; Delgado, S. *Synthesis* **1999**, 326–329. (c) Graebe, C.; Ullmann, F. *Justus Liebigs Ann. Chem.* **1896**, *291*, 16–24. (d) Molina, A.; Vaquero, J.; Garcia-Navio, J.; Alvarez-Builla, J. *Tetrahedron Lett.* **1993**, *34*, 2673–2676. (e) Hagan, D.; Chan, D.; Schwalbe, C.; Stevens, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 915–923. (f) Hutchinson, I.; Mc Carroll, A.; Heald, R.; Stevens, M. *Org. Biomol. Chem.* **2004**, 220–228.
9. (a) For a recent review see: Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250–6284. (b) Besson, T.; Brain, C. In *Heterocyclic Chemistry Using Microwave Assisted Approaches*; Tierney, J. P., Lidström, P., Eds.; Microwave Assisted Organic Synthesis; Blackwell: Oxford, 2005; Chapter 3, pp 44–74.
10. (a) Appel, R.; Janssen, H.; Siray, M.; Knoch, F. *Chem. Ber.* **1985**, *118*, 1632–1643. (b) Rees, C. W. *J. Heterocycl. Chem.* **1992**, *29*, 639–651. (c) Kim, K. *Sulfur Rep.* **1998**, *21*, 147–207.
11. (a) Katritzky, A.; Lan, X.; Yang, J.; Denisko, O. *Chem. Rev.* **1998**, *98*, 409–548. (b) Katritzky, A. *J. Heterocycl. Chem.* **1999**, *36*, 1501–1522.
12. Nietzki, R.; Prinz, N. *Chem. Ber.* **1893**, *26*, 2956–2960.
13. Skyler, D.; Heathcock, C. *J. Nat. Prod.* **2002**, *65*, 1573–1581.
14. (a) Commarmot, R.; Didenot, R.; Gardais, J. F. French Patent 84/03496, 1986; *Chem. Abstr.* **1986**, *105*, 17442. (b) Ferguson, J. D. *Mol. Diversity* **2003**, *7*, 281–286.

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron 62 (2006) 1904
Tetrahedron

Corrigendum

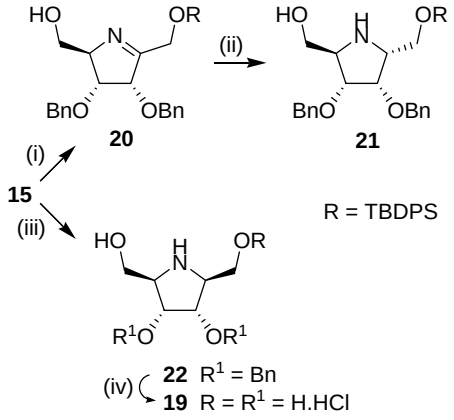
Corrigendum to "Polyhydroxylated pyrrolidines, III. Synthesis of new protected 2,5-dideoxy-2,5-iminohexitols from D-fructose" [Tetrahedron 61 (2005) 11697]

Isidoro Izquierdo,* María T. Plaza, Miguel Rodríguez, Francisco Franco and Alicia Martos

Department of Medicinal and Organic Chemistry, Faculty of Pharmacy, University of Granada, 18071 Granada, Spain

Available online 20 December 2005

A subsequent research on compounds **21** and **22** has revealed that there is an error in the structural assignment of both compounds in the manuscript and graphical abstract. Compound **21** is (2*R*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyloxy-2,5-bis(hydroxymethyl)pyrrolidine, whereas **22** is (2*S*,3*S*,4*R*,5*R*)-3,4-dibenzyloxy-2′-*O*-*tert*-butyldiphenylsilyloxy-2,5-bis(hydroxymethyl)pyrrolidine. Scheme 5 and Figure 3 should thus be changed to the following:



Scheme 5. Synthesis of partially protected polyhydroxylated pyrrolidines **21** and **22**. Reagents and conditions: (i) Ph_3P/THF, reflux; (ii) $NaCNBH_3$/THF/AcOH, 0°C; (iii) Raney-Ni/H_2/MeOH; (iv) (a) *n*-$Bu_4N^+F^-$ 3 H_2O/THF; (b) H_2/10% Pd–C/MeOH, HCl.

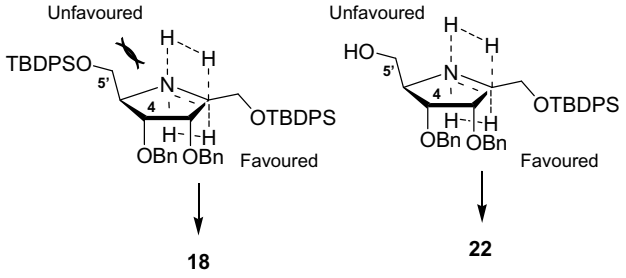


Figure 3. Transition states for catalytic hydrogenation of **14** and **15**.

The first paragraph in the left column on page 11700 should read as follows:

'Comments merit the high stereoselectivity found in the catalytic hydrogenation of **14** and **15** (see Fig. 3). Thus, our results were in accordance with those previously reported,[13] where the authors stated that the stereochemistry of five-membered ring system is controlled by that at C(4).'

Finally, in Experimental (page 11703) the whole paragraph: 4.2.14 (2*R*,3*R*,4*S*,5*R*)-3,4-dibenzyloxy-2,5-bis(hydroxymethyl)pyrrolidine (**23**), must not be considered.

DOI of original article: 10.1016/j.tet.2005.09.043
* Corresponding author. Tel.: +34 958 249583; fax: +34 958 243845; e-mail: isidoro@ugr.es

doi:10.1016/j.tet.2005.11.075