ELSEVIER

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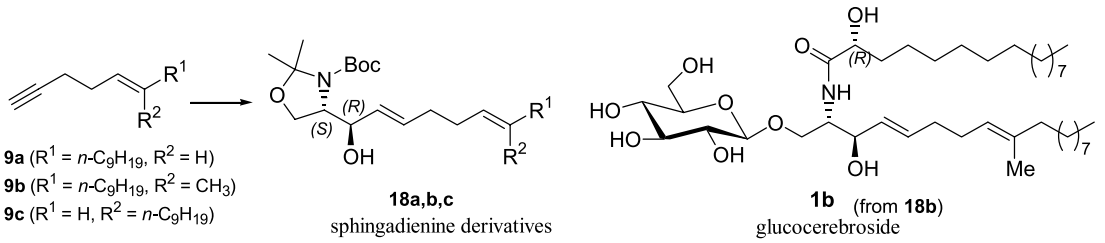
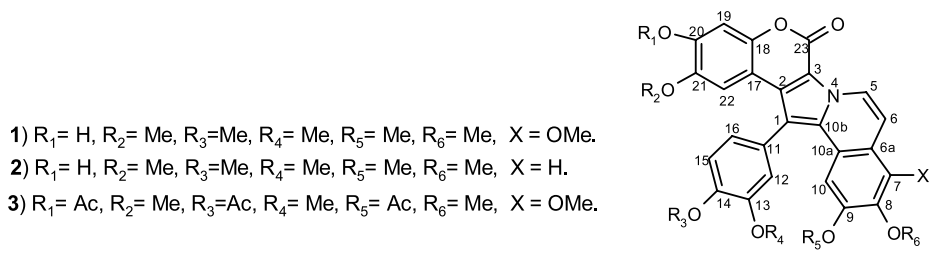
Contents

REPORT

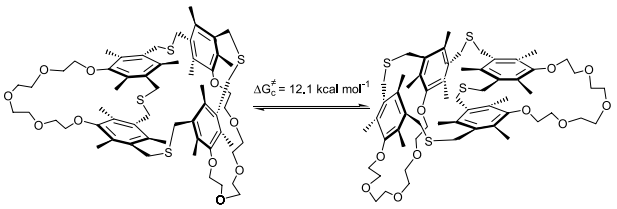
The methods for the synthesis of *cis*-decalins have been reviewed. The report contains ~250 references.

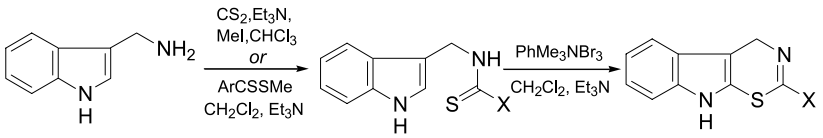
ARTICLES





Four new and several known lamellarin alkaloids have been isolated and characterized by the study of their spectral data. Cytotoxic activity against coloractal cancer cell lines has been evaluated.





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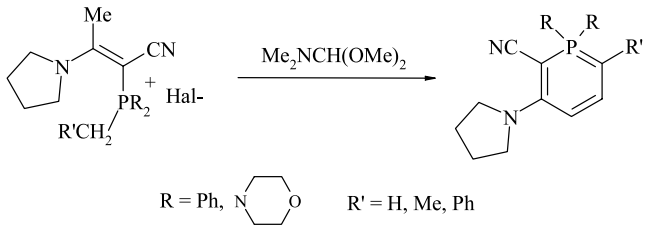
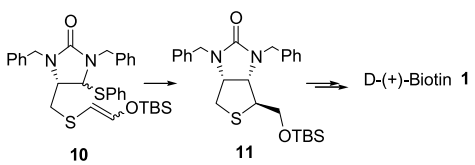
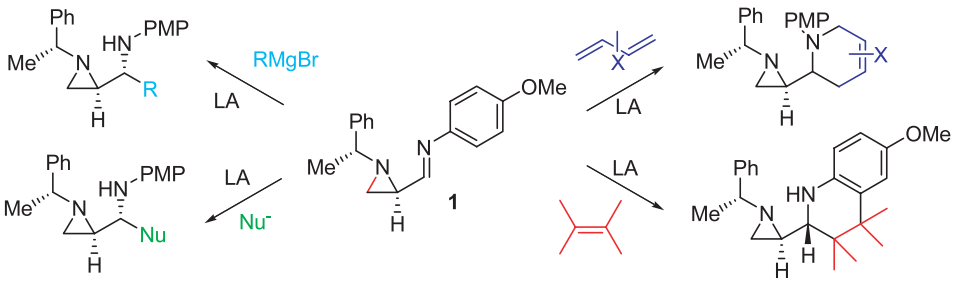
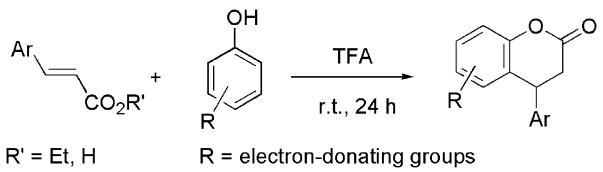
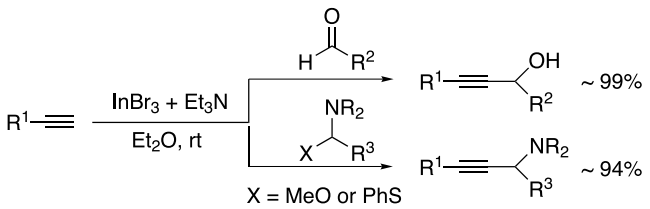
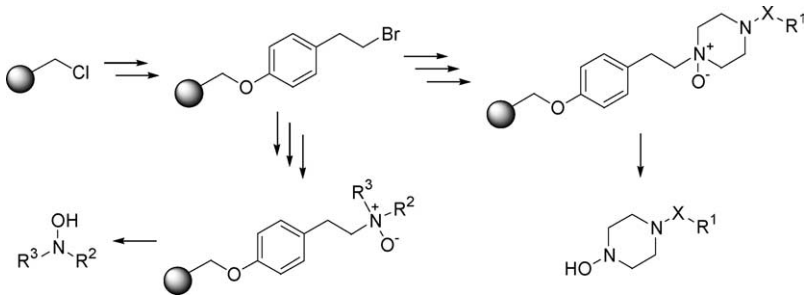


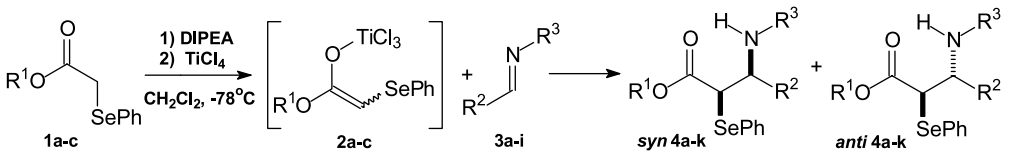


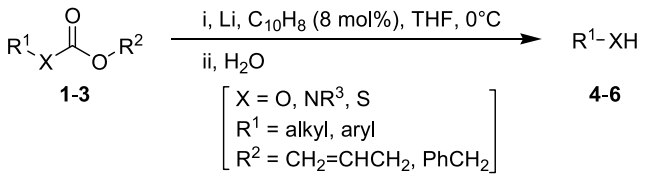


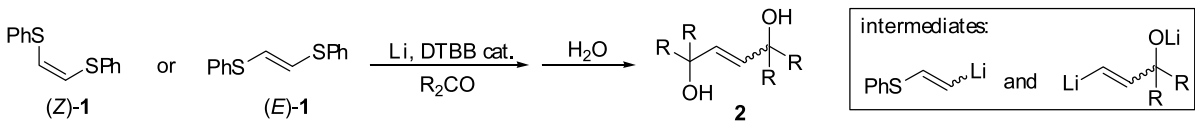


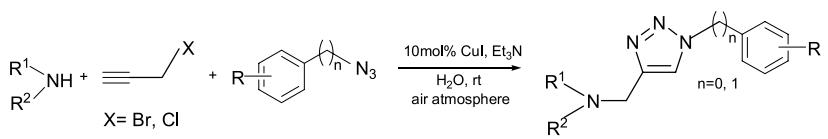


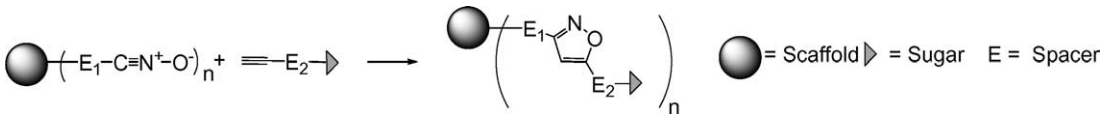


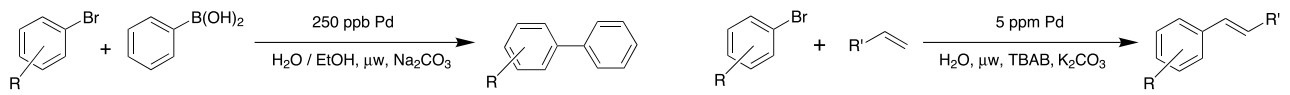


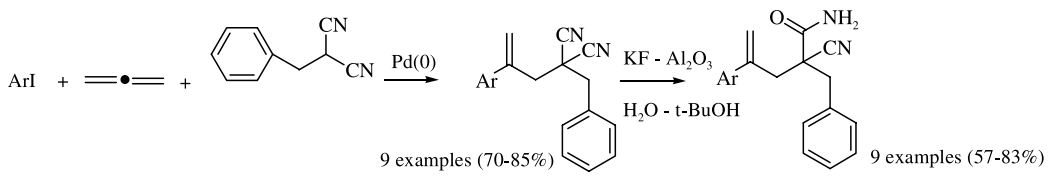


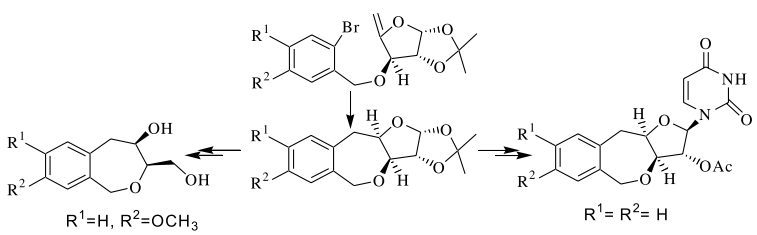


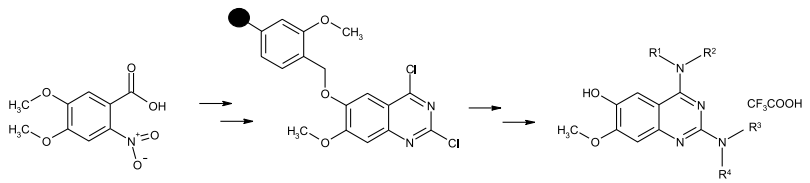




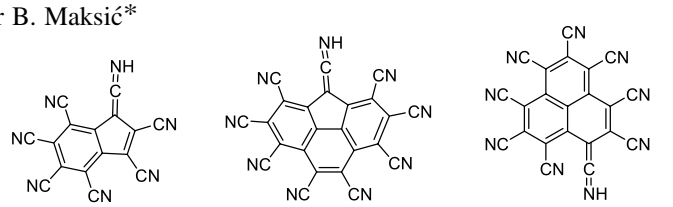








NR^1R^2 = primary or secondary aliphatic amines, NR^3R^4 = secondary aliphatic amines.

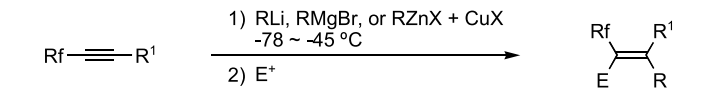


ΔH_{acid} = 262.5 kcal mol^{-1} pK_a(DMSO) = -16.5

ΔH_{acid} = 263.0 kcal mol^{-1} pK_a(DMSO) = -13.0

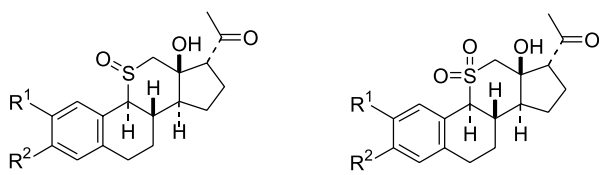
ΔH_{acid} = 254.6 kcal mol^{-1} pK_a(DMSO) = -17.9

Keteneimine tautomers of heptacyanoindene, nonacyanocyclopentaphenanthrene and nonacyano-1*H*-phenalene are powerful organic superacids in the gas-phase and DMSO as revealed by DFT calculations.



Rf = CF_3, CHF_2, etc.
R^1 = Aryl, Alkyl

Highly Regio- and Stereoselective



OTHER CONTENTS

*Corresponding author
ⓘ+ Supplementary data available via ScienceDirect

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Recent approaches towards synthesis of *cis*-decalins

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Contents

1. Introduction

The *cis*-decalin framework is present in the molecular structure of various classes of natural products such as *cis*-clerodanes,[1] kalihinenes,[2] thelepoganes,[3] cadinanes,[4] eremophilanes,[5] and valeranones.[6] While the terpenoids belonging to the cadinane, eremophilane, and valerane families were among the first to be isolated, agelasine A **1a**[7a,b] and its derivative **1b**,[7c] *cis*-clerodane diterpenoids, and nakamurol A **2**,[3] having a new framework belonging to thelepogane, and kalihinene X **3**[2c] (Fig. 1) were isolated recently from marine sponges. Many more natural products having *cis*-clerodane or related frameworks continue to be isolated.[7–9] Apart from the aforementioned types, natural products such as vinigrol **4**,[10a] macrolides as nodusmicin **5a** and deoxynodusmicin **5b**,[10b] and many others containing a *cis*-decalin framework were also isolated recently.[10c–e] In addition, a few steroids such as ouabain **6** also contain a *cis*-decalin ring system in their structure.

Many of these *cis*-decalin-based natural products exhibit wide-ranging and interesting biological activities, for example, agelasine A **1a** a *cis*-clerodane diterpene alkaloid isolated from the Okinawan marine sponge, *Agelus nakamurai*, exhibits antimicrobial activity and strongly inhibits the activity of the enzyme Na, K-ATPase.[7a] Kalihinene X **3**, which was isolated from a Japanese marine sponge, *Acanthella cavernosa*, is known to inhibit the attachment and metamorphosis of cyprid larvae of the barnacle, *Balanus amphitrite*.[2c]

Vinigrol **4**, isolated from a fungal strain, *Virgaria nigra*, was found to decrease arterial blood pressure in rats and inhibits platelet-activating factor and epinephrine-induced platelet aggregation. Similarly, nodusmicin **5a** is active against drug-resistant bacteria.

It is evident that many of these natural products have varying degrees of substitution patterns and four or more contiguous stereogenic centres on the decalin skeleton and, hence, pose a considerable synthetic challenge. The structural complexity of these natural products coupled with their interesting biological properties have led to significant interest in the development of new and efficient

Keywords: *cis*-Decalin; Diels–Alder; Cyclisation; 3,3-Sigmatropic shift.
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doi:10.1016/j.tet.2005.06.102

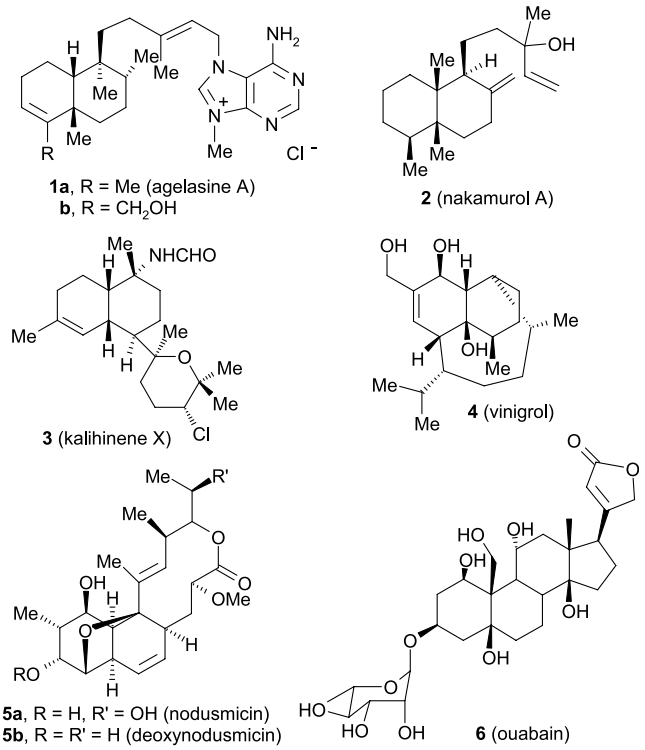


Figure 1.

methods for the synthesis of *cis*-decalins and the aforementioned natural products. While there is no exclusive review on the synthesis of *cis*-decalins, there are some earlier reports, which have partly dealt with this aspect.[11,12a] A review on various annulation routes to *trans*-decalins was published recently.[12b]

In this review, we wish to highlight the recent developments in the synthesis of *cis*-decalin. We have made an attempt to include the work in this area primarily after 1984 and up until 2004.

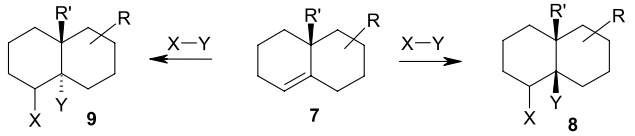
2. Synthetic routes to *cis*-decalins

Initially, efforts towards the synthesis of *cis*-decalin were made in context with the natural products having the cadinane, erimophilane, valerane and valeranone skeleta, as these were isolated earlier. The various approaches towards these classes of compounds have been reviewed comprehensively.[11] Of the various strategies for the synthesis of the *cis*-decalin framework, Robinson annulation is one of the earliest and has been used extensively, especially in most of the earlier syntheses. The second most popular strategy involves the Diels–Alder (both inter- and intra-) reaction for the construction of *cis*-decalins. Further, as work in this area intensified, more and more new strategies and methods were devised. Broadly, most of these strategies for the construction of the *cis*-decalin framework can be divided into four categories: (1) syntheses starting with Wieland–Miescher type ketones or decalenes, (2) cyclisation strategies, (3) Diels–Alder reactions, and (4) Cope rearrangements.

It may be mentioned that the first category, that is, syntheses starting with Wieland–Miescher type ketones (decalenes), can also be considered as a part of cyclisation strategies, as these diketones are generally made by Robinson annulation/Diels–Alder reactions or, sometimes, even by a Cope rearrangement in bicyclo[2.2.2]octenones. For the sake of convenience, however, the aforementioned distinction has been made.

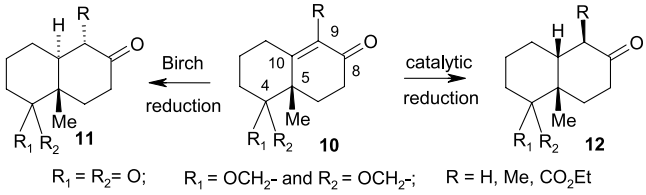
2.1. Synthesis of *cis*-decalins from Wieland–Miescher (WM) type ketones (decalenes)

In many of the syntheses, the key step in the formation of *cis*-decalins involves the saturation of the double bond at the ring junction in the decalenes such as **7** (Scheme 1). Alternatively, these decalenes can also be converted into the *trans*-decalins **9** using different reagents/conditions. In most cases, these decalenes are synthesised employing Robinson annulation or Diels–Alder reactions. Various methods for the synthesis of decalenes such as **7**, their transformation into the corresponding *cis*-decalins **8** (Scheme 1) and the application of this methodology towards the synthesis of *cis*-decalin based natural products are presented below.



Scheme 1.

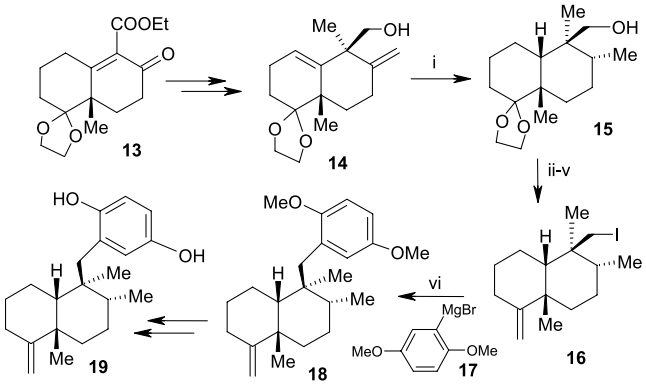
The ketones of type **10** have been widely used as starting materials for the synthesis of both *trans*- and *cis*-decalin frameworks. The Birch reduction of **10** gives the *trans*-decalin skeleton **11**, while the catalytic reduction, which occurs from the less hindered side gives the *cis*-decalin framework **12** (Scheme 2).[13] The stereoselectivity of both reactions is usually very good. This methodology is useful for the asymmetric synthesis, since the Wieland–Miescher ketones of type **10** may be prepared in an enantiomerically pure form.[14]



Scheme 2.

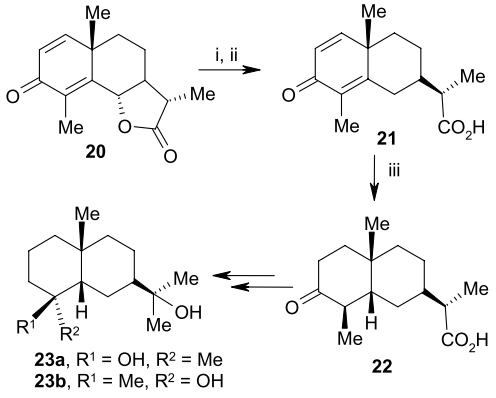
Wiemer and Scott examined the effect of C-9 substituents on the regio- and stereoselectivity of A-ring reactions in the WM type ketones and developed methods for the synthesis of *cis*-fused decalin systems.[15a,b] Further, they accomplished the synthesis of arenarol **19**, a marine natural product [8,15c,d] having a *cis*-decalin core (Scheme 3). Thus, the protected WM type ketone **13** was elaborated into the dienol **14** that, on hydrogenation over an iridium catalyst under high pressure, gave a single diastereomer **15**. The *cis*-decalin **15** was elaborated into neopentyl iodide **16**, which, on coupling with aryl Grignard reagent **17** in the presence of (dppf)$NiCl_2$ and $ZnCl_2$–dioxane, furnished **18**. The

compound **18** was then transformed into arenarol **19** (Scheme 3).[15b]



Scheme 3. Reagents and conditions: (i) H_2 (1000 psi), $[Ir(cod)(PCy)_3(py)]^+PF_6^-$, 97%; (ii) 2% aq HCl, THF, rt, 97%; (iii) $Zn(CH_2ZnBr)_2 \cdot THF$, $TiCl_4$, 74%; (iv) MsCl, Et_3N, 94%; (v) NaI, DMPU, 80 °C, 98%; (vi) **17**, (dppf)$NiCl_2$, 45%.

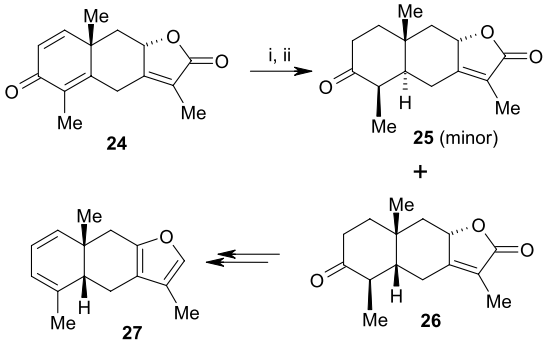
Ando and co-workers synthesised *cis*-decalin-based eudesmanes such as **23a**,**b** and suggested a revised structure of a natural eudesmane-4,11-diol isolated from a Pakistani medicinal plant, *Pluchea arguta Boiss*.[16a] The precursor **22** was prepared from α-santonin **20**, as shown in Scheme 4, following a methodology developed earlier.[16b] Santonin was first transformed into 6-episantonin, which, on reduction with Zn, gave the dienone carboxylic acid **21**. Catalytic hydrogenation of **21** gave the *cis*-decalin **22**,[16b] which was then elaborated to the eudesmanes **23a**,**b**.[16a]



Scheme 4. Reagents and conditions: (i) HCl (g), DMF, 47%; (ii) Zn, AcOH, MeOH, 85%; (iii) H_2, 5% Pd/C, KOH/EtOH, 53%.

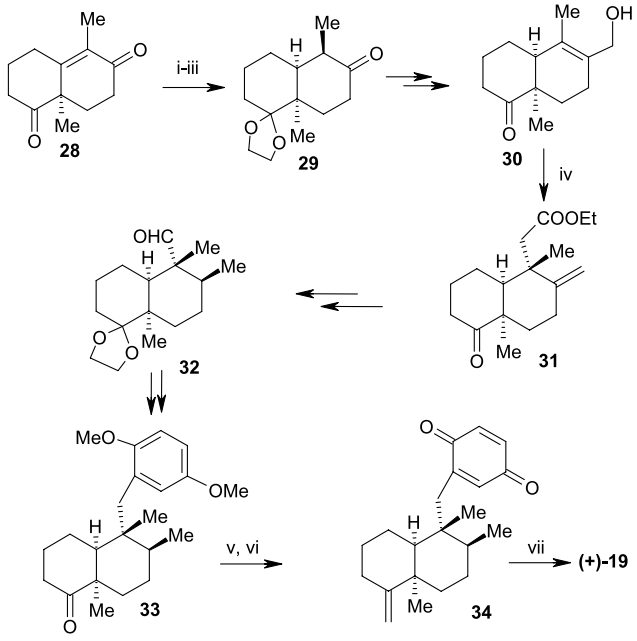
Pedro and co-workers[16c] synthesised the furanoeudesmane **27** isolated from *Tubipora musica*[16d] starting from santonin and also established the absolute configuration of the natural product (Scheme 5). Thus, the ketobutenolide **24**, readily available from santonin, on hydrogenation over 5% Pd/C followed by treatment with acid gave the *cis*-fused ketobutenolide **26** as the major product (75%), along with a minor amount of the *trans*-isomer **25** (5%). The *cis*-fused ketobutenolide **26** was then elaborated to the furanoeudesmane **27** (Scheme 5).

Terashima et al. synthesised (+)-arenarol in an enantioselective manner starting from the enantiomerically pure



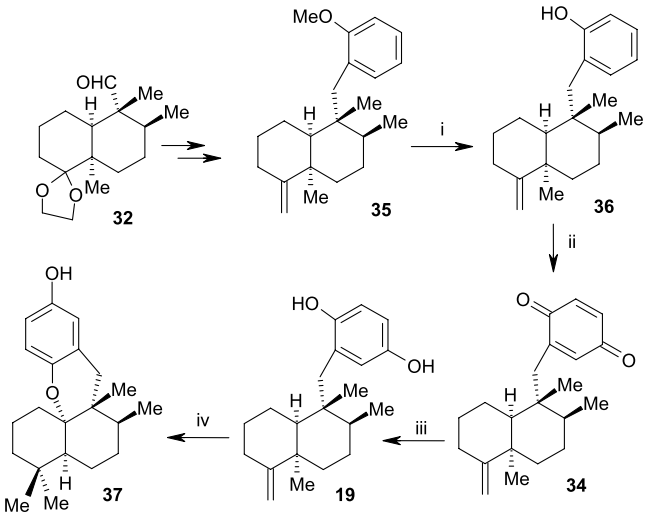
Scheme 5. Reagents and conditions: (i) H_2, Pd/C; (ii) *p*-TsOH, benzene, Δ, 75% for (i) and (ii).

(−)-ketone **28** (Scheme 6).[17a] Thus, ketalisation, and hydrogenation of **28** followed by base-catalysed epimerisation furnished the *cis*-decalin **29**. It was then elaborated to the alcohol **30**. The orthoester Claisen rearrangement in **30** gave a mixture of isomers in a ratio of 3:2 in 50% yield, from which the required isomer **31** was separated and converted into the key intermediate **32**. The aldehyde **32** was then elaborated into **33**, which was further transformed into (+)-arenarol **19** via the quinone **34** (Scheme 6).

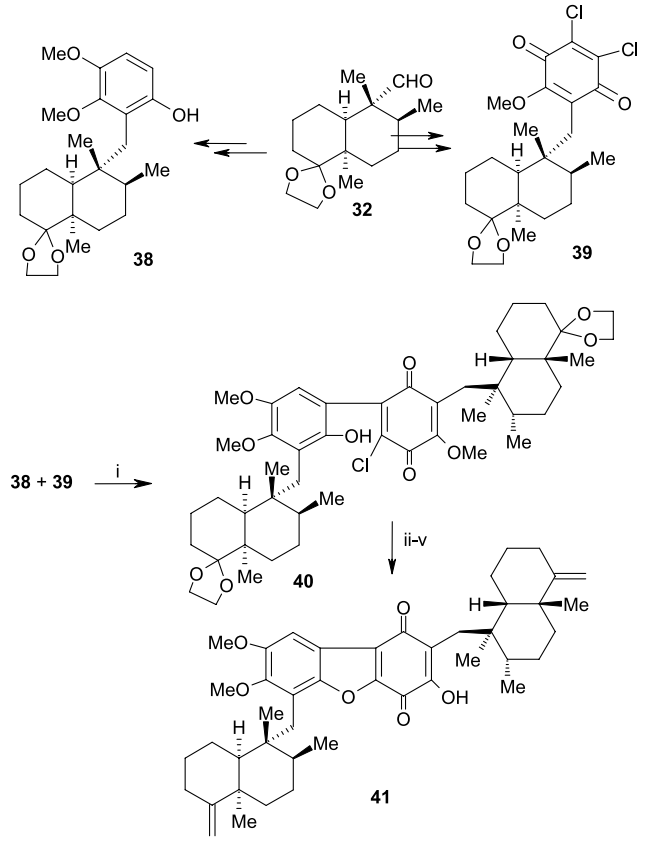


Scheme 6. Reagents and conditions: (i) ethylene glycol, *p*-TsOH, benzene, Δ, 89%; (ii) H_2, Pd–C, piperidine, rt; (iii) MeONa, MeOH, reflux, 77% for (ii) and (iii); (iv) $MeC(OEt)_3$, hydroquinone, 180 °C, 30%; (v) CH_2Br_2, Zn, $TiCl_4$, THF, 83%; (vi) $(NH_4)_2Ce(NO_3)_6$, MeCN–H_2O, rt, 33%; (vii) $Na_2S_2O_4$, THF–H_2O, rt, 75%.

Katoh and co-workers also employed the aforementioned method for the synthesis of (+)-aureol **37** (Scheme 7)[17b] and 8-*O*-methylpoplohuanone E **41** (Scheme 8)[17c] from the precursor **32**. The step involving the oxidative cleavage to deliver the corresponding quinone in the aforementioned sequence (Scheme 6), however, was not clean and the yield was poor. In order to circumvent this step, an alternate route was devised. Thus, the precursor **32** was converted via **35** into the phenolic compound **36**, which on oxidation



Scheme 7. Reagents and conditions: (i) *n*-BuSLi, HMPA, 100 °C, 84%; (ii) O_2, salcomine, DMF, rt, 91%; (iii) $Na_2S_2O_4$, THF–H_2O, rt, 76%; (iv) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −40 °C, 97%.

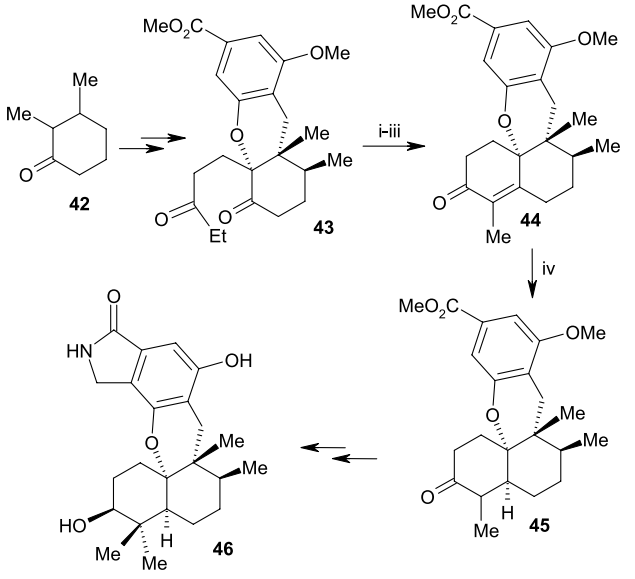


Scheme 8. Reagents and conditions: (i) **38**, NaH–THF, rt, **39**, −78 °C, 94%; (ii) Amberlite IRA-900 THF, rt 80%; (iii) 1 M HCl, MeOH, rt, 100%, (iv) CH_2Br_2, Zn, $TiCl_4$, THF, rt, 26%; (v) ^{n}BuSLi, HMPA, 110 °C, 34%.

furnished the quinone **34**. The quinone was reduced to give arenarol **19** that, upon $BF_3{\cdot}OEt_2$-promoted rearrangement, gave (+)-aureol **37**,[17b] a natural product originally isolated from the marine sponge, *Smenospongia aurea*.[17d]

Further, Katoh et al. enantioselectively synthesised 8-*O*-methylpopolohuanone E **41**, isolated from Pohnpeimarine sponge, *Dysidea* sp.,[8] in a highly convergent fashion utilising the earlier methodology (Scheme 7).[17c] Thus, the segments **38** and **39** were synthesised from the bicyclic compound **32**. Coupling of these segments gave **40**, which was then elaborated to 8-*O*-methylpopolohuanone E **41** (Scheme 8).

Mori and co-workers[18] reported the first total synthesis of the natural product, (±)-stachyflin **46**, isolated in their laboratories from a culture of *Stachybotrys* sp. RF-7260. Thus, 2,3-dimethylcyclohexanone **42** was elaborated into the diketone **43**, which on intramolecular aldol condensation gave the decalenone **44**. The decalenone **44**, on hydrogenation, gave the desired *cis*-decalin **45** as a major product along with some *trans*-isomer. The *cis*-isomer **45** was then elaborated into the natural product **46** (Scheme 9).

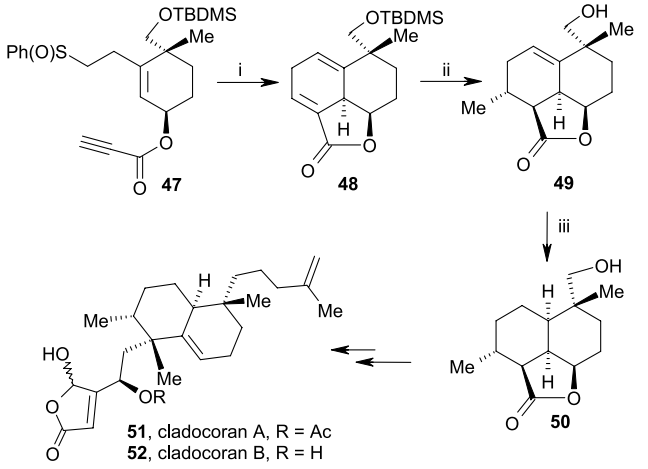


Scheme 9. Reagents and conditions: (i) NaOMe, MeOH, THF; (ii) $SOCl_2$, Py, CH_2Cl_2; (iii) NaOMe, MeOH, 75% for (i), (ii) and (iii); (iv) H_2, 5% Rh–C, Me_2CO, 52%.

Yamada and co-workers clarified and revised the structure of the sesquiterpenoids, cladocorans A **51** and B **52**, by an unambiguous synthesis (Scheme 10).[19a] Thus, the lactone **49** was prepared from the embellished cyclohexene **47** via **48** via sulphoxide elimination and intramolecular Diels–Alder reaction according to a methodology developed earlier in their group.[19b] Stereoselective hydrogenation of the lactone **49** in the presence of PtO_2 and acetic acid afforded the *cis*-decalin **50** as a sole product, which was then elaborated into the cladocorans **51** and **52** (Scheme 10).

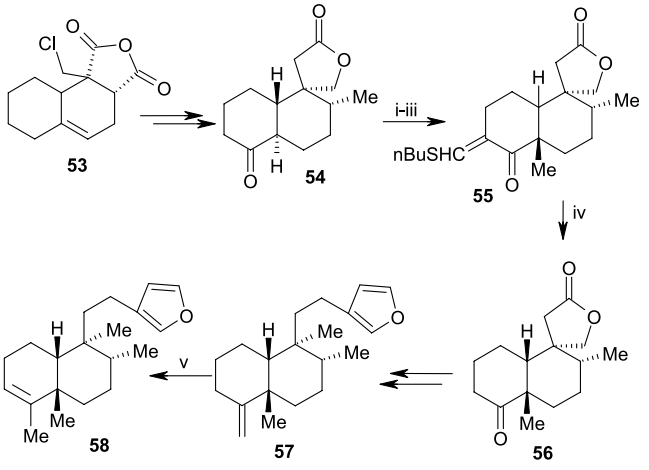
Though the stereoselectivities achieved during the hydrogenation of decalenes in the aforementioned and many other examples have been good, in some cases catalytic reduction is known to give a mixture of *cis*- and *trans*-isomers and the ratio depends on the substitution pattern.[20,21]

In context with the synthesis of a diterpene, portulal, and (±)-15,16 epoxy-*cis*-cleroda-3,13(16),14-triene **58**, Tokoroyama and his co-workers developed a route to *cis*-decalin **56** from the readily available precursor **53**, which was



Scheme 10. Reagents and conditions: (i) Py, ethylpropiolate, PhMe, reflux, 89%; (ii) Me_2CuLi, Et_2O, 91%; (iii) $^tBuNH_4F$, 100%; (iv) H_2, PtO_2, 89%.

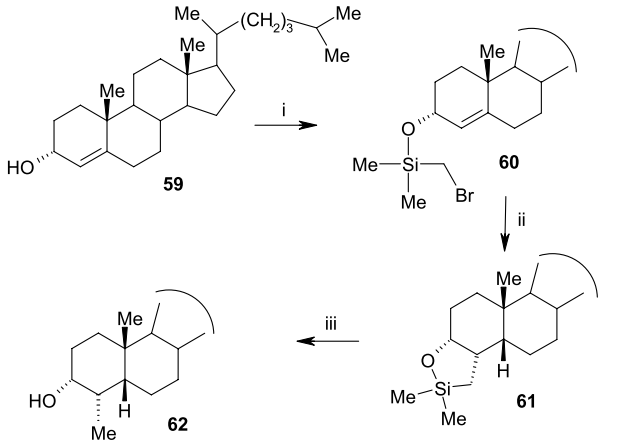
elaborated into the decalone **54**. Protection of α-methylene in **54** as a thioenol ether followed by alkylation with methyl iodide gave methylated derivative **55** containing a *cis*-decalin framework (Scheme 11).[22] Removal of the protecting group gave the dealone system **56**, which was elaborated into **57**. Isomerisation of the exocyclic double bond in **57** furnished the natural product **58** (Scheme 11).



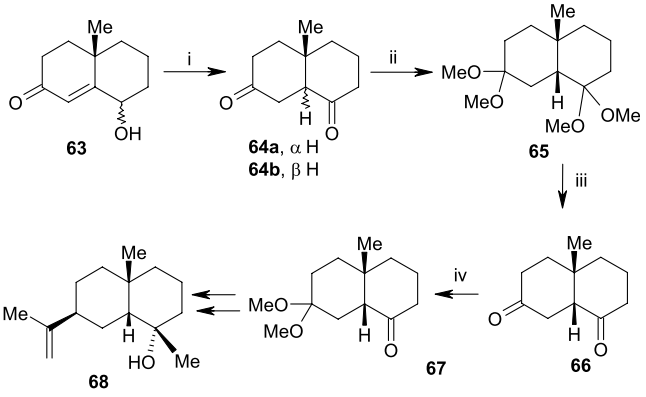
Scheme 11. Reagents and conditions: (i) HCO_2Et, NaH, PhH; (ii) ^nBuSH, TsOH, PhH, Δ; (iii) MeI, KO^{t}Bu, $^tC_5H_{11}OH$; (iv) H_2O, KOH, $HO(CH_2)_2$-OH, Δ; (v) $KNH(CH_2)_3NH_2$, $NH_2(CH_2)_3NH_2$.

Stork et al. developed an elegant method for the generation of cis and trans junctions via a radical cyclisation–desilylation process.[23] Thus, 4-cholesten-3α-ol **59** was first converted into the silyl bromide derivative **60**. Treating the silyl bromide derivative **60** with TBTH in the presence of AIBN produced the cyclic siloxane **61** as a result of radical cyclisation. This siloxane, on further treatment with potassium *t*-butoxide in DMSO, furnished the alcohol **62** with a *cis*-stereochemistry at the ring junction (Scheme 12).[23a] Similarly, the 4-cholesten-3β-ol gave the corresponding *trans*-stereochemistry at the ring junction.

Wijnberg, de Groot and co-workers developed an interesting methodology for the synthesis of *cis*-decalins like **66**, starting from a bicyclic 8-hydroxy enone **63** (Scheme 13).[24]



Scheme 12. Reagents and conditions: (i) $Me_2Si(CH_2Br)Cl$, Et_3N, DMAP; (ii) TBTH, AIBN; (iii) KO^{t}Bu, DMSO (80% overall).

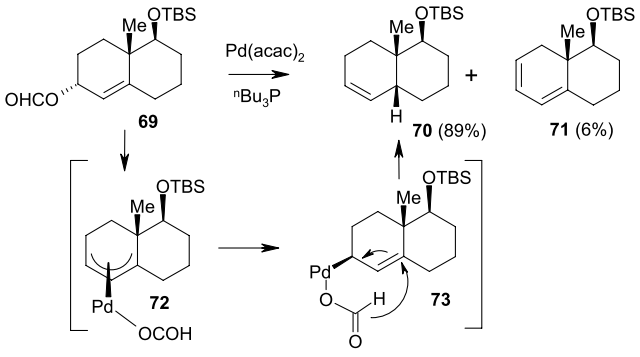


Scheme 13. Reagents and conditions: (i) HBr, Et_2O; (ii) $(MeO)_3CH$, H^+, MeOH, 70%; (iii) PPTS, H_2O, Me_2CO, quant.; (iv) $(MeO)_3CH$, PTSA, CH_2Cl_2, 96%.

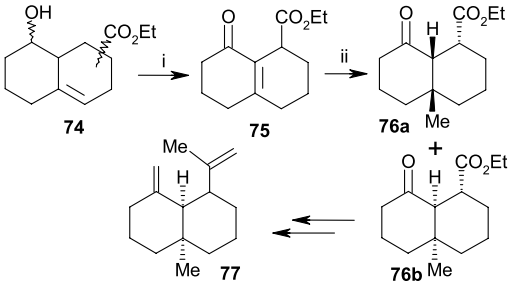
Thus, the acid-catalysed isomerisation of **63** using hydrogen bromide in ether furnished a 2:1 mixture of *trans*- and *cis*-fused diones **64a**,**b**. Treatment of this mixture with trimethyl orthoformate and acid gave exclusively the *cis*-fused diacetals **65**. Hydrolysis followed by treatment with trimethyl orthoformate in the presence of PTSA afforded the ketone **67** (Scheme 13).[24a] The keto-acetal **67** was then elaborated to amiteol **68**.[24c]

Tsuji and co-workers devised a novel stereocontrolled method for generating the cis-ring junction in decalin and steroid systems via a palladium-catalysed decarboxylation–hydrogenolysis of allylic formates.[25] Thus, treatment of the 3α-formate **69** with Pd(0) furnished the *cis*-fused decalin **70** as the major product, along with a minor amount of the diene **71** formed due to elimination (Scheme 14). The initial step involves the formation of a π-allyl complex such as **72**, which after transfer of hydride at the ring junction to **73** gives the *cis*-decalin **70** (Scheme 14). Similarly, the 3β-formates furnish the corresponding *trans*-decalins.

Battiste et al. have developed a route to *cis*-decalins from the decalene **74**, readily available via a Diels–Alder reaction of 3-vinylcyclohex-2-en-1-ol and ethyl acrylate (Scheme 15). Thus, oxidation of the regioisomeric mixture



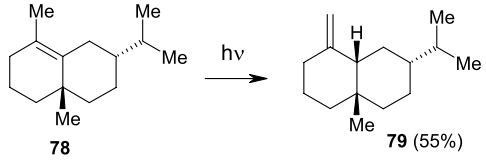
Scheme 14.



Scheme 15. Reagents and conditions: (i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −50 °C followed by 6 N HCl, 53%; (ii) Me_2CuLi, Et_2O 0 °C, 90%.

of the hydroxy-ester **74** gave the keto-ester **75** as a major product. Conjugate addition in **75** gave a diastereomeric mixture of **76a** and **76b**, from which the isomer **76b** was isolated and elaborated into 8,9-*epi*-β-gorgonene **77**.[26a]

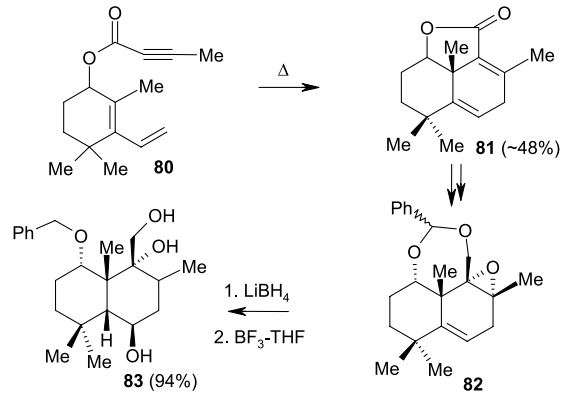
Towards the synthesis of valeranone, Bhide and co-workers employed photoisomerisation in octalin **78** to generate the compound **79** having a cis-ring junction (Scheme 16).[26b] The compound **79** was then converted into an intermediate for the synthesis of valeranone.



Scheme 16.

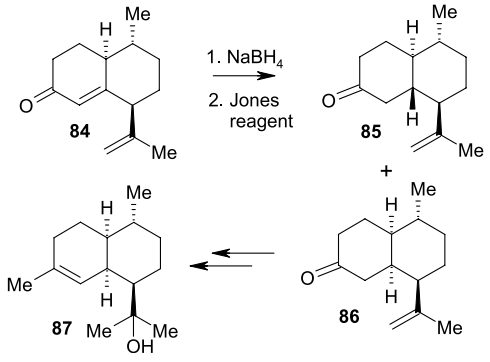
Lett and co-workers developed a route a highly functionalised *cis*-decalin **83** in context with a synthesis of forskolin.[27] The tricyclic compound **81**, prepared by an intramolecular Diels–Alder reaction in **80**, was elaborated into the epoxide **82**. Treatment of the epoxide **82** with $LiBH_4/BF_3$–THF furnished the *cis*-decalin **83** in a regio- and stereospecific manner (Scheme 17).[27]

Brown et al. have reported the first total synthesis of the amorphane sesquiterpene **87** and other related natural products from the commercially available, (−)-isopulegol.[28a] Thus, the bicyclic dienone **84** was synthesised from (−)-isopulegol via oxidation, Michael addition and aldol condensation. Reduction of **84** with sodium



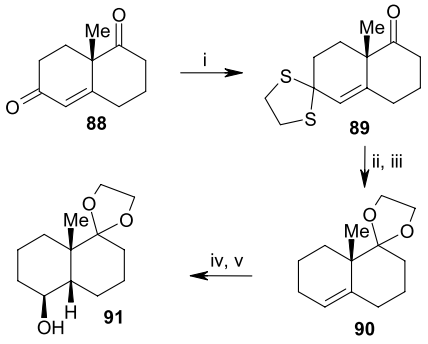
Scheme 17.

borohydride furnished a mixture of *trans*- and *cis*-decalins, which upon oxidation gave the corresponding ketones **85** and **86**. The *cis*-ketone **86** was then separated and elaborated into the amorphane sesquiterpene **87** (Scheme 18).



Scheme 18.

Vandewalle et al. developed an enantioselective synthesis of the alcohol **91** starting from the (+)-Wieland–Miescher ketone **88** (Scheme 19) in context with the synthesis of vitamin D_3.[28b] Thus, the thioacetalisation of the (+)-Wieland–Miescher ketone **88** gave **89**. Protection followed by desulphurisation gave the decalene **90**, which upon hydroboration–oxidation gave the *cis*-decalin **91**.

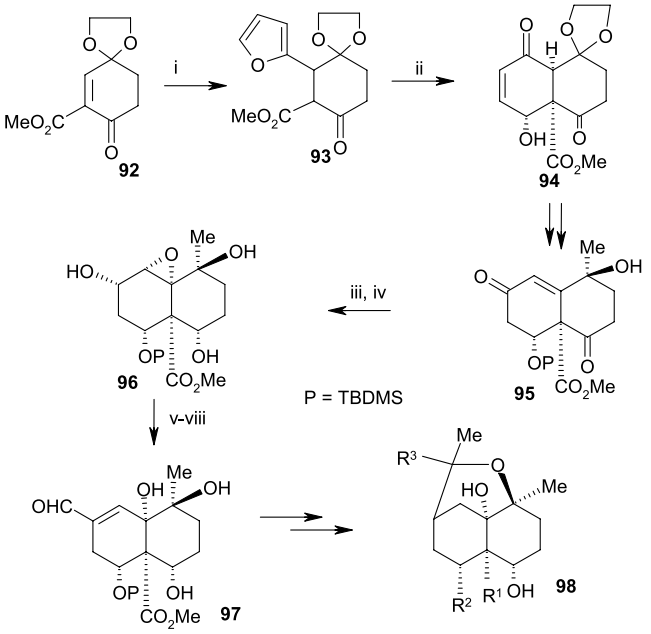


Scheme 19. Reagents and conditions: (i) $(CH_2SH)_2$, AcOH, PTSA, rt; (ii) $(CH_2OH)_2$, PTSA, PhMe, reflux; (iii) Na, liquid NH_3, THF, reflux, 78% for (i) (ii) and (iii); (iv), $BH_3 \cdot THF$, 0 °C to rt; (v) NaOH, H_2O_2, reflux, 88% for (iv) and (v).

As part of their studies towards the synthesis of the naturally occurring agarofurans, Ducrot and co-workers have

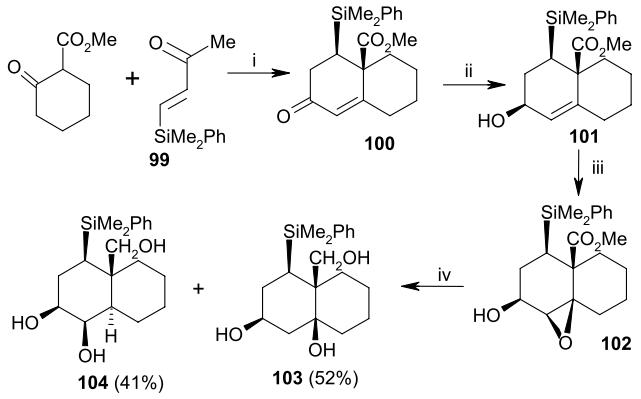
developed a novel synthetic route to *cis*-decalin ring systems and have also investigated a possible equilibrium between naturally occurring furano–agarofurans and their pyrano–agrofuran analogues through isomerisation of the decalinic ring junction.[29]

Their approach for the synthesis of the *cis*-decalin ring system is presented in Scheme 20. Thus, the keto-ester **92** upon treatment with furan in the presence of $BF_3 \cdot OEt_2$ furnished the furano-keto-ester **93**. The reaction of the furano-ketone **93** with dimethyl-dioxirane gave the highly functionalised *cis*-decalin **94** via ring opening of the furan ring and cyclisation (Scheme 20).[29a] The precursor **94** was then employed for the synthesis of polyhydroxylated pyrano–agarofurans.[29b] The precursor **95**, prepared from **94** in several steps, upon reduction followed by epoxidation furnished the hydroxy-epoxide **96**. This epoxide was then converted into the aldehyde **97** that was elaborated into polyhydroxylated pyrano–agarofurans of type **98** (Scheme 20).[29b] Further, the authors have also developed an asymmetric synthesis of the *cis*-decalins.[29c]



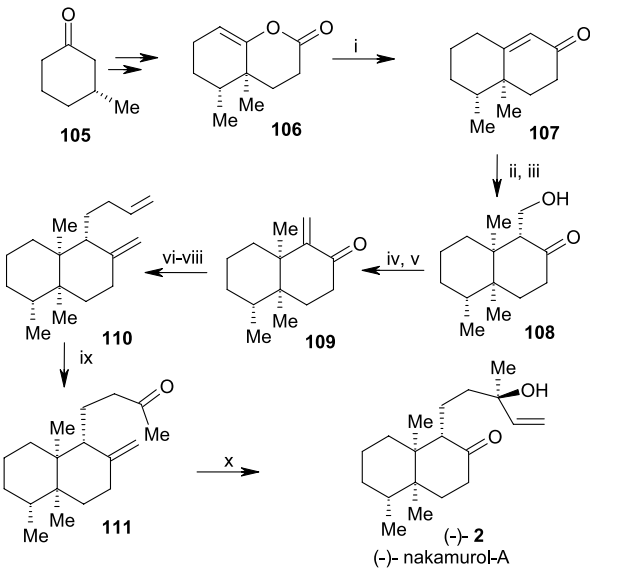
Scheme 20. Reagents and conditions: (i) furan, $BF_3 \cdot OEt_2$, CH_2Cl_2, −60 °C; (ii) dimethyl-dioxirane, Me_2CO, 2 h, then, $MgSO_4$; (iii) LAH, Et_2O, −10–0 °C; (iv) *m*CPBA, CH_2Cl_2, rt, 70%; (v) Tf_2O CH_2Cl_2, 2,6-di^{t}butyl-4-methyl pyridine CH_2Cl_2, −10 °C; (vi) $(Et)_4NCH$, CH_2Cl_2, rt, 74%; (vii) DIBAL-H, CH_2Cl_2, −10 °C; (viii) 5% aq H_2SO_4, rt, 67%.

Recently, Jung and his associates have synthesised several novel hydroxylated *cis*-decalin derivatives like **103** as potential intermediates for the synthesis of the AB ring system of the important cardiotonic steroid, ouabain (Scheme 21).[30] The first step in these highly functionalised intermediates is the Robinson annulation of carbomethoxy-cyclohexanone and the silyl-3-buten-2-one **99** to give the octalone **100** with good diastereoselectivity. Reduction to **101** followed by epoxidation to **102** and further reduction furnished the desired triol **103**, along with the regiomeric triol **104** (Scheme 21). Besides, studies pertaining to the selectivity of the ring opening and manipulation of these intermediates were also reported.



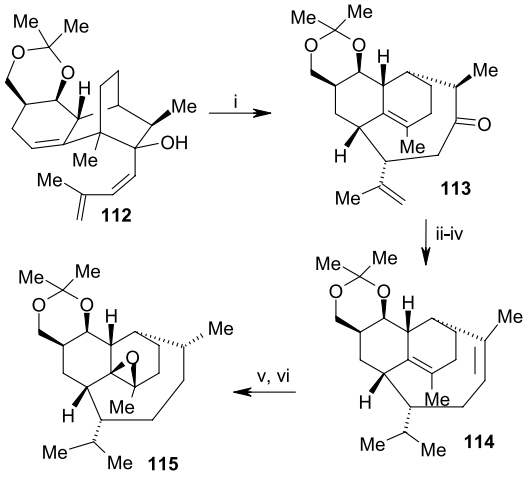
Scheme 21. Reagents and conditions: (i) Na, MeOH, 40%; (ii) $NaBH_4$, $CeCl_3$, 98%; (iii) *m*CPBA, 99%; (iv) $LiAlH_4$, 93%.

The first total synthesis of (±)-nakamurol-A **2** that also constituted the first synthetic entry into the epogane framework was reported by Bonjoch and co-workers.[31a] Recently, the author also reported the synthesis of (−)-nakamurol-A that allowed the absolute configuration of the (+)-nakamurol-A to be established (Scheme 22).[31b] Thus, the commercially available (*R*)-3-methylcyclohexanone **105** was converted into the enantiopure enol lactone **106** by a known procedure. Treatment of the lactone **106** with the lithium salt of dimethyl methylphosphonite gave the bicyclic enone (−)-**107**. Introduction of the methyl group by a conjugate addition using Me_2Zn–$Ni(acac)_2$ followed by trapping of the enolate by HCHO gave **108** as a single diastereomer in a highly stereoselective manner. The keto-alchohol **108** was then converted into the enone **109**, which upon conjugate addition of allyltrimethylsilane, followed by Wittig olefination, furnished the intermediate **110**. Wacker-type oxidation in **110** gave the ketone **111** that, on reaction with vinylmagnesium bromide, gave (−)-nakamurol-A (Scheme 22).[31b]



Scheme 22. Reagents and conditions: (i) $(MeO)_2POMe$, BuLi, 60%; (ii) $(Me)_2Zn$, $Ni(acac)_2$; (iii) HCHO, 50%; (iv) MsCl, $^i Pr_2EtNH$, CH_2Cl_2; (v) DBU, THF, 90%; (vi) $CH_2{=}CHCH_2SiMe_3$, $TiCl_4$, (vii) KF, EtOH, 92%; (viii) $Ph_3P{=}CH_2$, THF, 70%, (ix) $PdCl_2$, CuCl, O_2, DMF, H_2O, 63%; (x) $CH_2{=}CH_2MgBr$, THF, 47%.

Hanna and co-workers have reported an efficient entry into the carbocyclic skeleton of vinigrol, a diterpenoid natural product.[32] Thus, the annulated bicyclooctenol **112** was prepared in many steps from the commercially available 2,6-dimethylcyclohexanone. Oxy-anion Cope rearrangement in bicyclooctenol **112** gave the bridged decalene **113**, which was then elaborated into the diene **114**. Regio- and stereoselective epoxidation of the diene **114** followed by hydrogenation, led to the formation of the epoxide **115** having a *cis*-fused decalin moiety in addition to the other stereoisomer (Scheme 23).



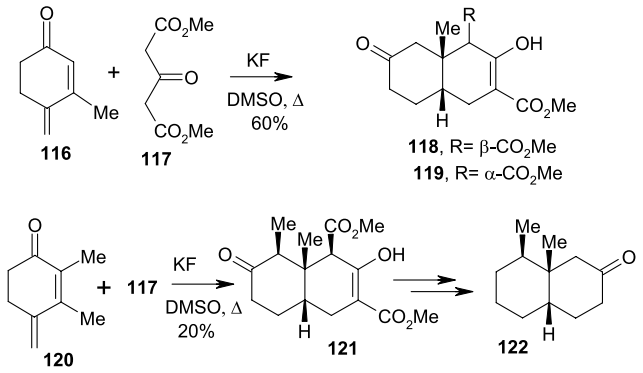
Scheme 23. Reagents and conditions: (i) NaH, THF, Δ, 72%; (ii) H_2, Rh–Al_2O_3, EtOAc, 3 h, 100%; (iii) $LiAlH_4$, THF; (iv) $POCl_3$, Py, 75.6% (both steps); (v) *m*CPBA, $NaHCO_3$, CH_2Cl_2, 95%; (vi) H_2, Rh–Al_2O_3, 94%.

2.2. Cyclisation methods

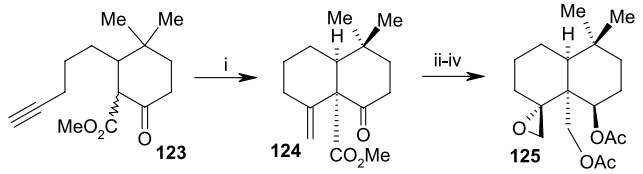
Among the various cyclisation strategies, Robinson annulation has been extensively used for the synthesis of the decalin ring systems. The Robinson annulation, however, has various problems associated with the efficiency, and the regio- and stereocontrol of both steps in the annulation. These, and other related, issues have been discussed in detail in the excellent reviews by Jung,[33a] and by Gawley.[33b] Recently, some new methods of cyclisation have been developed that are presented below.

Irie and co-workers reported a general and stereoselective synthesis of *cis*-decalins via a double Michael reaction of 3-methyl-4-methylenecyclohex-2-enone derivatives with dimethyl 3-oxoglutarate **117**.[34a,b] Thus, the treatment of cyclohexenone **116** and ketoglutarate **117** with potassium fluoride in DMSO furnished the *cis*-decalins **118** and **119** (Scheme 24). This method was employed for the synthesis of the dione **122** from **120** via **121**. The dione **122** is an important intermediate for the synthesis of a number of natural products.[34a]

Ley et al. synthesised the *cis*-fused decalin derivative **125** containing epoxydiacetate functions (a potential anti-feedant) by a stereospecific route, which is sufficiently flexible to prepare other similar analogues (Scheme 25).[35] The β-keto-ester **123**, prepared from 4,4-dimethylcyclohexenone, upon treatment with Lewis acid underwent cyclisation to give the *cis*-decalin **124**. Reduction of **124**



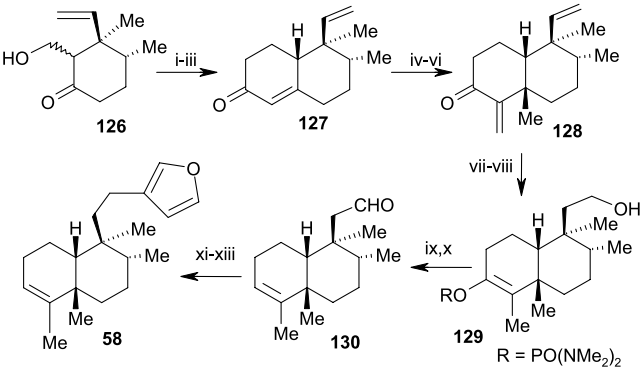
Scheme 24.



Scheme 25. Reagents and conditions: (i) $SnCl_4$–CH_2Cl_2 or ZnI_2-PhMe, Δ, 100%; (ii) $LiAlH_4$, THF, 89%; (iii) *m*CPBA, CH_2Cl_2; (iv) Ac_2O, Py, 4-Me_2NPy, 79% (for (iii) and (iv)).

with lithium aluminium hydride, followed by epoxidation and acetylation, provided **125** (Scheme 25).[35a]

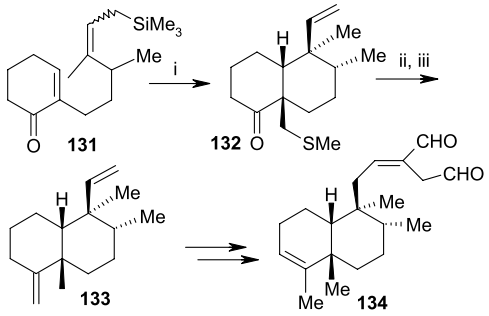
Tokoroyama et al. developed a method for the synthesis of octalone derivatives of the type **127**, which served as a key intermediate for the synthesis of both *cis*- and *trans*-clerodanes.[36a] Thus, the octalone **127** was prepared from the precursor **126** via mesylation, S_N^2 displacement with ethyl acetoacetate, decarboxylation and aldol condensation. Conjugate addition of a methyl group, followed by the trapping of enolate with formaldehyde and subsequent dehydration, gave the enone **128**. The enone **128** was then elaborated into the enol phosphate **129**. Reduction of **129**, followed by Swern oxidation, gave the aldehyde **130**, which was transformed into **58**, a natural *cis*-clerodane diterpene,



Scheme 26. Reagents and conditions: (i) MsCl, Et_3N, CH_2Cl_2, 93%; (ii) $MeCOCH_2CO_2Me$, NaOMe, MeOH, PhH, Δ; (iii) 2 M HCl, MeOH, Δ, ~80% (for (ii) and (iii)); (iv) Me_2CuLi, ether–pentane, −20 °C; HCHO, 46%; (v) MsCl, Et_3N, CH_2Cl_2; (vi) DBU, 80% (for (v) and (vi)); (vii) $LiB(CHMeEt)_3H$, THF, −78 °C, $(Me_2N)_2POCl$, HMPA (51%); (viii) thexylborane, H_2O_2, NaOH; (ix) Li, $EtNH_2$, ^tBuOH, 56% (for (vii)–(ix)); (x) DMSO, oxalyl chloride, CH_2Cl_2, Et_3N, 60%; (xi) 3-furyl-Li, Et_2O; (xii) Ac_2O, Py, 99% (for (xi), (xii)); (xiii) Li, liquid NH_3, −78 °C, 76%.

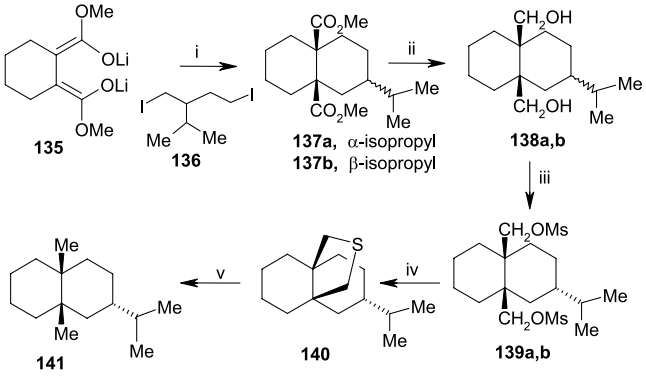
isolated from *Solidago arguta* (Scheme 26; see also Scheme 11).

Tokoroyama and his co-workers also developed a highly stereoselective ring-closure reaction leading directly to the *cis*-decalin framework via an intramolecular Hosomi–Sakurai reaction in an appropriately designed cyclohexenone of the type **131** (Scheme 27).[36b,c] Thus, the treatment of **131** in the presence of $TiCl_4$ and $ClCH_2SMe$ in dichloromethane afforded stereoselectively the *cis*-decalone **132**. The *cis*-decalone **132** upon reduction and olefination gave **133**, which was elaborated into linaridial **134**, a *cis*-clerodane- based natural product (Scheme 27).[36c]



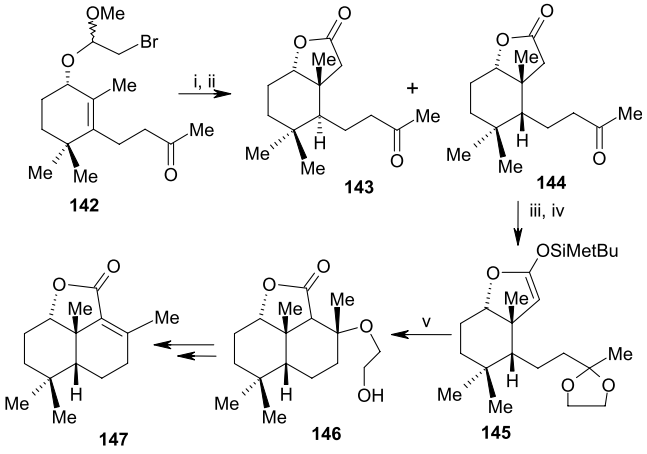
Scheme 27. Reagents and conditions: (i) $TiCl_4$, $ClCH_2SMe$, CH_2Cl_2; (ii) Raney Ni, EtOH; (iii) CH_2Br_2, Zn, $TiCl_4$, THF.

Garratt et al. reported a short synthesis of (±)-valerane starting from dilithium dimethyl 1,2-cyclohexanedioate **135** (Scheme 28).[37] Thus, the addition of **135** to the diiodide **136** gave a mixture of diesters **137a**,**b** containing the *cis*-decalin ring system. Reduction of this mixture gave the diol **138**, from which the desired isomer was separated and converted into the dimesylate **139**. Transformation of **139** into **140**, followed by desulphurisation, gave the (±)-valerane **141**.



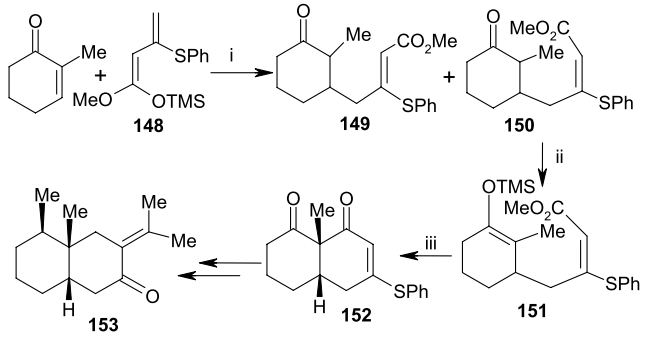
Scheme 28. Reagents and conditions: (i) THF, 47%; (ii) $LiAlH_4$, Et_2O, 85%; (iii) MsCl, Py, 83%; (iv) KSEt, PhH, 83%; (v) Raney Ni, EtOH, 78%.

During their work towards the synthesis of forskolin, Pattenden and co-workers developed a synthesis of *cis*-fused decalins related to the forskolin framework (forskolin has a *trans*-fused decalin core).[38] This methodology involves a stereoselective intramolecular radical-mediated cyclisation and an intramolecular Mukaiyama aldolisation as the key steps. Thus, the bromoacetal **142** derived from hydroxy β-ionone underwent a stereoselective 5-exo-trigonal radical cyclisation upon treatment with TBTH to give a mixture of the cyclic acetals, which, on hydrolysis and oxidation with Jones reagent, gave the readily separable bicyclic lactones **143** and **144**. The lactone **144** was then converted into the silyl ether **145**, which underwent a smooth intramolecular Mukaiyama cyclisation on treatment with titanium tetrachloride to furnish the *cis*-decalin **146** (Scheme 29) The lactone ether **146** was then elaborated to the enone **147** and other functionalised compounds.[38]



Scheme 29. Reagents and conditions: (i) TBTH, AIBN, 90%; (ii) Jones reagent, 73%; (iii) ethylene glycol, PTSA, PhH, 93%; (iv) LHDMS, TBDMSCI, 97%; (v) $TiCl_4$, CH_2Cl_2, 23%.

Chan and his co-workers developed a novel and general annelation reaction, based on a tandem Michael–Claisen condensation, wherein 3-(phenylthio)-1-(trimethylsiloxy)-1-methoxy-1,3-butadiene **148** undergoes Michael addition with α,β-unsaturated ketones in the presence of a Lewis acid. Most of the resulting Michael adducts undergo Claisen cyclisation in the presence of potassium *t*-butoxide or lithium thiophenoxide to form six-membered rings.[39] Thus, **148** underwent Michael addition with 2-methylcyclohexenone in the presence of $TiCl_4$–$Ti(O^iPr)_4$ to give the isomeric adducts **149** and **150**. The isomer **150** was then converted into its enol silyl ether **151**, which on reaction with potassium *t*-butoxide underwent cyclisation to give the *cis*-decalin **152** (Scheme 30).[39a] The *cis*-decalin **152** was then employed for the synthesis of (±)-fukinone **153**.[39b] Chan and co-workers have reported the synthesis of highly oxygenated decalins by using the same concept.[39c]



Scheme 30. Reagents and conditions: (i) $TiCl_4$–$Ti(O^iPr)_4$, CH_2Cl_2, 86%; (ii) HMDS, TMSI, 100%; (iii) KO^tBu, THF, DMF, 63%.

In an interesting series of investigations, Shibasaki and co-workers have explored the enantiotropic group selective ring closure in prochiral monocyclic compounds of the type **154** catalysed by palladium(II) acetate with a chiral ligand.[40] Thus, treatment of compounds of the type **154** with $Pd(OAc)_2$, (*R*)-BINAP (see Fig. 2 for structure) and K_2CO_3 gave the *cis*-decalins **155** with 92% ee (Scheme 31).[40b,c]

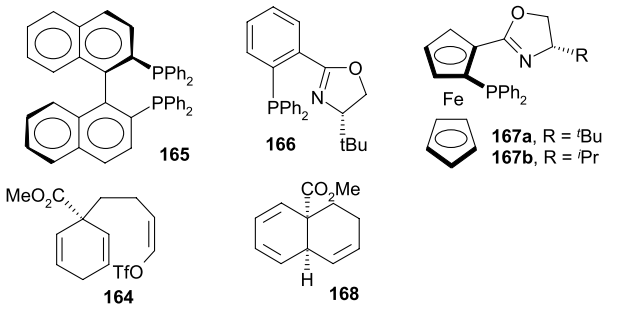
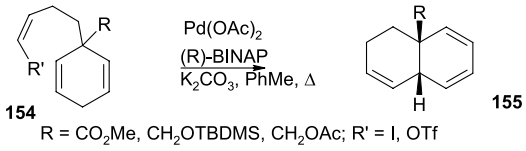
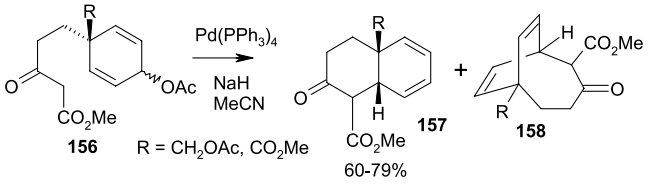


Figure 2.



Scheme 31.

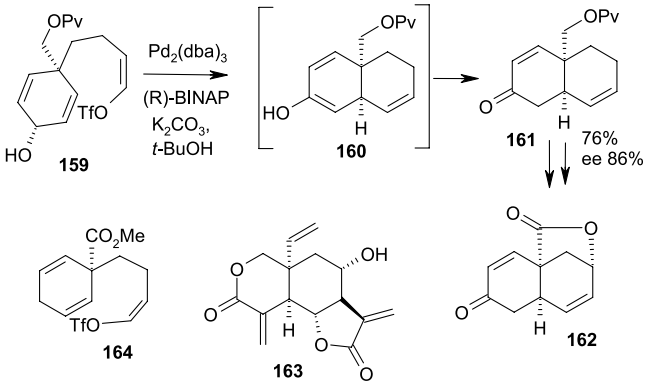
Shibasaki and co-workers also synthesised *cis*-decalins of the type **157** in high yield by treatment of compounds like **156** with $Pd(PPh_3)_4$ and NaH (Scheme 32).[41a] Further, a catalytic asymmetric synthesis of *cis*-decalin derivatives using $Pd(OAc)_2$, BuLi, (*R*)-(*S*)-BPPFA and NaH was also reported. In all cases, along with the *cis*-decalin **157**, some bridged bicyclic compounds of the type **158** were also formed (Scheme 32).[41b]



Scheme 32.

Further, Shibasaki and co-workers used the Heck cyclisation as a key step towards the aymmetric synthesis of the lactone **162**, an intermediate for vernolepin **163** (Scheme 33).[41c] Thus, the Heck cyclisation of the triflate **159** gave the enone **161** via **160** in 76% yield and 86% ee. This enone **161** was then elaborated into the lactone **162**, which has been elaborated into vernolepin. These workers also, devised an alternate catalytic asymmetric synthesis of the lactone **162** from the readily available vinyl triflate **164** and determined the absolute stereochemistry of vernolepin.[41d]

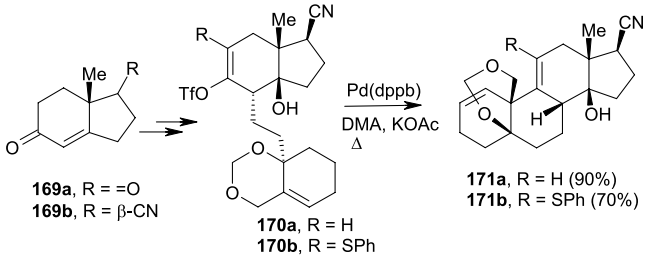
Recently, Guiry and Kiely screened BINAP **165** and a range of oxazoline-containing phosphinamine ligands like **166**, **167a**,**b** and **168** (Fig. 2) for a similar transformation on the ester **164** to the *cis*-decalin derivative **168** via palladium-catalysed asymmetric Heck cyclisation.[42]



Scheme 33.

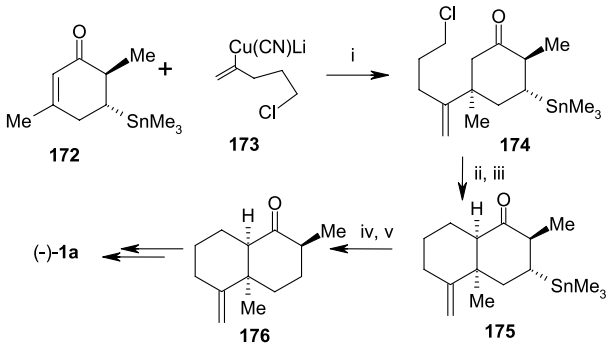
The diphenylphosphinoferrocenyloxazoline ligand **167a** afforded an optimal ee of 85% for the range of phosphinamine ligands tested. Variation of the solvent and base indicated that this system is sensitive to catalyst deactivation and that a combination of either toluene or *N*-methylpyrrolidine with K_2CO_3 as base was required for an acceptable catalytic activity. In addition, it was found that the catalysts prepared from palladium complexes of diphenylphosphinoaryloxazoline ligands were less reactive than the corresponding BINAP catalysts.

Overman and his co-workers developed a novel and enantioselective synthesis of complex steroid ring systems related to cardenolides having *cis*- A/B and C/D ring fusions using an intramolecular Heck reaction as a key step.[43a] Thus, the triflate **170a** was prepared from the ketone **169a**, which on Heck cyclisation furnished the steroid **171a**[43a] (Scheme 34). Further, a more concise synthesis of a related intermediate **171b** containing a thiophenyl functionality at C-11 was also synthesised starting from the ketone **169b** via Heck cyclisation of the triflate **170b** (Scheme 34).[43b]



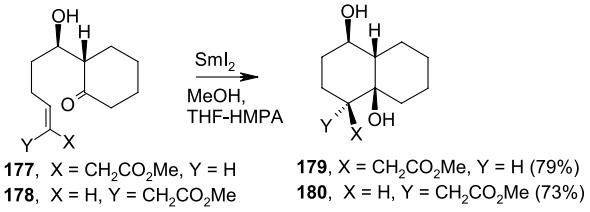
Scheme 34.

Piers et al. achieved the first total synthesis of (−)-agelasine A (−)-**1a** via the *cis*-decalone derivative **176** (Scheme 35).[44] Thus, the enone **172** was prepared from (*R*)-5-methylcyclohex-2-enone and converted into **174** by a stereoselective conjugate alkylation with **173**. Intramolecular alkylation in **174** gave the *cis*-decalin **175** that upon reductive removal of the stannyl moiety, followed by oxidation, gave the decalone **176** (Scheme 35).[44a] This decalone **176** was then employed for the synthesis of (−)-agelasine A (−)-**1a** and related *cis*-clerodanes.[44b]



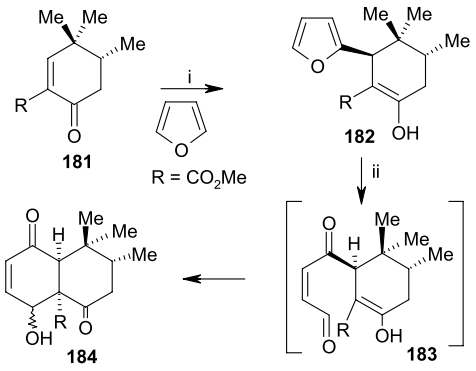
Scheme 35. Reagents and conditions: (i) TMSCI, $BF_3 \cdot OEt_2$; (ii) NaI, Me_2CO, 82% (both steps); (iii) LDA, THF, 93%; (iv) Li, NH_3, ^tBuOH, THF, 89%; (v) $Pr_4N^+RuO_4^-$, NMO, CH_2Cl_2, 96%.

An interesting stereoselective hydroxy group-directed cyclisation induced by samarium(II) iodide was reported by Matsuda, Shirahama and co-workers.[45a] The treatment of hydroxy-ketones **177** and **178** with samarium(II) iodide resulted in the formation of the *cis*-decalins **179** and **180**, respectively, as a result of the keto–olefin coupling (Scheme 36). The same authors also synthesised the *cis*-decalin ring system of vinigrol, a tricyclic diterpene, employing this methodology.[45b]



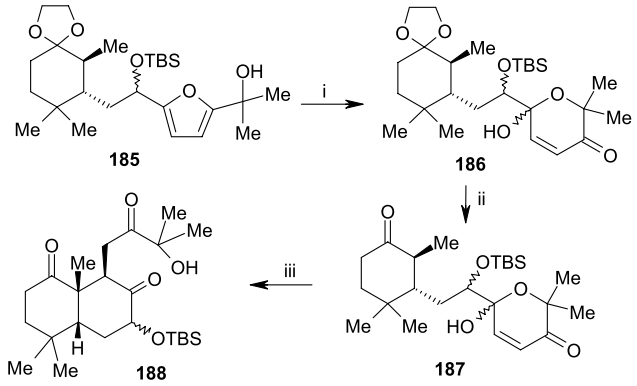
Scheme 36.

As part of their synthetic studies aimed towards the construction of the decalin moiety of ajugareptensin, Lallemand et al. have developed an interesting stereoselective route to highly functionalised *cis*- and *trans*-decalins, wherein the Lewis acid-mediated addition of furan to an unsaturated keto-ester and oxidative opening of the furan, followed by aldol condensation, are the key steps.[46] Thus, the Lewis acid-mediated addition of furan on the keto-ester **181** gave **182** as a single isomer (Scheme 37). Oxidative ring opening of **182** with *m*CPBA, followed by an intramolecular aldol condensation in the resulting intermediate **183**, furnished a mixture of the two diastereomeric *cis*-decalins **184** (Scheme 37).[46b]



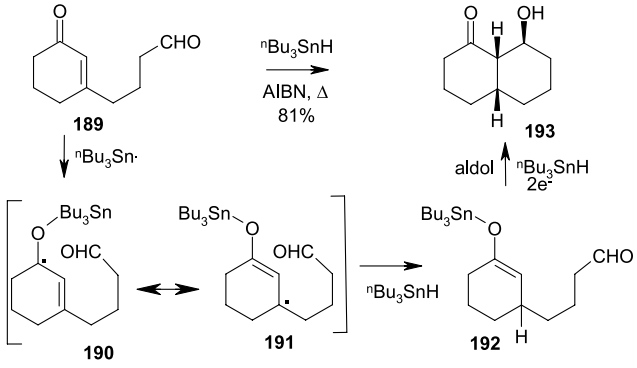
Scheme 37. Reagents and conditions: (i) $BF_3 \cdot OEt_2$, CH_2Cl_2, −30 °C, 78%, (ii) *m*CPBA, MeOH, 0 °C, 3 days, 100%.

With the aim of developing a route for the basic skeleton of polyoxygenated labdanes, Blechert et. al devised a route to the compound **188** containing a *cis*-decalin framework (Scheme 38).[47] Thus, the precursor **185** was prepared from 2,4,4-trimethyl-3-allylcyclohexanone and treated with *m*-chloroperbenzoic acid to give the rearranged product **186**, which, upon deketalisation, furnished the hydroxy-dihydropyranone derivative **187**. Intramolecular Michael addition in **187** gave the highly functionalised *cis*-decalin system **188** (Scheme 38).



Scheme 38. Reagents and conditions: (i) *m*CPBA, CH_2Cl_2, 0 °C to rt, 12 h, 92%; (ii) Py, TsOH, Me_2CO–H_2O, Δ, 98%; (iii) K_2CO_3, MeOH, rt, 12 h, 33–55%.

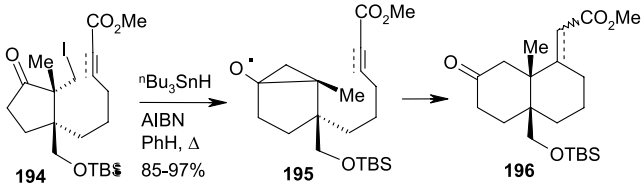
A conceptually interesting and new approach to *cis*-decalin involving the formation of *O*-stannylketyls, followed by aldol-type carbonyl addition promoted by tributyltin hydride, was developed by Enholm and co-workers.[48] The treatment of **189** with tributyltin hydride gave the *cis*-decalone **193** in good yield. The cyclisation proceeds via the radicals **190** and **191**. The radical **191**, upon abstraction of a hydrogen radical, gives the intermediate **192**. The intermediate **192** then undergoes an aldol-type condensation to give the final product **193** (Scheme 39).



Scheme 39.

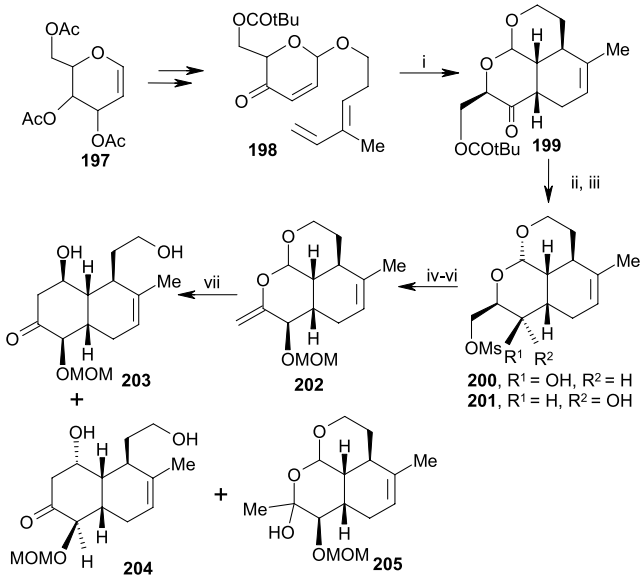
Nemoto and co-workers developed a novel stereocontrolled route to angularly disubstituted *cis*-decalins via a tandem radical ring expansion–cyclisation process.[49] Thus,

α-iodomethylcyclopentanones like **194** when treated with TBTH in the presence of AIBN underwent a tandem radical ring expansion and cyclisation via the cyclopropylalkoxy radical **195** to give the angularly disubstituted *cis*-decalin **196** (Scheme 40).



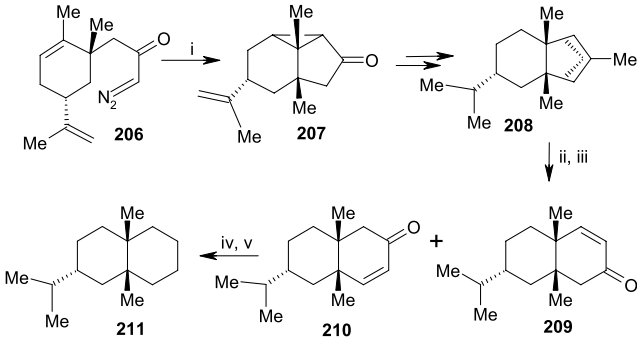
Scheme 40.

Chapleur and co-workers developed a new route to enantiomerically pure highly oxygenated *cis*-decalins, starting from carbohydrates, which involved intramolecular Diels–Alder reaction and Ferrier carbocyclisation reactions as the key steps.[50] Thus, the tri-*O*-acetyl-D-glucal **197** was converted into the enone-diene **198**, which underwent an intramolecular Diels–Alder reaction to give the adduct **199** as a single isomer. The reduction of the adduct **199**, followed by mesylation, gave the easily separable mesylates **200** and **201**. The mesylate **200** was then converted into the key intermediate **202**. Ferrier cyclisation of **202** under various conditions, however, gave a mixture of products **203**–**205**, having **205** as the major product. The compound **205** could be transformed into the *cis*-decalin **203** under basic conditions in a protic medium in 50% yield, thereby increasing the overall efficiency of this transformation (Scheme 41).



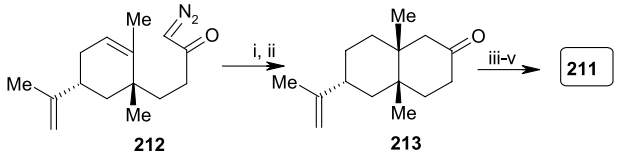
Scheme 41. Reagents and conditions: (i) PhMe, hydroquinone, 155 °C, sealed tube, 78% (from **197**); (ii) $LiAlH_4$, THF; (iii) MsCl, Py; (iv) NaI, butanone, Δ, 82%; (v) MOMCl, NEt^iPr_2, 62%; (vi) AgF, Py, 87%; (vii) $HgSO_4$, H_2SO_4, dioxane, 84%.

Srikrishna and co-workers reported two enantiospecific routes to (+)-valerane **211**, starting from (*R*)-carvone, using intamolecular diazoketone cyclopropanation as a key step.[51] Thus, in the first route,[51a] (*R*)-carvone was converted into the diazoketone **206**. Copper(II) sulfate-catalysed decomposition of this diazoketone led to an intramolecular insertion of the resultant ketocarbenoid into the olefin in a regio- and stereospecific manner, affording the cyclopropane-ketone **207**. This ketone **207** was further elaborated into the isomeric olefins **208**. Ozonolysis of the olefins, followed by reductive work up, furnished a mixture of keto-aldehydes, which, on intramolecular aldol condensation, furnished the regioisomeric enones **209** and **210**. These enones were then elaborated into (+)-valerane **211** (Scheme 42).



Scheme 42. Reagents and conditions: (i) $CuSO_4$, hν, 4 h, 57%; (ii) O_3, O_2, PPh_3; (iii) KOH, MeOH, THF, rt, 60% (both steps); (iv) $NaCNBH_3$, $BF_3{\cdot}OEt_2$, THF, reflux, 10 min, 89%; (v) H_2, Pd–C, 1 atm, 12 h, 80%.

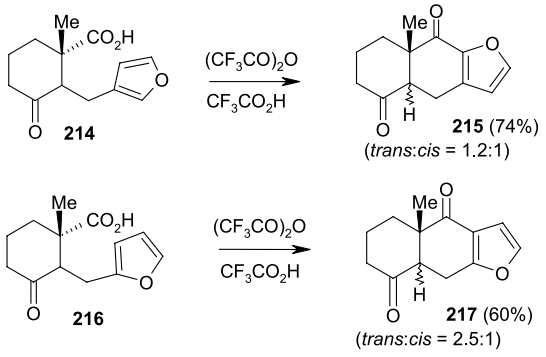
In order to avoid the formation of many regioisomers during the aforementioned synthesis, an alternative route was developed.[51b] Thus, (*R*)-carvone was converted into the diazo-ketone **212**, which, on intramolecular diazo-ketone cyclopropanation, followed by reductive cleavage of the cyclopropane ring, gave the ketone **213**, which was efficiently converted into (+)-valerane **211** (Scheme 43).[51b]



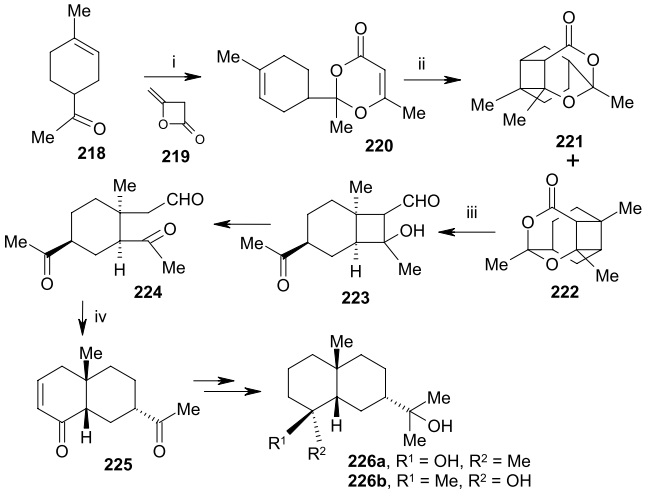
Scheme 43. Reagents and conditions: (i) Cu–$CuSO_4$, 51%; (ii) Li–liquid NH_3, 55%; (iii) H_2, 10%, Pt–C, 98%; (iv) $(CH_2SH)_2$, BF_3OEt_2, 95%; (v) Raney Ni, 82%.

As part of the in synthetic studies towards furosesquiterpenes, Ray et al. synthesised **215** and **217**, a linearly fused A/B *trans*- and A/B *cis*-furo[3,2-*b*]decalin derivatives (Scheme 44).[52a] Thus, the keto-acid **214**, derived from Hageman's ester, on intramolecular cyclisation gave **215** as a mixture of *cis*- and *trans*-isomers. Similarly, the keto-acid **216** gave **217**, a linearly fused A/B *trans*- and A/B *cis*-furo[2,3-*b*]decalin derivative (Scheme 44).

Hatsui and co-workers reported a stereoselective synthesis of *cis*-eudesmane-4,11-diols **226a**,**b** utilising an intramolecular photocycloaddition and an acid-catalysed cyclisation as the key steps (Scheme 45).[52b] Thus, the reaction of diketene **219** with the 4-acetylcyclohexene **218** gave the dioxin-4-one **220**. Photocycloaddition of **220** furnished a 1:1 mixture of the lactones **221** and **222**. Reduction of **222** gave a mixture of **223** and **224**, which, on



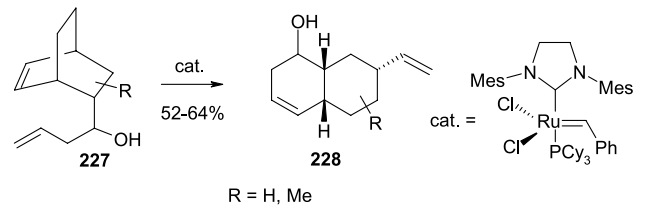
Scheme 44.



Scheme 45. Reagents and conditions: (i) dry PhH, TsOH, reflux, 70%; (ii) hν, Me_2CO–MeCN (9:1), 56%; (iii) DIBAL-H, PhMe, −78 °C; (iv) TsOH, Δ, 42% for (iii) and (iv).

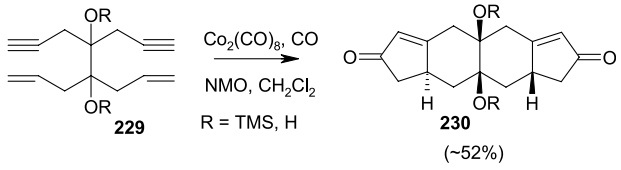
acid catalysed cyclisation, gave the *cis*-decalin **225** as the major isomer, along with two other isomers. The ene-dione **225** was then elaborated to the eudesmane-4,11-diols **226a**,**b**.

Recently, Phillips et al. reported a novel synthesis of decalins via a tandem ring-openingring-closing metathesis of bicyclo[2.2.2]octenes.[53] Thus, the bicyclo[2.2.2]octenols **227** with a four-carbon side chain, on treatment with a second-generation Grubbs catalyst, underwent a tandem ring-opening ring-closing metathesis to furnish the *cis*-decalins **228** in good yield (Scheme 46).



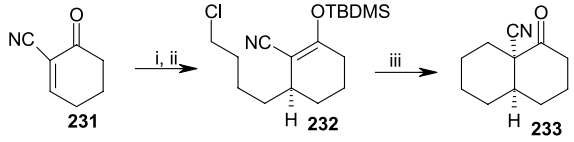
Scheme 46.

A unique entry into *cis*-fused decalins of the type **230** was achieved by Cook et al. by an intramolecular Pauson–Khand reaction.[54] Thus, a tandem Pauson–Khand reaction in the diene-diynes **229** mediated by dicobalt octacarbonyl resulted in the formation of [5.6.6.5]dicyclopenta[*b*,*g*]decalins with a *cis*-fused decalin core like **230** (Scheme 47).[54a] The highlight of this transformation is that it begins with an acyclic molecule in which six carbon–carbon bonds are formed in a one-pot process.

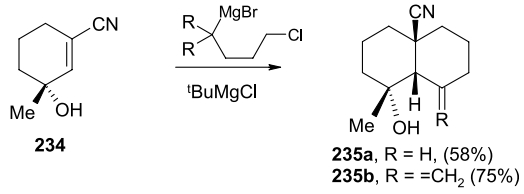


Scheme 47.

Fleming et al. have employed β-siloxy unsaturated nitriles as excellent common intermediates for the synthesis of both *cis*- and *trans*-decalins.[55a,b] Thus, the enone **231** was converted into the β-siloxy unsaturated nitrile **232** by treating with the Grignard reagent derived from 1-chloro 4-bromobutane, followed by the addition of TBDMSCl, which, upon reaction with *n*-Bu_4NF, gave the *cis*-decalin **233** (Scheme 48). They also reported the first anionic annulation with α,β-alkenenitriles, furnishing various *cis*-bicyclo[3.3.0]octane, hydrindane and decalin ring systems.[55c] Thus, ω-chloro Grignard reagents chelate with cyclic γ-hydroxy-α,β-alkenenitriles like **234** to trigger a conjugate addition–alkylation annulation to give the corresponding *cis*-fused decalin systems like **235a**,**b** in a single synthetic operation (Scheme 49).[55c]



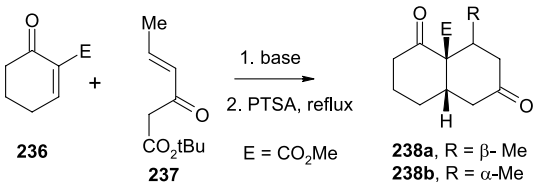
Scheme 48. Reagents and conditions: (i) $Cl(CH_2)_4MgBr$, THF; (ii) TBDMSCl, 66%; (iii) $^n Bu_4NF$, 90%.



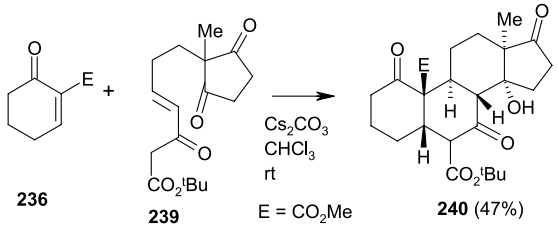
Scheme 49.

It may be mentioned that the aforementioned methodologies involving the nitrile anion cyclisations were not well known. Apart from offering a novel route to the decalin framework with defined stereochemistry, these methodologies have also shed light on the stereoelectronic features of both the enolate as well as the nitrile anion-mediated cyclisations.

Deslongchamps and co-workers have reported a base-catalysed cyclisation of the methyl-substituted Nazarov reagent **237** with 2-carbomethoxy-2-cyclohexenone **236**, followed by heating with *p*-toluenesulfonic acid, to give the



Scheme 50.



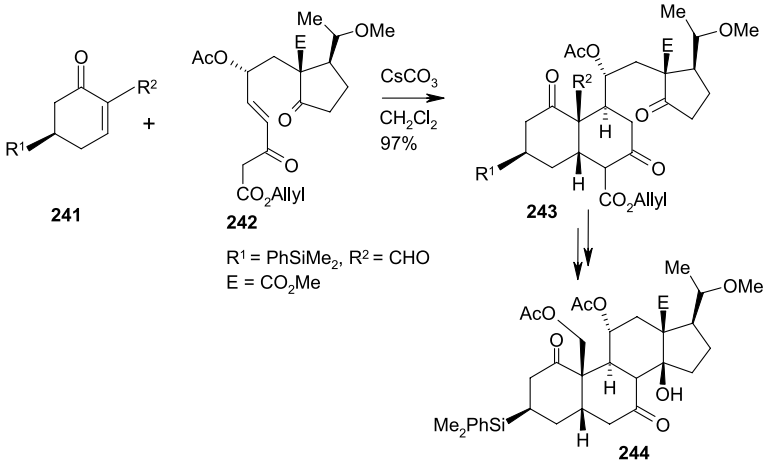
Scheme 51.

cis-decalins **238a**,**b** (Scheme 50).[56a] The product ratio was found to be highly dependent on the solvent. Reaction in polar solvents gave a mixture of both **238a**,**b**, whereas the use of a less polar solvent led to a very high selectivity in favour of the *cis–cis* isomer **238a**. Further studies by the authors showed evidence for the existence of a Diels–Alder mechanism in the less polar solvent, while, in the more polar solvent, the reaction was thought to take place via a sequential double Michael addition.

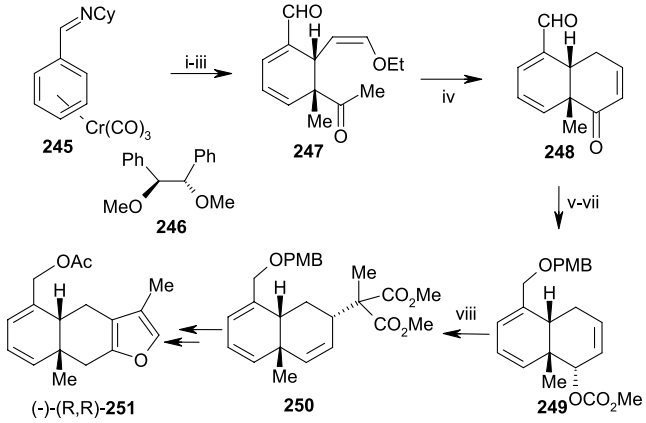
Towards an application of the above methodology, these authors have reported a one-step construction of a 13α-methyl-14α-hydroxy-steroid **240**, having six contiguous chiral centres (Scheme 51).[56b] Thus, the base-catalysed reaction of 2-carbomethoxy-2-cyclohexenone **236** with the substituted Nazarov reagent **239**, followed by heating with *p*-toluenesulphonic acid, furnished the steroid **240** in 47% yield (Scheme 51). Similarly, reaction with more complex Nazarov reagents also gave the corresponding tetracyclic compounds having new and interesting steroidal backbones.[56c]

As part of their studies directed towards the asymmetric synthesis of cardioactive steroids like batrachotoxin and ouabain, Deslongchamps et al. have further explored this anionic polycyclisation between various optically active cyclohexenones like **241** and Nazarov reagents such as **242**, which led to the precursor **243** that was transformed into a steroidal framework of type **244** with complete control of stereochemistry (Scheme 52).[56d]

Kundig and co-workers reported a novel asymmetric synthesis of both enantiomers of the marine furanosesquiterpenoid, acetoxytubipofuran **251**, that involves tricarbonylchromium-mediated dearomatisation as a key feature.[57a] Thus, the enantioselective nucleophilic addition of lithiated ethyl vinyl ether to the imine complex **245** in the presence of a chiral ligand **246**, followed by acylation/alkylation and imine hydrolysis, gave **247** in 76% ee. Hydrolysis of the enol ether moiety, followed by intramolecular aldol condensation, afforded the highly enantioenriched *cis*-decalin **248** (99% ee) upon recrystallisation. The enone **248** was then elaborated into the acetoxytubipofuran (−)-(*R*,*R*)-**251** via the intermediates **249** and **250** (Scheme 53). Similarly, the other enantiomer of acetoxytubipofuran was also synthesised.

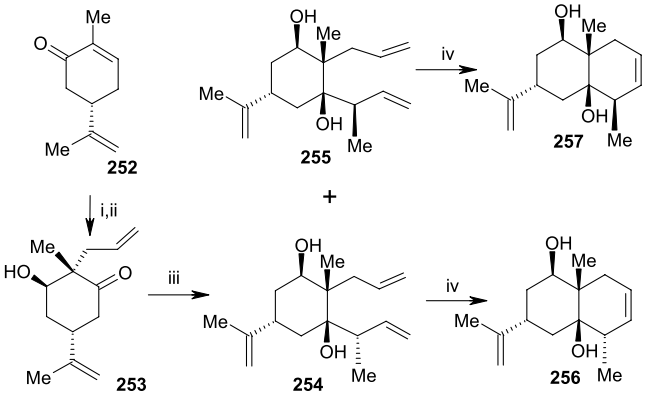


Scheme 52.



Scheme 53. Reagents and conditions: (i) LiCH=CHOEt, (*S*,*S*)-**246**, THF; (ii) MeI, CO, THF, HMPA; (iii) NaOEt, MeI, 42% (three steps); (iv) 2 N HCl, 89%; (v) $NaBH_4$, $CeCl_3$, MeOH, 98%; (vi) NaH, PMBI, DMF, 88%; (vii) $ClCO_2Me$, Py, CH_2Cl_2, 95%; (viii) $Pd(dppe)_2$, $CHMe(CO_2Me)_2$, NMP, NaH, 99%.

Mehta et al. developed a general and enantiospecific approach to polyfunctional eudesmane, eremophilane and agarofuran sesquiterpenoids from (−)-carvone, where the ring-closing metathesis was employed as a key step.[57b] Thus, carvone **252** was elaborated into the hydroxyketone **253**. Addition of the Grignard reagent derived from 3-chloro-1-butene in a stereoselective manner to **253** in the presence of Ce(III) furnished the isomeric addition products **254** and **255**. Ring-closing metathesis reactions in **254** and **255** provided the *cis*-decalins **256** and **257**, respectively, having a functionalised eudesmane framework (Scheme 54). The compounds **256** and **257** were further elaborated to polyfunctional eremophilane and agarofuran derivatives.



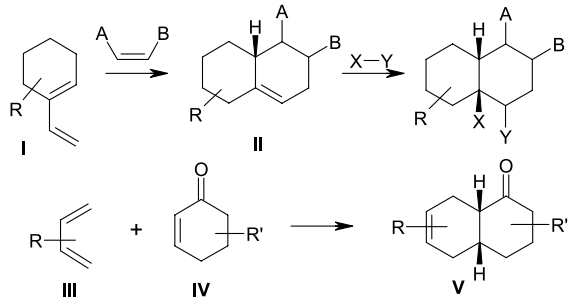
Scheme 54. Reagents and conditions: (i) H_2O_2, 6 N NaOH, MeOH, 0 °C, 92%; (ii) Li, liquid NH_3, CH_2=CH–CH_2Br, Et_2O, −78 °C, 60%; (iii) CH_2=CHCH(Me)MgCl, $CeCl_3$, THF, −78 °C, 95%; (iv) Grubbs cat., PhH, Δ, (95% for **257**; 89% for **256**).

Kozmin and Reddy disclosed an efficient and general approach to *cis*-decalins and have developed a synthesis of eremophilanes employing a siloxyalkyne–alkene metathesis reaction as the key step.[57c] Thus, the embellished cyclohexene **258**, prepared by a Diels–Alder reaction between 3-methyl methacrolein and 1-(benzyloxyethyl)-butadiene, was elaborated into the required precursor **261** via the esters **259** and **260**. A ring-closing metathesis in **261**, followed by removal of the silicon moiety, furnished the compound **262** having a *cis*-decalin framework and the necessary functional groups and substitutents. The ketone **262** was readily elaborated into α-eremophilane **263** (Scheme 55) and other congeners.[57c]

2.3. Diels–Alder cycloaddition

The Diels–Alder reaction is one of the most powerful methodologies in organic synthesis.[58] Inter- and intramolecular Diels–Alder reactions have been extensively employed for the synthesis of *cis*-decalin ring systems and both approaches are presented in the following sections.

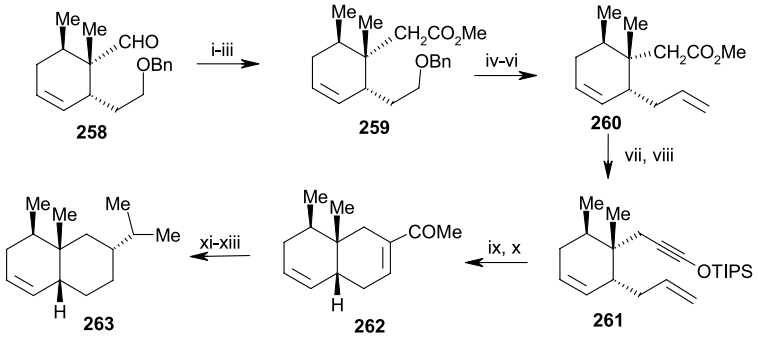
2.3.1. Intermolecular cycloaddition. The intermolecular Diels–Alder reaction has been applied extensively for the construction of *cis*-decalins. In general, two types of Diels–Alder reactions have been utilised for the construction of *cis*-decalins (Scheme 56).



Scheme 56.

In the first type, wherein 1-vinylcyclohexene derivatives such as **I** are used as the diene component, a decalene of type **II** having a double bond at the ring junction is generated, which has to be manipulated to give *cis*-decalins. Examples of this type have already been discussed in Section 2.1.

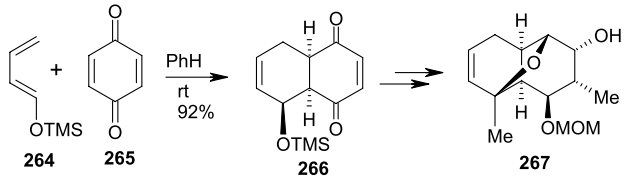
In the second type of Diels–Alder reaction, cyclic enones such as **IV** are used as the dienophile and its Diels–Alder reaction with a diene such as **III** furnishes the *cis*-decalin **V** directly. Most often, the products are formed in a regio- and stereospecific manner. Though there are many advantages in the Diels–Alder reaction of this type, there are certain limitations, too. For example, for the Diels–Alder reaction to occur, both the diene and dienophile have to be



Scheme 55. Reagents and conditions: (i) Ph_3P=CHOMe, THF, −78 °C; (ii) CrO_3, H_2SO_4; (iii) CH_2N_2, Et_2O, 74% (for three steps); (iv) H_2, Pd–C, EtOAc; (v) Swern oxidation; (vi) Ph_3PMeBr, ^{n}BuLi, Et_2O, 75% ((iv)–(vi)); (vii) CH_2Br_2, LiTMP, THF, −78 °C, (viii) LHMDS, ^{n}BuLi, TIPSOTf, −78 °C, 73% ((vii), (viii)); (ix) second gen. Grubbs cat., PhH, 50 °C; (x) HF, MeCN, 85% ((ix),(x)); (xi) H_2–Pd–C, EtOAc, 95%; (xii) Ph_3P=CH_2; (xiii) H_2, Pd–C, 95% (for (xii) and (xiii)).

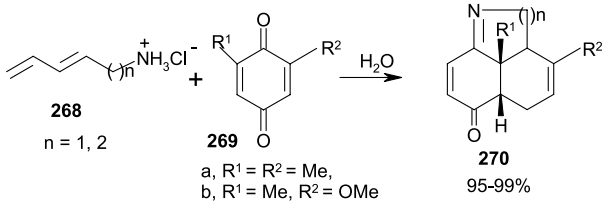
appropriately activated. Thus, though simple cyclohexenone reacts with most dienes readily, the corresponding α- or β-alkyl-substituted cyclohexenones are reluctant dienophiles. This problem is usually circumvented by placing an electron-withdrawing group like an ester at the α- or-β position.[59a,b] Another alternative in such cases is the use of a more reactive diene like the Danishefsky diene.[59c] In some cases, catalysis has also been known to increase the efficiency of the cycloaddition.[59d,e]

As part of his synthetic studies towards nargenicin macrolides, Kallmerten has reported the synthesis of the oxa-bridged octalin **267**.[60a] Thus, the Diels–Alder reaction of benzoquinone **265** with 1-trimethylsilyloxy-1,3-butadiene **264** efficiently furnished the compound **266**, which was then elaborated to the oxa-bridged octalin **267** (Scheme 57). Valderrama and his associates also reported the cycloaddition of silioxydiene **264** with various quinones to give the corresponding adducts in excellent yields.[60b,c]



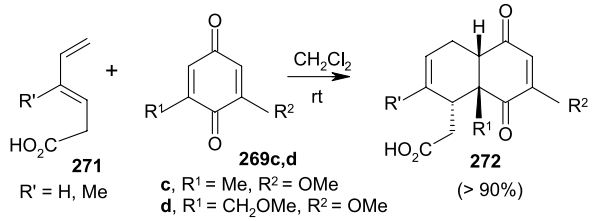
Scheme 57.

Grieco and co-workers reported a remarkably fast Diels–Alder reaction of dienyl ammonium salts of the type **268** with various dienophiles including various quinones **269a**,**b** in aqueous media that led to the adducts **270** in excellent yields (Scheme 58).[60d]



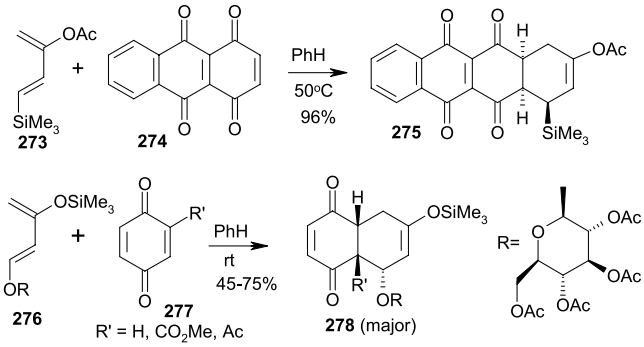
Scheme 58.

In context with the synthesis of the BCD ring system of quassinoids, Kloc and co-workers prepared the compound **272** by the cycloaddition of dienes of the type **271** with 2,6-disubstituted quinones **269c**,**d** (Scheme 59).[60e] The adduct **272** was then converted into its *trans*-isomer and employed further.



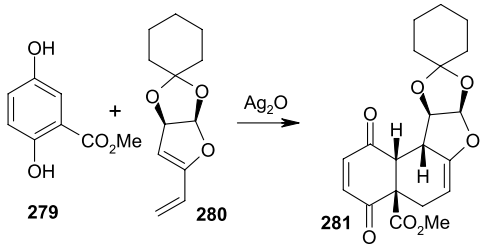
Scheme 59.

In context with the synthesis of anthracyclinones, Ley and his associates[61a] reported the cycloaddition of 3-acetoxy-1-trimethylsilylbutadiene **273** with the quinone **274**, which gave the adduct **275** in excellent yield. Stoodley and co-workers[61b] reported the cycloaddition of siloxydiene **276** containg a sugar moiety with benzoquinones of the type **277** to give adducts of the type **278** as the major product (Scheme 60). Cycloadditions of some other silyldienes with quinones and naphthoquinones have also been reported.[61c–e]



Scheme 60.

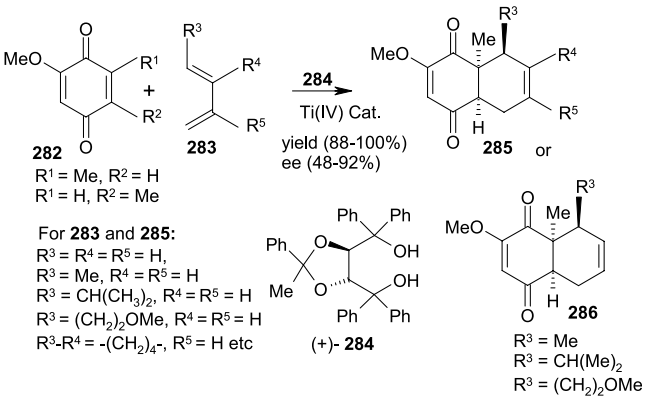
Bhakuni and co-workers synthesised the compound **281**, in order to develop a route to clerodanes.[62] Thus, the Diels–Alder reaction of the in situ-generated 2-methoxycarbonyl-*p*-quinone from the oxidation of **279** and the diene **280** gave the adduct **281** (Scheme 61) that was used further in synthesis.[62b] In context with synthesis of complex carbocyclic systems, cycloaddition of quinones with more complex dienes have also been reported.[62c,d]



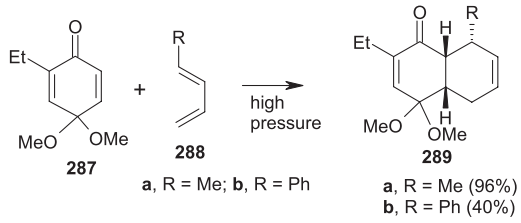
Scheme 61.

Engler and co-workers developed an asymmetric Diels–Alder reaction between quinones of type **282** with dienes such as **283** in the presence of a titanium catalyst derived from the diol **284**. The cycloaddition proceeded to give the adduct **285** and/or **286** in good yield with good enantiomeric excess (Scheme 62).[63a] Cycloaddition of vinylcyclohexene with quinones leading to an efficient route to tricyclic compounds having a functionalised decaline framework has also been reported.[63b,c]

Recently, a high-pressure Diels–Alder reaction of quinone monoketals such as **287** with acyclic dienes **288a**,**b** was reported to give the corresponding adducts **289a**,**b** having a functionalised decalin ring system in good yields (Scheme 63).[63d] Other quinone ketals and dienes also undergo efficient cycloaddition. Cycloadditions of iminoquinone ketals with 1,3-butadienes have also been recently reported.[63e]

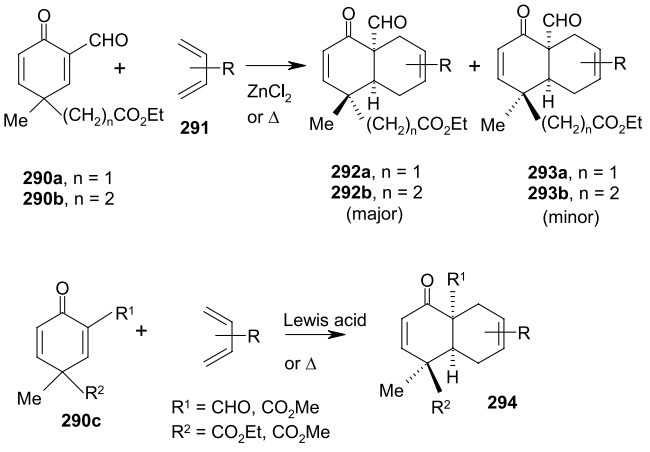


Scheme 62.



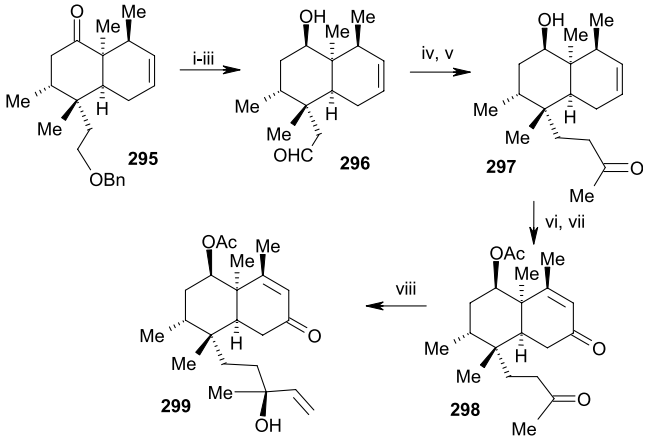
Scheme 63.

Liu et al. examined the facial selectivity in the Diels–Alder reaction of 4,4-disubstituted-2,5-cyclohexadienones **290a–c** with several dienes of the type **291**.[64a] It was observed that, in the case of the cyclohexadienones **290a**,**b**, the addition occurred preferentially from the C-4 methyl side, giving rise to **292a**,**b** as the predominant products, as expected on steric grounds, and **293a**,**b** as the minor products. In the case of cyclohexadienones of the type **290c**, however, a reversal of facial selectivity was observed, wherein the cycloaddition proceeded virtually exclusively from the C-4 ester face, giving rise to the adduct **294** (Scheme 64).



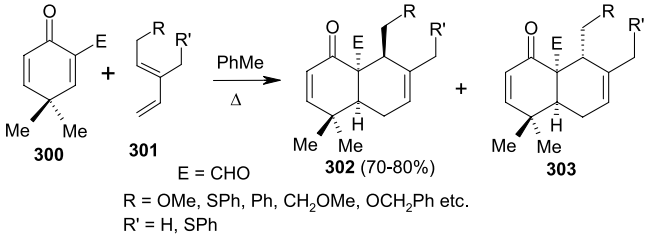
Scheme 64.

Further, Liu and co-workers developed a versatile approach towards *cis*-clerodanes[64b,c] and have also recently reported[64d] the synthesis of (±)-6β-acetoxy-2-oxo-kolavenool **299**, a natural product isolated from several Mexican *Stevia* sp.[64e] The ketone **295** was prepared according to their methodology[64b] and elaborated into the keto-alcohol **297** via the hydroxyaldehyde **296**. Acetylation of **297**, followed by oxidation with singlet oxygen, gave the enone **298** that, upon addition of vinylmagnesium bromide, furnished **299** as the major product (Scheme 65). The authors also reported an improved method for the synthesis of the intermediate **295**.[64f]



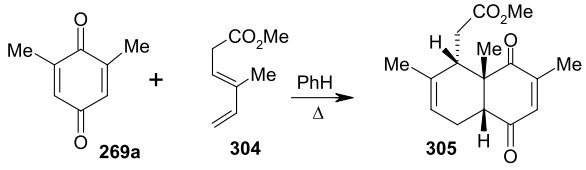
Scheme 65. Reagents and conditions: (i) $LiAlH_4$, THF, 0 °C, 1 h, 95%; (ii) Li-naphthalide, THF, −20 °C, 94%; (iii) $(Ph_3P)_3RuCl_2$, PhH, rt, 3 days, 90%; (iv) $Ph_3P{=}C(OMe)Me$, THF; (v) $HClO_4$, ether, 65%; (vi) Ac_2O, DMAP, CCl_4; (vii) O_2, Py, hν, TPP, rt, 56 h, 61%; (viii) $CH_2{=}CHMgBr$, THF, −20 °C, 40%.

In context with the synthesis of new analogues of bioactive terpenoids, Bhat and co-workers reported the intermolecular Diels–Alder reaction of cyclohexadienone **300** with acyclic dienes of the type **301**, which gave a mixture of *endo* and *exo* adducts **302** and **303** containing the *endo* adducts as the major products (Scheme 66).[65] These adducts were then employed for the synthesis of various drimane and labdane derivatives.



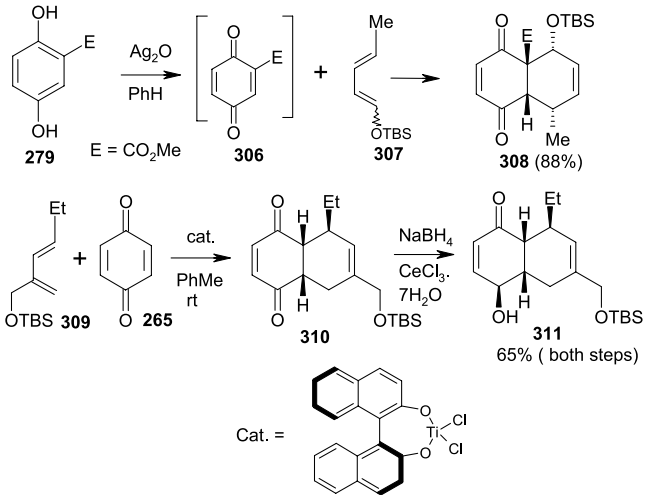
Scheme 66.

In context with their studies towards the synthesis of the AB ring system of taxol, Fetizon et al. reported a Diels–Alder reaction between 2,6-dimethylbenzoquinone **269a** and the diene **304**, to give the adduct **305** containg a *cis*-decalin framework in a regio- and stereoselective fashion (Scheme 67).[66]



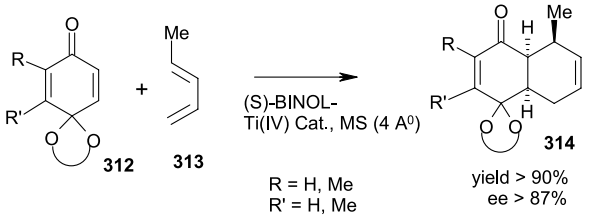
Scheme 67.

Towards the synthesis of euonyminol and 3,4-dideoxymaytol, White and co-workers employed the diene–dione **308** as a precursor that was synthesised by a Diels–Alder reaction of the diene **307** with the in situ-generated 2-carbomethoxybenzoquinone **306** (Scheme 68).[67a] Towards the synthesis of (−)-ibogamine, recently, White and Choi reported a Diels–Alder reaction of **309** with benzoquinone in the presence of a chiral catalyst to give the *endo* adduct **310** in good ee (Scheme 68). The adduct was converted into the alcohol **311**, since it was found to be unstable.[67b,c] Chiba and Tada reported[67d,e] a Diels–Alder reaction of quinones generated by the electrochemical oxidation of hydroquinones of the type **279** with acyclic dienes that provided good yields of the corresponding adducts.



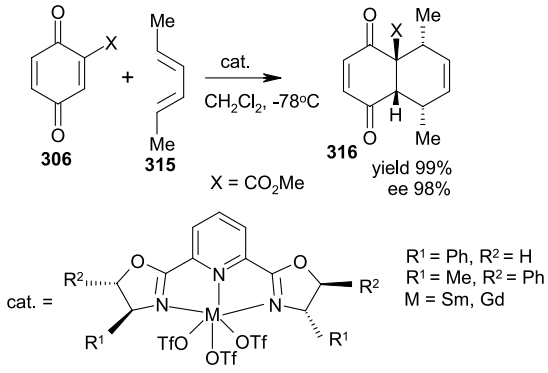
Scheme 68.

Corey and co-workers achieved high ees in the Diels–Alder reactions of 1,4-quinone monoketals **312** with acyclic dienes such as (*E*)-1,3-pentadiene **313** to give chiral *cis*-decalins **314** (Scheme 69).[68a] The catalyst used for this purpose was prepared by stirring (*S*)-BINOL and Cl_2-Ti(O^iPr)$_2$ (Mikami catalyst). For a variety of 1,4-quinone monoketals, very good yields, *endo*/*exo* selectivity and enantioselectivity were observed. The enantioselectivities for cycloaddition with other dienes such as butadiene, 2,3-dimethybutadiene and isoprene were also explored. Recently, a chiral oxazaborolodinium-catalysed Diels–Alder reaction of various quinones with various dienes, leading to the *cis*-adducts in excellent ees, was reported.[68b,c] This methodology provided access to a variety of compounds in optically pure form and led to the enantioselective synthesis of many natural products.[68b,c]



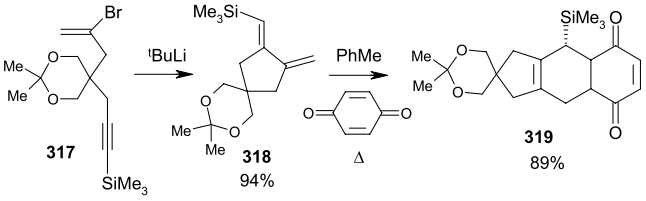
Scheme 69.

A highly enantioselective Diels–Alder reaction of the quinone **306** with acyclic diene **315**, leading to adduct **316** in the presence of a chiral catalyst derived from pyridylbis-oxazoline ligands and samarium and gadolinium triflates was described by Evans and Wu (Scheme 70).[68d] The reaction is general and gives excellent ees with other dienes and quinones.[68d] A diastereoselective cycloaddition between a chiral diene with a quinone derivative leading to chiral decalin ring system has also been reported.[68e]



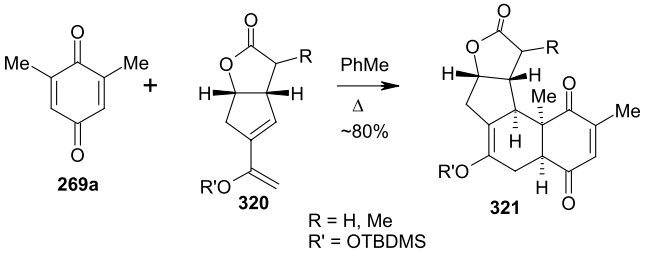
Scheme 70.

Ovaska and co-workers have reported an interesting cycloaddition of dienes of the type **318**. Thus, treatment of a vinyl halide such as **317** with ^{t}BuLi gave the diene **318**, which underwent cycloaddition with benzoquinone to furnish the adduct **319** in good yield (Scheme 71).[69a] This methodology is also applicable for the enantioselective synthesis.



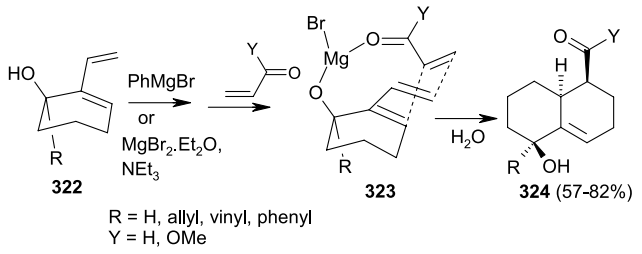
Scheme 71.

Burnell et al., as part of their synthetic studies towards the kempane diterpenes, explored the Diels–Alder reactions of bicyclic dienes of the type **320** with 2,6-dimethyl-*p*-benzoquinone **269a** (Scheme 72).[69b] The cycloaddition was found to be highly regio- and stereoselective, giving rise to adducts of the type **321**. Only in one case was a very minor amount of the other regioisomer formed.



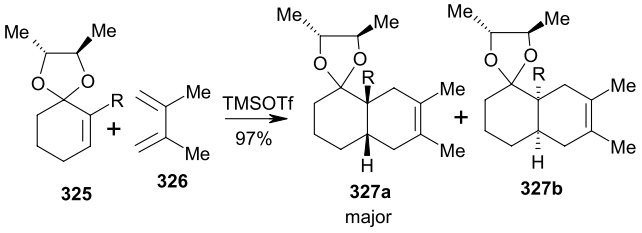
Scheme 72.

Barriault and co-workers developed a novel and general hydroxyl group-directed Diels–Alder reaction of semicyclic dienes with dienophiles such as methyl acrylate, methacrolein, acrolein and *N*-phenylmaleimide.[70] Thus, dienes of the type **322** on treatment with phenylmagnesium bromide or $MgBr_2 \cdot Et_2O$ and Et_3N, followed by the addition of the activated dienophiles, result in the formation of the decalenes of type **324** in a highly regio- and diastereoselective manner via the transition state **323** (Scheme 73). Cycloaddition between a variety of dienes and dienophiles has been reported, giving good yields of the cycloadducts.



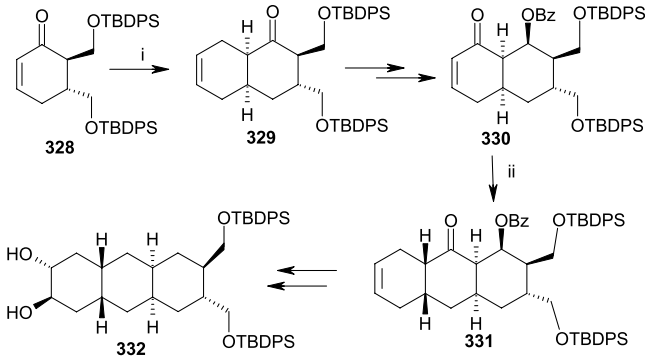
Scheme 73.

Anderson and co-workers explored the possibility of the asymmetric ionic Diels–Alder reaction, leading to the formation of *cis*-decalins in an enantioselective manner.[71a] Thus, the reactions of chiral acetals of the type **325** were examined with a variety of dienes in the presence of Lewis acids and the cycloaddition of **325** with 2,3-dimethylbutadiene **326** gave the adduct **327a** as a major product and **327b** as the minor component (Scheme 74).



Scheme 74.

Koert et al. reported a iterative Lewis acid-catalysed Diels–Alder reaction for the synthesis of perhydroanthracenes such as **331** and **332** as possible transducers for molecular signals (Scheme 75).[71b] Thus, the cyclohexenone derivative



Scheme 75. Reagents and conditions: (i) 1,3-butadiene, $AlCl_3$, $AlMe_3$, 80%; (ii) 1,3-butadiene, $AlBr_3$, 86%.

328, readily available via the cycloaddition of 1-trimethylsilyloxy-1,3-butadiene and diethyl fumarate, was treated with butadiene in the presence of $AlCl_3$–$AlMe_3$ to give the *cis*-decalin **329** in very good yield. The *cis*-decalin **329** was further manipulated to the enone **330**, which, upon Diels–Alder reaction with butadiene, gave the tricyclic compound **331** (Scheme 75). Further manipulation led to the functionalised perhydroanthracene derivative **332**.

2.3.2. Intramolecular cycloaddition. The intramolecular Diels–Alder reaction has also been employed to construct the decalin framework. Thus, a triene such as **VI** may undergo an intramolecular Diels–Alder reaction to give either the *cis*-fused decalins such as **VII** or the *trans*-fused decalins such as **VIII**, depending on the transition state (Fig. 3).

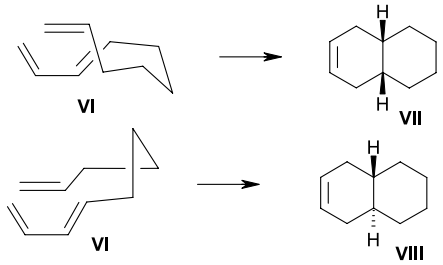


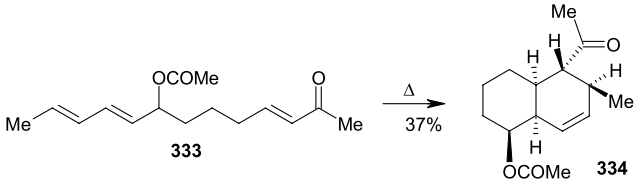
Figure 3.

It is not always easy, however, to predict the stereochemistry, as it depends on the cumulative effects of various factors such as the competing conformational, steric and electronic effects in the transition states. This, in turn, depends on the nature and position of substituents in the substrate. The addition of a Lewis acid also has, in many cases, a profound effect on the cis–trans ratio. These factors are discussed in detail.[72] It appears that the stereochemistry of the ring fusion is largely independent of the geometry of the dienophile moiety, suggesting that secondary orbital interactions do not play a dominating role in most of the cases. Some examples are known where, in the presence of a Lewis acid, the secondary orbital interactions become more important. The placement of a functional group can sometimes change the product distribution, for example, in many cases it has been found that the presence of a carbonyl group in conjugation with the diene moiety helps in the formation of the trans product, while, if the carbonyl group is in conjugation with the double bond in the dienophile, the cis products tend to predominate.

Unlike intermolecular Diels–Alder reactions, intramolecular Diels–Alder reactions are carried out at a later stage of the synthesis and one limitation of this methodology is that the preparation of the requisite precursor becomes a considerable synthetic task in itself. Despite the aforementioned difficulties and limitations, a number of intramolecular Diels–Alder reactions have been studied. Some significant examples are presented below.

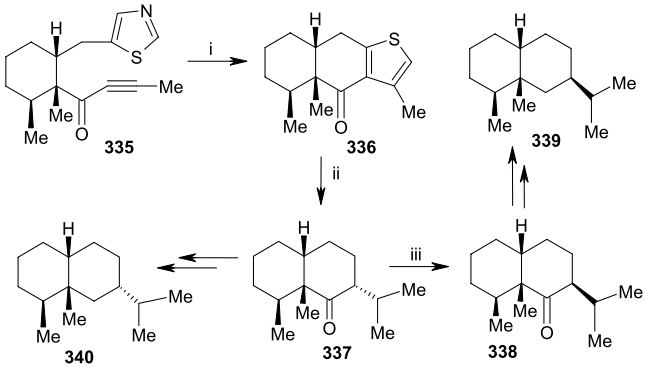
In context with the synthesis of nargenicin antibiotics, the framework of which contains a *cis*-decalin moiety, Jones and Tunnicliffe reported an intramolecular Diels–Alder

reaction in the trienone **333**. Thus, heating of trienone **333** in oxygen-free xylene gave a stereoisomeric mixture of decalins, from which the *cis*-isomer **334** was obtained in 37% yield (Scheme 76).[73]



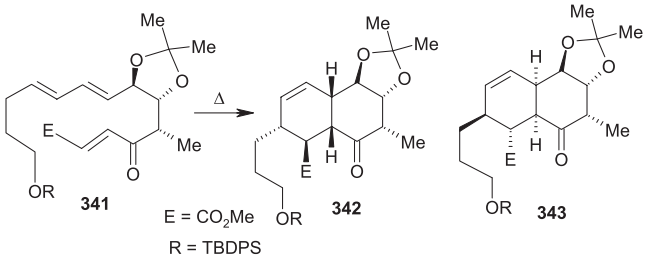
Scheme 76.

Jacobi et al. described a novel synthesis of 7α- and 7β-eremophilanes, wherein the intramolecular Diels–Alder reaction of an acetylenic thiazole and reduction of the resulting fused-ring thiophene are the key steps.[74] Thus, acetylenic thiazole **335** underwent an intramolecular Diels–Alder reaction, followed by extrusion of HCN, to furnish the tricyclic ketone **336** containing a *cis*-decalin fused thiophene ring. Reduction of **336** with Raney nickel furnished the ketone **337** in a stereoselective manner. Epimerisation in **337** led to **338**, which was then elaborated to 7β-eremophilane **339**. Similarly, the ketone **337** upon deoxygenation gave **340** (Scheme 77).



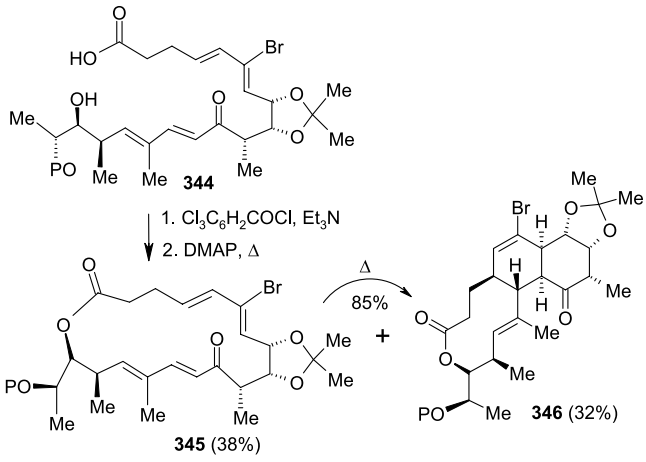
Scheme 77. Reagents and conditions: (i) decalin, 350 °C, 21 h, 74%; (ii) Ra-Ni, 87%; (iii) NaOMe–MeOH, 95–99%.

Towards the synthesis of nargenicin A1, Roush and Coe explored the intramolecular Diels–Alder reaction of the trienes **341**, with a view to prepare the adduct **343** via a chair-like transition state (Scheme 78).[75a] On heating, however, the trienes **341** gave the *cis*-decalins **342** as a single product, presumably via a boat-like transition state. Further, the authors examined the intramolecular Diels–Alder reaction in a series of structurally related trienes, in order to uncover the factors responsible for this surprising result. They concluded that, assuming the transition state is early, the boat form is actually free of destabilising eclipsing or other unfavourable non-bonded steric interactions and, additionally, there is a stabilising eclipsing sp^3–sp^2 interaction between the diene and the allylic C–H bond in the boat-type transition state.[75b]



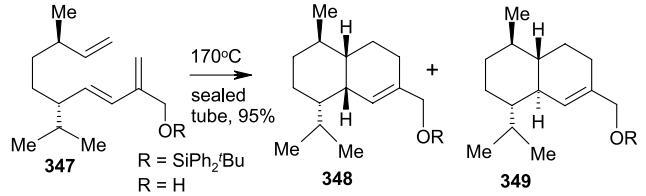
Scheme 78.

In continuation of their interest in this area, Rousch and co-workers developed a synthesis of the carbon skeleton of nargenicin A1 via a transannular Diels–Alder reaction as the key step.[76] Thus, addition of the mixed anhydride generated by treatment of the acid **344** with 2,4,6-trichlorobenzoyl chloride to a solution of DMAP at 80 °C gave the macrolide **345**, the adduct **346** and a minor amount of the C-10 epimer of **346**. Interestingly, heating the lactone **345** produced only the adduct **346** in excellent yield (Scheme 79).



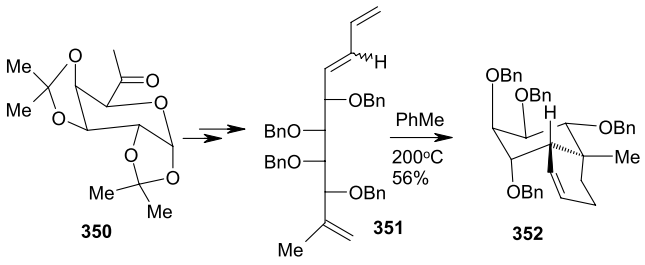
Scheme 79.

Meinwald and co-workers described a route to both cadinane- and amorphane-type sesquiterpenes utilising intramolecular Diels–Alder reaction as the key step.[77a] Thus, the trienes **347**, prepared from (−)-menthone, on heating underwent an intramolecular Diels–Alder reaction to give the adducts **348** as the major product along, with the *trans* isomers **349** (Scheme 80).



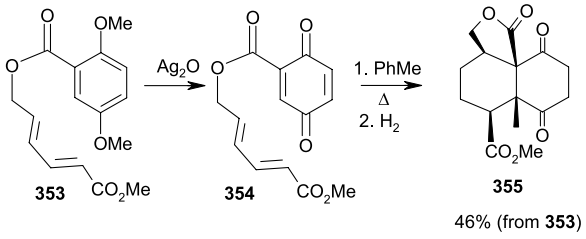
Scheme 80.

Lukacs and co-workers[77b] synthesised a chiral poly-substituted *cis*-fused decalin containing an angular C-methyl group by an intramolecular Diels–Alder reaction. Thus, the triene **351**, prepared from 7-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galacto-heptopyranos-6-ulose **350**, on heating in toluene furnished the *cis*-decalin **352** as a single product (Scheme 81).



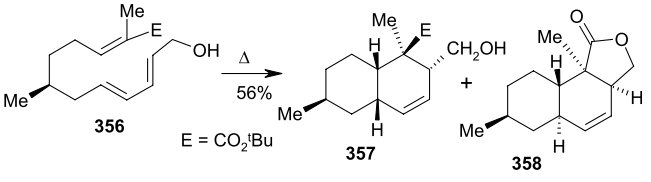
Scheme 81.

Danishefsky and co-workers[78a] examined the intramolecular cycloaddition in the quinone **354**, obtained by the oxidation of **353**. Surprisingly, the cycloaddition was slow, and heating the quinone gave the adduct, which was always acompanied by the corresponding hydroquinone. Hence, the cycloaddition product mixture was hydrogenated, from which the *cis*-decalin system **355** was isolated (Scheme 82).



Scheme 82.

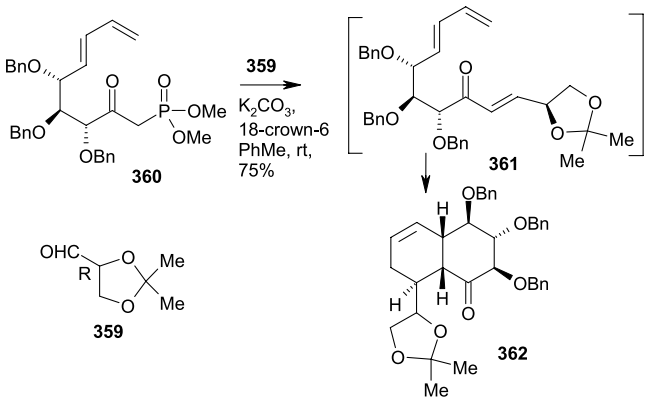
Shing and Yang described a short synthesis of (−)-oblongolide **358** via intramolecular Diels–Alder reaction.[78b] The triene **356**, prepared from (3*S*)-(−)-citronellol, on heating gave a mixture of the (−)-oblongolide **358** having a *trans*-decalin framework and the *cis*-decalin **357** as a minor product. Interestingly, the compound **357** gave the *trans*-isomer **358** upon heating (Scheme 83).



Scheme 83.

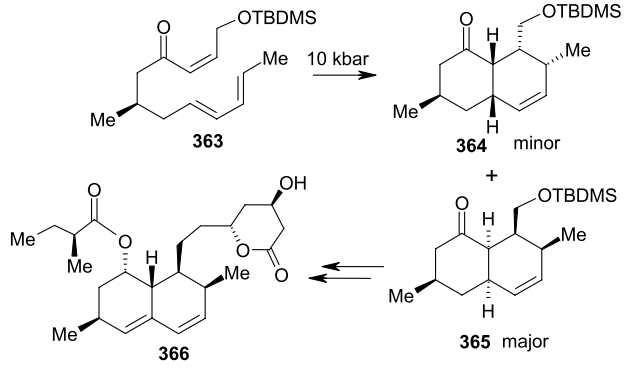
Jarosz and co-workers developed a route to enantiomerically pure, highly oxygenated *cis*-decalins via a tandem Wittig and intramolecular Diels–Alder reaction between sugar-derived phosphoranes/phosphonates and sugar aldehydes.[79] Thus, the reaction of sugar-derived phosphonates such as **360** and the sugar aldehyde of the type **359** directly gave the *cis*-decalin **362** via the intermediate **361** (Scheme 84).[79b] The intermediate **361** could not, however, be isolated. This methodology seems to be of general applicability and several optically pure *cis*-decalins were synthesised.

Konoike et al. examined several intramolecular Diels–Alder reactions and reported an enantioselective total synthesis of



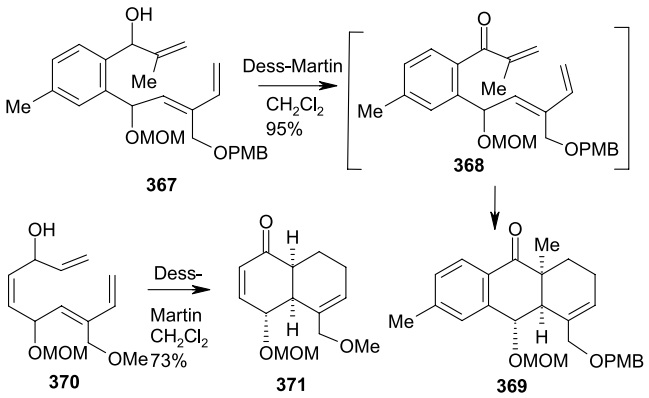
Scheme 84.

(+)-6-*epi*-mevinolin **366** and its analogues that involved the *cis*-decalin **365** as an intermediate, which was prepared by a high-pressure intramolecular Diels–Alder reaction as a key step.[80] The optically pure triene **363**, prepared from (*R*)-4-methyl-tetrahydropyran-2-one, underwent an intramolecular Diels–Alder reaction under high pressure to give the *cis*-decalins **364** and **365**, the latter as the major product. The *cis*-decalin **365** was then elaborated into (+)-6-*epi*-mevinolin **366** (Scheme 85).



Scheme 85.

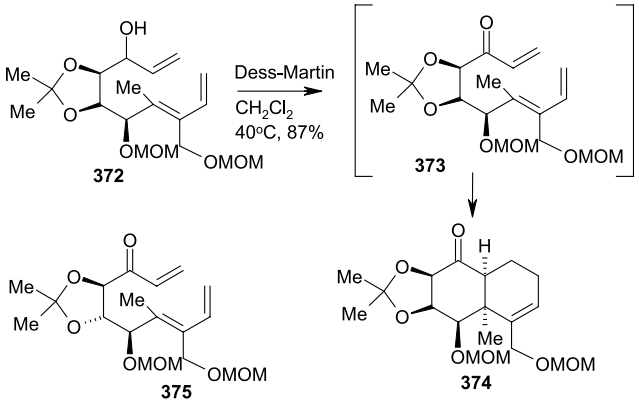
Fallis and co-workers studied the effect of an aromatic ring and the presence of a double bond in the side chain on intramolecular Diels–Alder (IMDA) reactions.[81a] Thus, trienes like **367** and **370**, containing an aromatic ring and a double bond, respectively, were synthesised and their



Scheme 86.

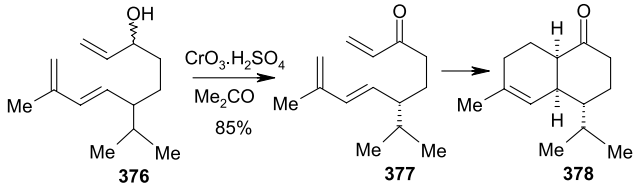
intramolecular Diels–Alder reaction was examined (Scheme 86). The tether groups have a profound influence on the ease of the intramolecular Diels–Alder reactions. Thus, the oxidation of **367** directly led via **368** to the adduct **369** in excellent yield. Similarly, the precursor **370** also gave the adduct **371** in very good yield.

As a continuation of the above studies, Fallis et al. further explored the tartrate- and carbohydrate-derived *trans*- and *cis*-isopropylidene acetals such as **372** and **375** (Scheme 87), respectively, for the asymmetric synthesis of decalins.[81b] It was observed that, compared to the *trans*-acetonides, the *cis*-acetonides undergo intramolecular Diels–Alder reaction in milder conditions. Thus, oxidation of the triene **372** gave the trienone **373**, which easily underwent an intramolecular Diels–Alder reaction to furnish the chiral *cis*-decalin **374**. The trienone **375**, however, required much more stringent conditions for the intramolecular Diels–Alder reaction. The authors also reported a route to chiral highly oxygenated nor-steroid and triterpenoid frameworks, utilising the aforementioned *cis*-isopropylidene acetal-controlled intramolecular Diels–Alder reaction, followed by an intermolecular Diels–Alder reaction.[81c]



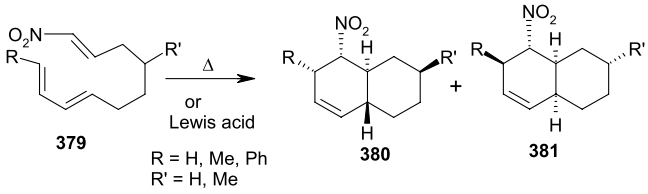
Scheme 87.

In context with their studies on the synthesis of kalihinanes, Wood and White developed an efficient approach to the functionalised *cis*-decalin **378**.[82] Thus, the oxidation of triene-ol **376** gave the trienone **377**, which, on intramolecular Diels–Alder reaction, gave the *cis*-decalin **378** as the major product (Scheme 88).



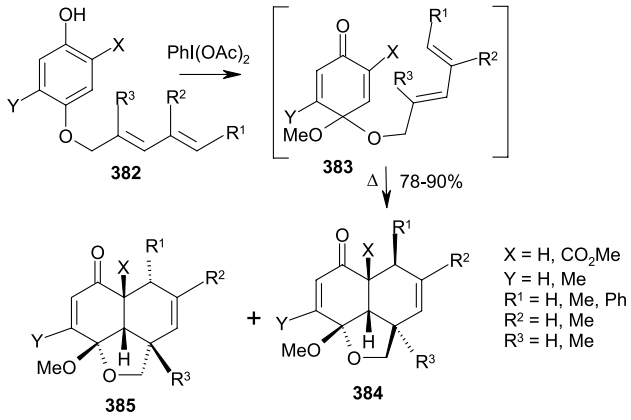
Scheme 88.

Williams and Brugel examined the intramolecular Diels–Alder reactions of various nitroalkenes of the type **379** in both thermal and Lewis acid-catalysed reactions, in order to probe their reactivity and stereoselectivity.[83] It was found that, in all cases, the *trans*-isomer **380** was the major product, while the *cis*-isomer **381** was the minor isomer (Scheme 89). In general, thermal cycloaddition led to better yields (63–80%), compared to the Lewis acid-catalysed reaction. The formation of the *trans*-decalin is attributed to a greater secondary orbital interaction (*endo* transition state). This methodology was further employed for the synthesis of norzoanthamine.



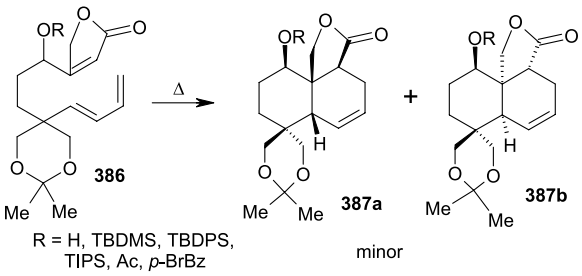
Scheme 89.

Liao et al. developed a method for the synthesis of highly functionalised *cis*-decalins via the intramolecular Diels–Alder reactions in masked *p*-benzoquinones such as **383**, which are generated in situ by the oxidation of phenols of the type **382**.[84] In most of the cases studied, the *endo* adduct of the type **385** was obtained as the predominant product (Scheme 90). In some examples, the *exo* adduct **384** was formed as a minor product.



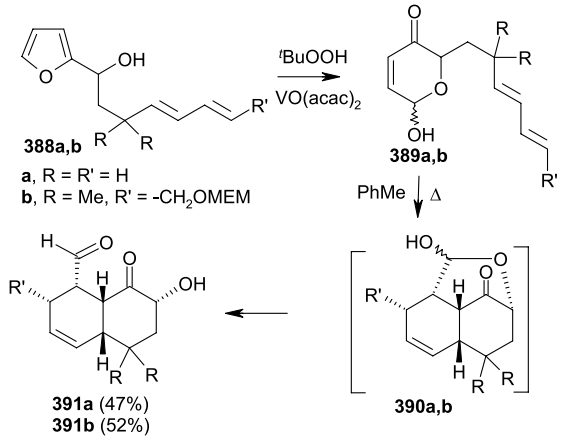
Scheme 90.

As part of their studies towards the asymmetric synthesis of azadirachtin, Murai et al. explored the intramolecular Diels–Alder reaction in various trienes such as **386** (Scheme 91).[85] These trienes **386**, however, gave a mixture of products containing the *cis*-decalins **387a**,**b** as minor products.[85a]



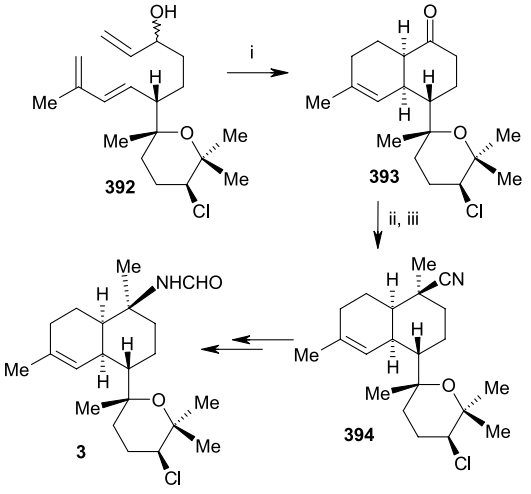
Scheme 91.

Maier and co-workers reported a novel route to the *cis*-decalins **391a**,**b** via an intramolecular Diels–Alder reaction in pyranones of the type **389a**,**b** (Scheme 92).[86] The pyranones of type **389a**,**b** were synthesised by an oxidative rearrangement of the corresponding furfuryl alcohols **388a**,**b** and heated in toluene to give the *cis*-decalins **391a**,**b** via the intermediates **390a**,**b** (Scheme 92).



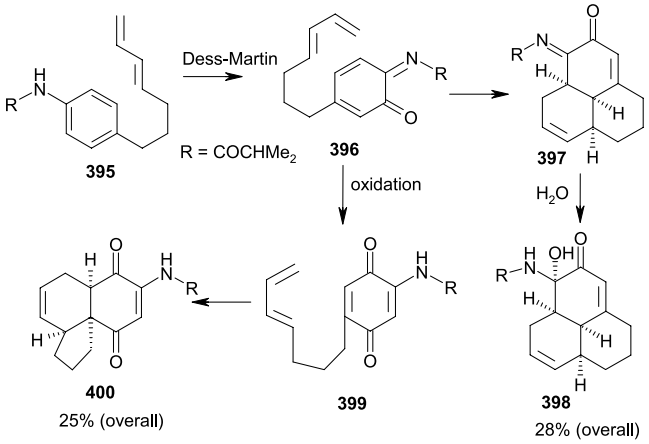
Scheme 92.

Yamada and co-workers reported a total synthesis of the marine diterpenoid, kalihinene X **3**, and also established its absolute configuration.[87] Thus, the triene **392**, synthesised from (*E*,*R*)-3,7-dimethylocta-2,7-diene-1,6-diol, on oxidation with Dess–Martin periodinane gave the corresponding enone, which underwent a spontaneous intramolecular Diels–Alder reaction to furnish the *cis*-decalin **393** in excellent yield as the sole product. The *cis*-decalin **393** was transformed into the nitrile **394** that was further elaborated into kalihinene X **3** (Scheme 93).



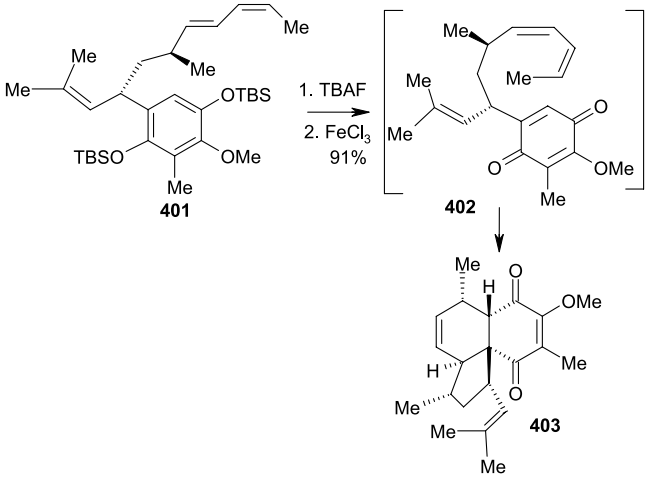
Scheme 93. Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, 93%; (ii) $TsCH_2NC$, ^{t}BUOK, DME-^{t}BUOH, 96%; (iii) KHDMS, MeI, PhMe, rt, 83%.

The intramolecular Diels–Alder reaction has been exploited in an elegant fashion by Nicolaou and his group for the synthesis of a number of natural products.[88a,b] In context with the synthesis of elisabethin A, they reported a novel route to the tricyclic compounds **398** and **400** from the aromatic precursor **395** (Scheme 94). Thus, oxidation of the amide **395** gave two products **398** and **400**. The product **398** is formed via the intermediate **396**, generated by oxidation of **395**, followed by intramolecular Diels–Alder reaction and subsequent addition of a water molecule to the adduct **397**. The tricyclic compound **400** is formed via the quinone **399**, which is generated by further oxidation of **396** (Scheme 94).[88b]



Scheme 94.

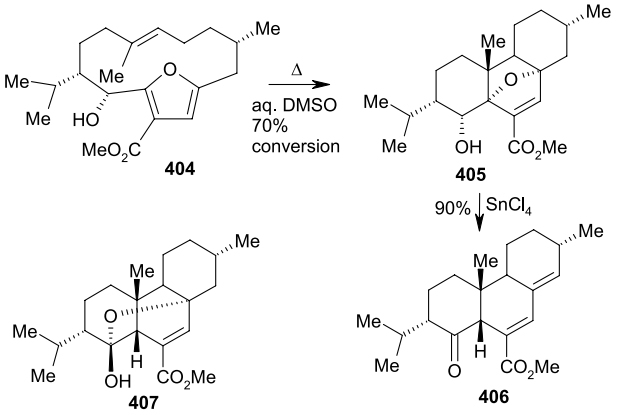
Mulzer and Heckrodt also reported a highly stereoselective synthesis of a *cis*-decalin **403** in context with their synthesis of the marine diterpenoid, elisabethin A.[88c] Thus, the highly substituted aromatic precursor **401**, prepared from 2,4-dimethoxy-3-methyl-benzaldehyde, was deprotected with tetrabutylammonium fluoride and oxidised with $FeCl_3$ to form the quinone **402**, which underwent intramolecular Diels–Alder reaction in situ to give the adduct **403** as a single stereoisomer (Scheme 95). The adduct **403** was then epimerised and elaborated into the desired target.



Scheme 95.

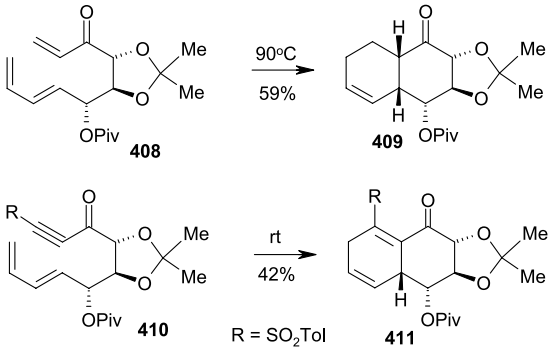
In connection with their synthesis of chatancin **407**, Deslongchamps et al. examined a transannular Diels–Alder reaction in furanophane.[89] Thus, the furanophane **404**, synthesised via ring-closing metathesis, on heating in

aqueous DMSO furnished the desired adduct **405**. The last step towards the synthesis of (+)-chatancin **407**, that is, the hydride shift-mediated oxygen transposition step using a Lewis acid, however, failed to give the required product and, instead, (+)-anhydrochatancin **406** was obtained (Scheme 96).



Scheme 96.

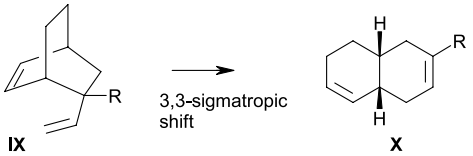
During the course of their synthetic studies towards hibarimicins and related metabolites, Sulikowski and co-workers examined several intramolecular Diels–Alder reactions.[90] Thus, the vinyl ketone **408**, upon heating, gave the single adduct **409**. Interestingly, the acetylenic ketone **410** underwent a Diels–Alder reaction at ambient temperature to give the adduct **411** (Scheme 97). The cycloadduct **409** has an array of four stereocentres common to the aglycon of hibarimicin and its congeners.[90]



Scheme 97.

2.4. Cope rearrangement

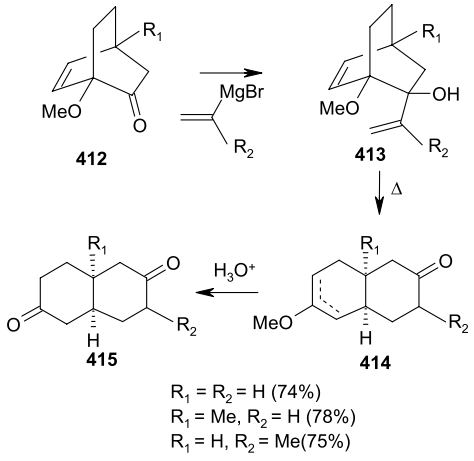
Another interesting route to *cis*-decalins is the Cope rearrangement[91] in bicyclo[2.2.2]octenones of the type **IX** to **X** (Scheme 98). There are many variations of the Cope rearrangement, for example, the oxy-Cope rearrangement



Scheme 98.

(when R=OH or OMe) and the anionic oxy-Cope rearrangement ($R=O^{-}M^{+}$).[91] The Cope rearrangement itself is of limited synthetic utility, due to the requirement of a high reaction temperature, low yields and the lack of general, flexible methods to synthesise such bicyclo-octenones. Oxy-Cope and oxy-anion Cope rearrangements, however, have greatly extended their utility, since these rearrangements occur at a lower reaction temperature and lead to higher yields of the Cope products in an irreversible manner. In the oxy-anion Cope rearrangement (where $R=O^{-}M^{+}$), a rate enhancement of up to 10^{10}–10^{17} was observed. Further, the Cope substrate is easily prepared by a Grignard-type addition of a vinyl metallic reagent to a carbonyl group in the bridged bicyclic systems. For these reasons, the oxy-anion Cope rearrangement has been very popular and has found widespread applications in synthesis.[92]

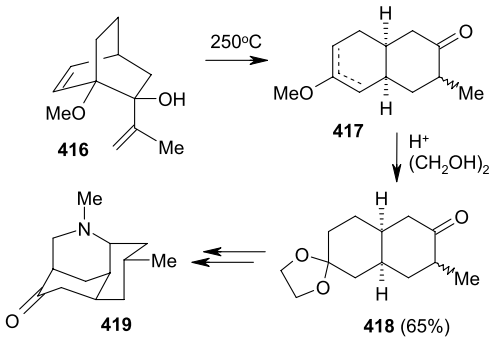
Evans and co-workers were among the first to develop general routes to *cis*-decalins of the type **412** (Scheme 99).[93a] Thus, the addition of vinylmagnesium bromide to bicyclooctenones of the type **412**, available via Diels–Alder reactions of dienes with the ketene equivalents, followed by hydrolysis of the adducts, furnished the bicyclo[2.2.2]octenones **413**, along with their *exo* stereo-isomers. The oxy-Cope rearrangement in the bicyclo[2.2.2]-octanes **413** smoothly furnished the *cis*-decalins **414** that, upon hydrolysis, provided the diones **415** (Scheme 99).[93b]



Scheme 99.

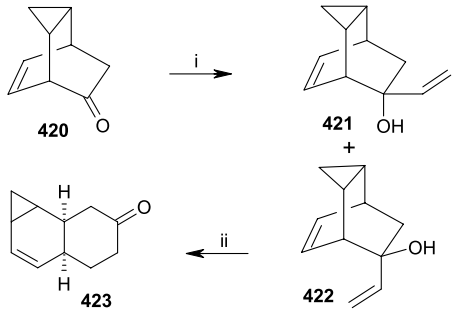
Further, Evans et al. demonstrated the potential of the aforementioned methodology by synthesising the alkaloid, (±)-luciduline **419**.[93c] Thus, the bicyclooctenone **416** was synthesised from 2,5-dihydroanisole and the ketene equivalent, 2-chloroacrylonitrile. Addition of the Grignard reagent derived from 2-bromopropene furnished the alcohol **417** that, upon oxy-Cope rearrangement, followed by ketalisation, gave the keto–ketal **418**. The keto–ketal **418** was elaborated into (±)-luciduline **419** (Scheme 100).[93c] This methodology was also employed towards studies on the synthesis of cannivonine and suggested that the proposed structure of cannivonine is incorrect.[93d]

Rigby et al. reported a novel entry into the tricyclic ring systems of aristolanes that involved an oxy-anion Cope



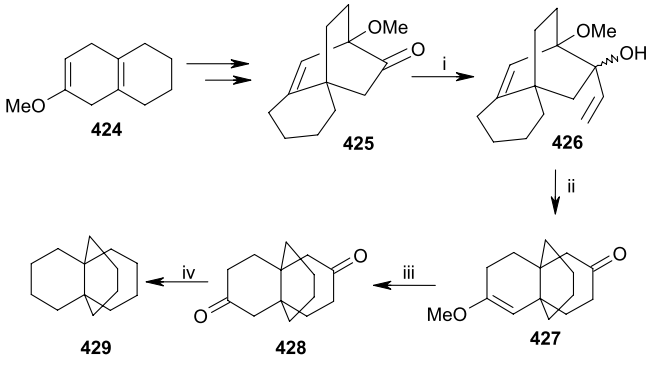
Scheme 100.

rearrangement in bicyclooctenes as the key step.[94] Thus, the readily available tricyclic ketone **420** was treated with vinylmagnesium bromide to furnish a mixture of the alcohols **421** and **422**, the latter as the major product. Oxy-anion Cope rearrangement in the *endo* isomer **422** furnished the tricyclic system **423** (Scheme 101).



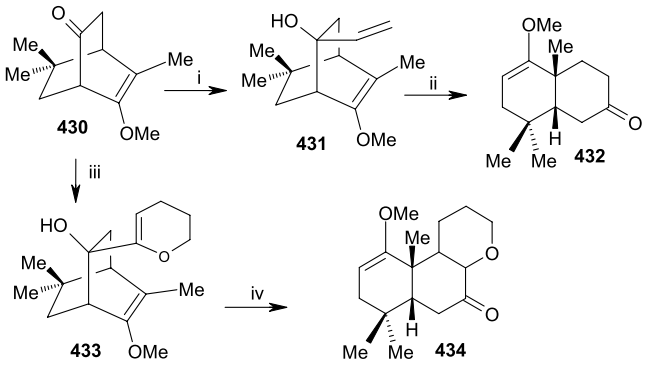
Scheme 101. Reagents and conditions: (i) CH_2=CHMgBr, THF, 91%; (ii) KH, THF, 57%.

Subba Rao and co-workers developed a general method for the synthesis of [4.4.4]propellane (Scheme 102).[95] Thus, the tricyclic compound **425**, readiliy available from 6-methoxy-5,8-dihydrotetralin **424**, on reaction with vinylmagnesium bromide gave a mixture of *endo*/*exo*-alcohols **426**. Oxy-anion Cope rearrangement in **426** gave the keto-enol ether **427**, in addition to the recovered *exo*-alcohol and other products. Hydrolysis of **427** gave the dione **428**, which, upon Wolff–Kishner reduction, furnished the [4.4.4]propellane **429** (Scheme 102).



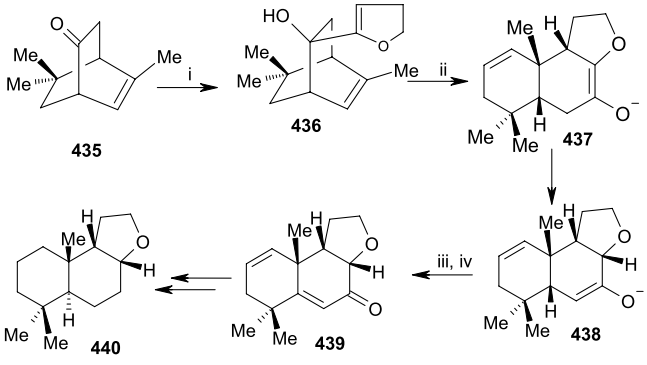
Scheme 102. Reagents and conditions: (i) CH_2=CHMgBr, THF; (ii) KH, THF, Δ, 16 h, (iii) H_2SO_4, MeOH; (iv) $NH_2 \cdot H_2O$, ethylene glycol, Δ (50% overall).

Paquette and his co-workers have extensively examined the oxy-anion Cope rearrangements.[96] In context with the synthesis of forskolin, they developed a route to various types of molecular frameworks containing a *cis*-decalin ring system. Thus, the requisite precursors such as **431** and **433** were prepared from the bicyclooctenone **430**. Treatment of **431** and **433** with KH in the presence of 18-crown-6 led to the formation of the bicyclic and tricyclic compounds **432** and **434**, respectively, in good yields (Scheme 103). More complex substrates containing functional groups in the dihydropyran ring did not, however, undergo 3,3-sigmatropic shifts.



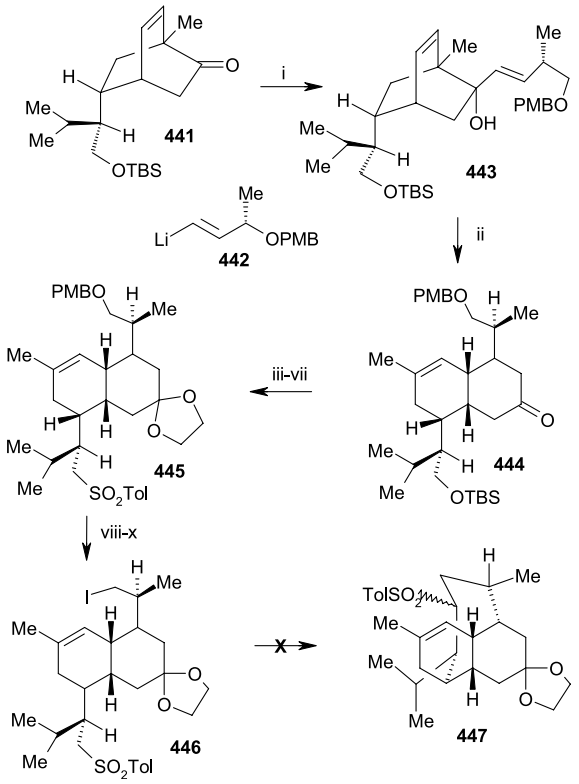
Scheme 103. Reagents and conditions: (i) CH_2=CHMgBr, THF, −78 °C, 29%; (ii) KH, 18-crown-6, THF, 1,2-dimethoxyethane, 66%; (iii) 2-lithiodihydropyran, 1,2-dimethoxyethane, 54%; (iv) KH, THF, 18-crown-6, Δ, 68%.

Paquette and co-workers employed an embellished *cis*-decalin ring system that was obtained via an oxy-anion Cope rearrangement for an enantioselective synthesis of (−)-9-*epi*-ambrox **440** that contains a *trans*-decalin in its core (Scheme 104).[97] Thus, the addition of 5-lithio-2,3-dihydrofuran to the optically pure ketone **435** gave the alcohol **436**, along with its epimer. Oxy-anion Cope rearrangement of the alcohol **436** at 80 °C induced two key sequential reactions. The, [3,3]-shift gave the enolate anion **437**, which undergoes equilibration in favour of **438**. Quenching of the enolate **438** with phenylselenyl chloride, followed by oxidative elimination of the phenylselenyl group, afforded **439** (Scheme 104), which was elaborated into (−)-9-*epi*-ambrox **440**.



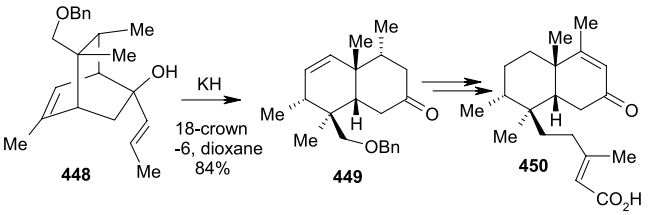
Scheme 104. Reagent and conditions: (i) ^{t}BuLi, 2,3-dihydrofuran, THF, −78 °C, $CeCl_3$, −78 °C, 65%; (ii) KH, 18-crown-6, THF, 80 °C; (iii) PhSeCl, −78 °C; (iv) $NaIO_4$, $NaHCO_3$, MeOH, 54% (from **436**).

Paquette and co-workers have carried out extensive studies on the synthesis of bicyclic systems and anionic oxy-Cope rearrangements in context with the synthesis of vinigrol and have developed a route to highly embellished octalin ring system (Scheme 105).[98] Thus, the required bicyclic ketone **441** was synthesised in an optically pure form and treated with **442** to give a mixture of alcohols, from which the *exo*alcohol **443** was isolated. An oxy-anion Cope rearrangement in **443** gave the highly appended and functionalised *cis*-decalin **444**, with four contiguous stereocentres on the decalin moiety. This *cis*-decalin was then elaborated into the iodide **446** via the intermediate **445**. Unfortunately, the iodide **446** failed to undergo the S_N^2 displacement under various conditions and reagents to give the desired compound **447** (Scheme 105).



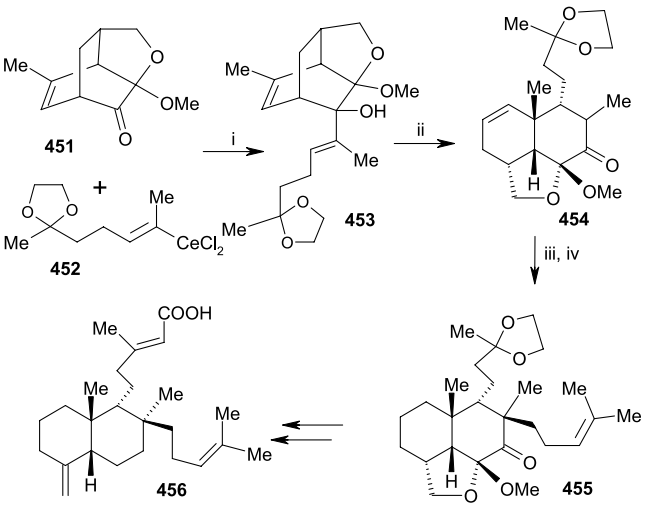
Scheme 105. Reagents and conditions: (i) **442**, THF, −78 °C, 58%; (ii) $KN(SiMe_3)_2$, 18-crown-6, THF, 120 °C, 72%; (iii) PTSA, $(CH_2OH)_2$, PhH, Δ, 84%; (iv) TBAF, THF 82%; (v) TsCl, DMAP, 91%; (vi) NaI, MEK, Δ; (vii) TsNa, DMF, Δ, 82%; (viii) DDQ, CH_2Cl_2, H_2O, 94%; (ix) TsCl, DMAP, CH_2Cl_2, 81%; (x) NaI, MEK, Δ, 82%.

Liao and co-workers have developed a versatile route to bridged bicyclic compounds and have extensively examined the oxy-Cope rearrangement.[99,100] They developed[99a] a stereoselective approach to *cis*-clerodanes using an intermolecular Diels–Alder reaction of a masked *o*-benzoquinone and an anionic oxy-Cope rearrangement as the key steps and also synthesised a *cis*-clerodane diterpenic acid **450** (Scheme 106).[99b] Thus, the bridged bicyclic precursor **448** was synthesised from 2-methoxy-5-methylphenol. Oxy-anionic Cope rearrangement in **448** furnished the *cis*-decalin **449** in good yield. Extension of the chain and introduction of a double bond in **449** led to the diterpenic acid **450** (Scheme 106).



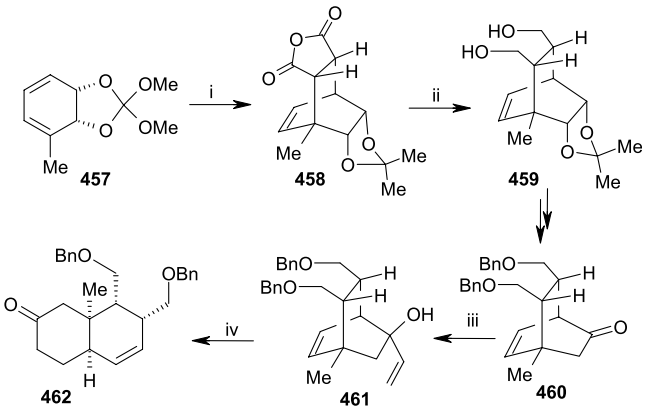
Scheme 106.

Liao and his co-workers have also reported a methodology for the stereocontrolled synthesis of highly substituted *cis*-decalins from 2-methoxyphenol derivatives.[100a,b] Further, the methodology was applied towards the synthesis of sesterpenic acids (Scheme 107).[100b] The tricyclic compound **451** was obtained via an intramolecular Diels–Alder reaction of a masked *o*-benzoquinone. Treatment of the ketone **451** with the cerium reagent **452** furnished the alcohol **453**, which underwent anionic oxy-Cope rearrangement to give the *cis*-decalin **454**. The keto–ketal **454** was converted into **455**, which was then elaborated into the sesterpenic acid **456**, a natural product isolated from the Red sea sponge, *Dysidea cinerea*.[100c]



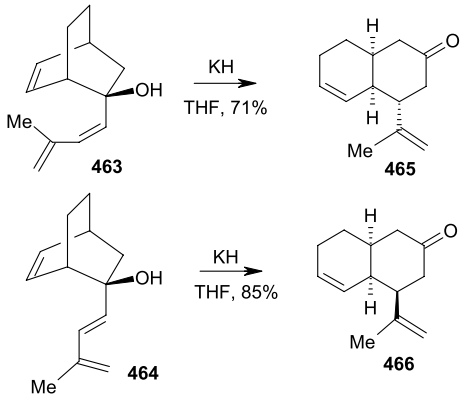
Scheme 107. Reagents and conditions: (i) THF, −78 °C, 76%; (ii) KH, 18-crown-6, THF, Δ, 97%; (iii) H_2, Pd, MeOH, 95%; (iv) NaH, homoprenyl iodide, 61%.

An excellent route to enantiopure *cis*-decalins was devised by Banwell and co-workers that involves anionic an oxy-Cope rearrangement as key step (Scheme 108).[101a] Thus, the acetonide **457**, prepared from microbially derived chiral *cis*-1,2-dihydrocatechol, on Diels–Alder cycloaddition with maleic anhydride gave the adduct **458**. Reduction of **458** with lithium aluminium hydride gave the diol **459**, which was then elaborated into ketone **460**. Addition of vinylmagnesium bromide to **460** gave the alcohol **461**, along with its epimer. Treatment of the *exo*alcohol **461** with potassium hydride in THF furnished the enantiopure *cis*-decalin **462** (Scheme 108). Simple modifications of the aforementioned synthetic sequences permitted the synthesis of other *cis*-decalins. Recently, application of this methodology towards the synthesis of a *cis*-decalin core related to the antimitotic agent, phomopsidin, has been reported.[101b]



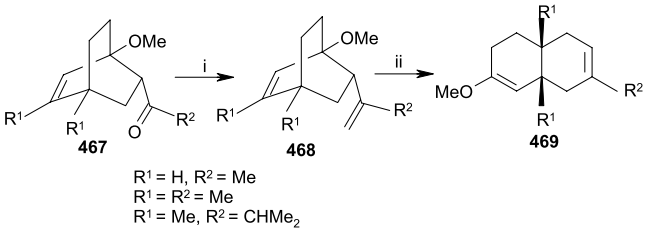
Scheme 108. Reagents and conditions: (i) maleic anhydride, CH_2Cl_2, 0–18 °C, 24 h, 68%; (ii) $LiAlH_4$, THF, 66 °C, 3 h, 88%; (iii) CH_2=CHMgBr, THF, 0 °C, 61%; (iv) KH, 18-crown-6, THF, 60 °C, 3 h, 80%.

During the course of their studies towards synthesis of vinigrol, Hanna and co-workers examined oxy-anion Cope rearrangements in a variety of systems leading to complex molecular frames.[32,102] They observed that, in sharp contrast to their isopropyl counterparts, a variety of (*Z*)-isopropenyl tertiary bicyclo[2.2.2]octenols undergo a facile anionic oxy-Cope rearrangement, leading to stereoselective incorporation of an isopropenyl group into polycyclic skeletons such as the tricyclic system of vinigrol, bicyclo[5.3.1]undecane and *cis*-decalin frameworks. Thus, the bicyclo[2.2.2]octenols **463** and **464** undergo oxy-anion Cope rearrangement to furnish the corresponding *cis*-decalins **465** and **466**, respectively, (Scheme 109).[102] Many other interesting examples of oxy-anion Cope rearrangements were also reported.[102]



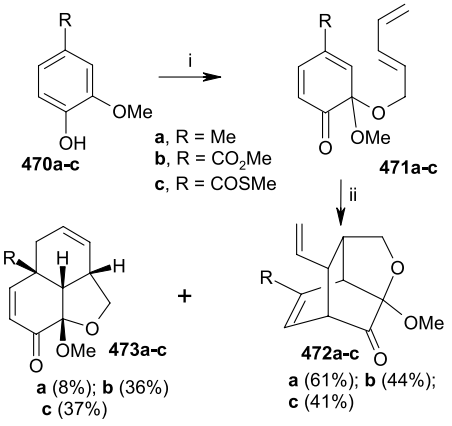
Scheme 109.

As mentioned before, the Cope rearrangements in the bicyclo[2.2.2]octenones have remained unexplored, as compared to their oxy-Cope or oxy-anion Cope rearrangements. Apart from the inherent limitation of the Cope rearrangements, compared to their oxy-anion counterparts, another drawback is the lack of a general and flexible route to the appropriate 1,5-dienes. One of the earliest strategies for the synthesis of bicyclooctenes containing a 1,5-diene moiety involved the Diels–Alder reaction of cyclohexadienes with vinyl ketones, followed by a Wittig reaction.[103] Thus, the ketones of type the **467** were subjected to Wittig reactions to give the corresponding dienes **468**, which upon heating underwent a Cope rearrangement to give the *cis*-decalins **469** (Scheme 110).[103a] Similarly, other bicyclic octadienes were also reported to undergo a 3,3-shift.[103b]



Scheme 110. Reagents and conditions: (i) CH_2=PPh_3, DMSO, 72–83%; (ii) sealed tube, 250 °C.

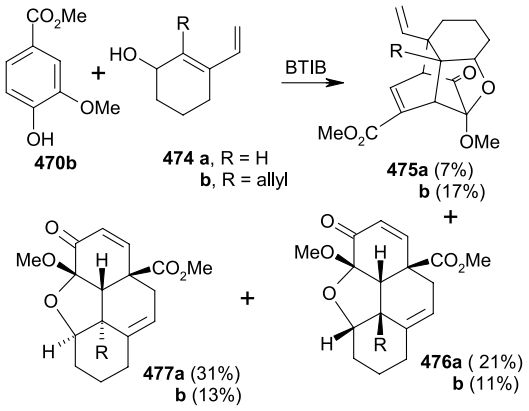
Rodrigo et al. developed a novel sequence involving an intramolecular Diels–Alder reaction of the *o*-quinonoid monoketals and a Cope rearrangement in the resulting adducts to give naphtha[1,8-*bc*]furan tricycles and utilised the sequence for the synthesis of a marine natural product, xestoquinone.[104a,b] Thus, the *o*-methoxyphenols **470a–c**, when treated with (*E*)-penta-2,4-dienol in the presence of bis(trifluoroacetoxy)iodosobenzene (BTIB), furnished the mixed monoketals **471a–c**, which, in turn underwent intramolecular cycloaddition to give the adducts **472a–c** as the major products, along with **473a–c** containing a *cis*-decalin ring system. Heating **472a** also gave **473a** as a result of a Cope rearrangement (Scheme 111). Other more complex molecular frameworks were synthesised via the reactions of benzoannulated analogues of methoxyphenols.[104a]



Scheme 111. Reagents and conditions: (i) (*E*)-2,4-pentadienol, $PhI(O_2CCF_3)_2$, $NaHCO_3$, 4-Me-2,6-(^{t}Bu)$_2$C$_6$H$_2$OH (for **470a**), THF; (ii) Δ.

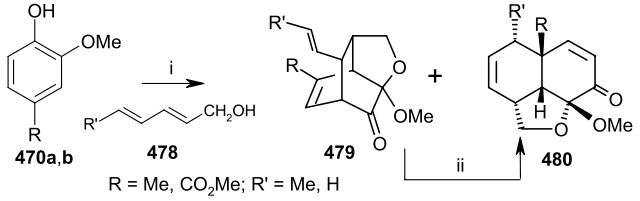
Rodrigo and co-workers further employed the aforementioned methodology for the naphthofurans and phenanthrofurans realated to (−)-morphine.[104b] While oxidation of *o*-methoxyphenols in the presence of penta-2,4-dienol gave more of the bridged bicyclic compounds of the type **472a–c**, which underwent Cope rearrangement upon heating (Scheme 111), oxidation of the methoxyphenol **470b** in the presence of 3-vinylcyclohexenols **474a**,**b** gave a mixture of three products **475**–**477** containing the bridged tetracyclic adduct **475a**,**b** only as a minor

product (Scheme 112). The compounds **475a**,**b** were then transformed into phenanthrofurans.



Scheme 112.

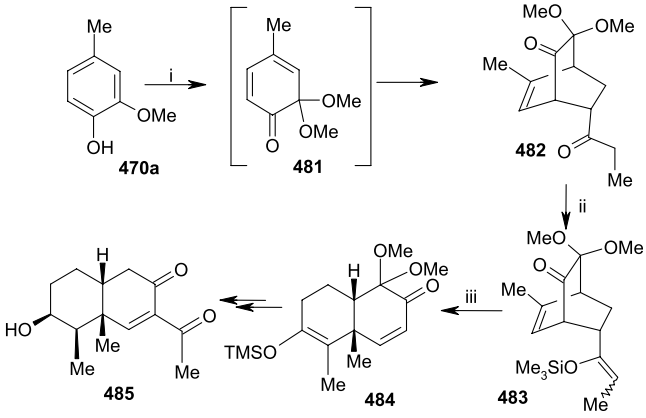
Liao and his associates also reported a methodology for the synthesis of highly functionalised *cis*-decalins that involves similar concepts as presented above.[105] Thus, the oxidation of 2-methoxyphenols **470a**,**b** by bis(trifluoroacetoxy)iodosobenzene (BTIB) in the presence of a variety of 2,4-dienols of the type **478** gave a mixture of bridged tricyclic compounds of the type **479** containing an *endo*vinyl group and tricyclic compounds of the type **480**. The bridged tricyclic compounds **479** underwent a Cope rearrangement on heating to give the compounds **480** (Scheme 113).



Scheme 113. Reagents and conditions: (i) $PhI(O_2CCF_3)_2$, THF, rt, 60–78%; (ii) mesitylene, 200 °C, 92–100%.

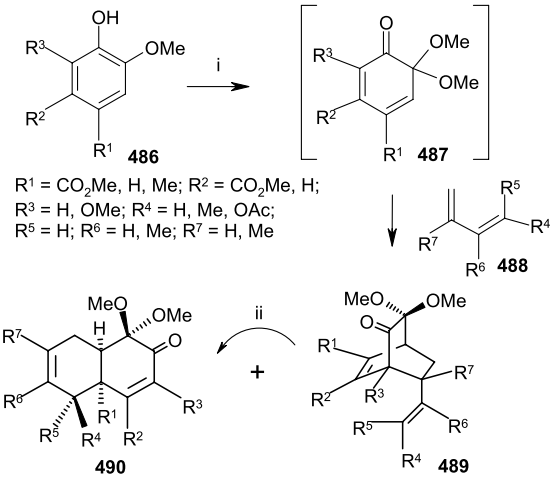
Liao and co-workers have extensively exploited the cycloaddition of cycohexadienone ketals for the synthesis of a variety of molecular frameworks.[106,107] They developed a synthesis of bicyclooctenones containing an *endo*silyl vinyl ether moiety and examined their Cope rearrangement that provided a general route to functionalised *cis*-decalins.[106a] These authors also reported a synthesis of (±)-eremopetasidione, a norsesquiterpenoid, using the same methodology (Scheme 114).[106b] Thus, oxidation of phenol the **470a**, followed by a Diels–Alder reaction of the resulting *o*-benzoquinone **481** with ethyl vinyl ketone, furnished the bicyclooctenone **482**. Conversion of the **482** into the silyl enol ether gave the required 2-silyloxy-1,5-dienone **483**, which upon Cope rearrangement furnished the *cis*-decalin **484** (Scheme 114). The dienone **484** was further elaborated into (±)-eremopetasidione **485**, a natural product isolated from *Petasites japonicus* MAXIM.[106c]

Liao and co-workers also developed a more direct route to



Scheme 114. Reagents and conditions: (i) DIAB, MeOH, EVK, rt, 96%; (ii) NEt_3, TMSOTf, PhH, rt, 96%; (iii) $HC(OMe)_3$, mesitylene, 220 °C, 70%.

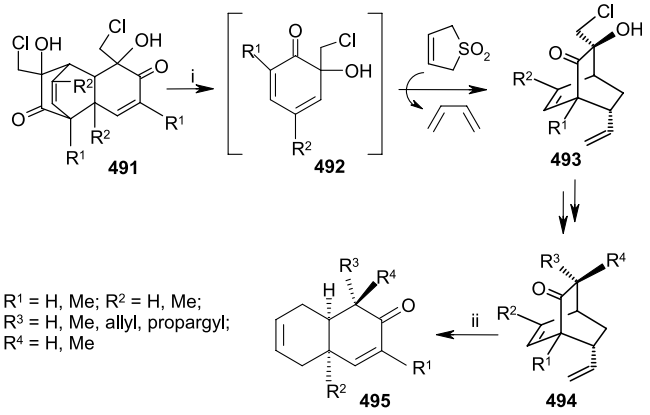
bridged bicyclic octenes containing an *endo*vinyl moiety and devised another route to functionalised *cis*-decalins.[107] Thus, the masked benzoquinones of the type **487**, generated in situ from 2-methoxyphenols of the type **486**, underwent intermolecular Diels–Alder cycloaddition with acyclic 1,3-dienes of the type **488** to give the bicyclooctenones such as **489**, along with the *cis*-decalins **490**, the latter also being obtained by the Cope rearrangement in the bicyclooctenones **489** (Scheme 115).



Scheme 115. Reagents and conditions: (i) $PhI(OA_C)_2$, MeOH, rt, 40–96%; (ii) $HC(OMe)_3$, mesitylene, 180–200 °C, 85–98%.

In a continuation of their studies on the development of new methodology employing the chemistry of cyclohexadienones,[108] Singh et al. devised a general and stereoselective strategy towards the synthesis of highly functionalised *cis*-decalins involving the cycloaddition of cyclohexa-2,4-dienones with acyclic dienes and Cope rearrangement as the key features.[109] Thus, the pyrolysis of the dimers of the type **491** in the presence of sulfolene gave the bicyclooctenones **493** having an *endo*vinyl moiety via an inverse electron-demand cycloaddition of the cyclohexadienones **492** and butadiene (both generated in situ) (Scheme 116). The bicyclooctenones **493** were further manipulated to the bicyclooctenones of the type **494** having various alkyl groups at the α-carbon. Heating of the bicyclooctenones **494**

led to a smooth Cope rearrangement to give the *cis*-decalins of the type **495**.

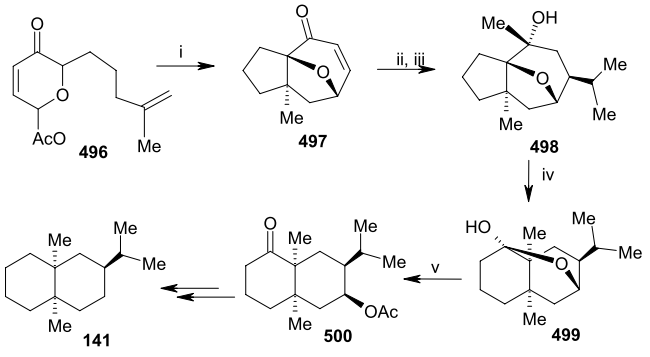


Scheme 116. Reagents and conditions: (i) $C_6H_4Cl_2$-1,2, 115–140 °C, 35–60%; (ii) $C_6H_4Cl_2$-1,2, 140–195 °C, 45–100%.

2.5. Miscellaneous methods

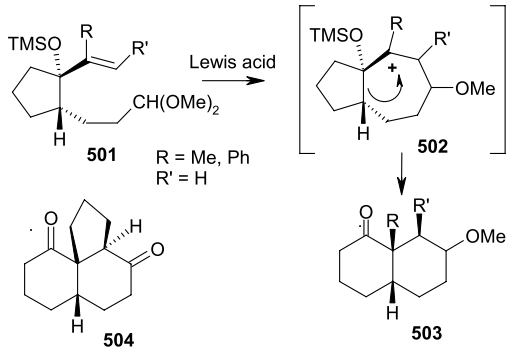
In this section, some of the other methods are presented, which could not be categorised as above. These include skeletal rearrangements, fragmentation etc. leading to a *cis*-decalin framework.

Sammes and his co-workers developed a novel route to *cis*-decalones by an acid-catalysed rearrangement of oxa-bridged perhydroazulenes, which, in turn, were synthesised from substituted furans employing intramolecular cyclo-addition of pyrilium ions.[110a,b] Further, this methodology was successfully utilised for the synthesis of many sesquiterpenes such as (±)-cryptofauronol, (±)-fauronyl acetate, (±)-valeranone and (±)-valerane.[110c] Thus, the pyranone **496**, prepared from a suitable furan derivative following a methodology developed in their group, upon heating in the presence of triethylamine furnished the adduct **497** in quantitative yield. Conjugate addition of isopropylmagnesium iodide in the presence of a Copper(I) complex, followed by reaction with methylmagnesium iodide, gave the perhydroazulenol **498** as a single isomer. Acid-catalysed rearrangement in **498** gave (±)-crypto-fauronol **499**. Treatment of **499** with acetic anhydride in the presence of sodium acetate afforded (±)-fauronyl acetate **500**, which was elaborated into (±)-valerane **141** (Scheme 117).



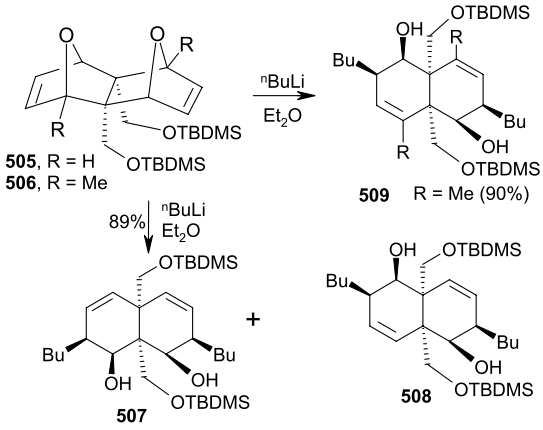
Scheme 117. Reagents and conditions: (i) Et_3N, MeCN; (ii) ^{i}PrMgBr, CuI–Me_2S, 86%; (iii) MeMgI, Et_2O, 85%; (iv) $TiCl_4$, CH_2Cl_2, 0 °C, 83%; (v) Ac_2O, NaOAc, 82%.

Overman et al. developed a novel Prins-pinacol rearrangement to form fused rings of various sizes including *cis*-decalins.[111] The sequence involves a Lewis acid-mediated Prins reaction in substrates of the type **501**, which gives the cationic species of the type **502**, which undergo rearrangement to give the decalones such as **503**. The yields, in general, are very good. More complex systems containing a decalin framework such as **504** have also been synthesised (Scheme 118).



Scheme 118.

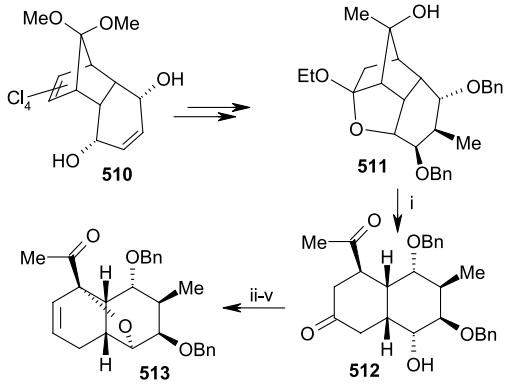
Lautens et al. developed a chemo-, regio- and stereo-controlled methodology for the synthesis of highly functionalised *cis*-decalins and related fused polycyclic systems based on the sequential nucleophilic ring opening of dioxacyclic compounds of the type **505** and **506** with butyllithium.[112] Thus, treatment of **505** with excess butyllithium gave a mixture of **507** and **508**, containing the former compound as the major product. The ring opening of the dimethyl analogue **506** gave **509** in excellent yield (Scheme 119). Ring opening with a chiral base was also examined.



Scheme 119.

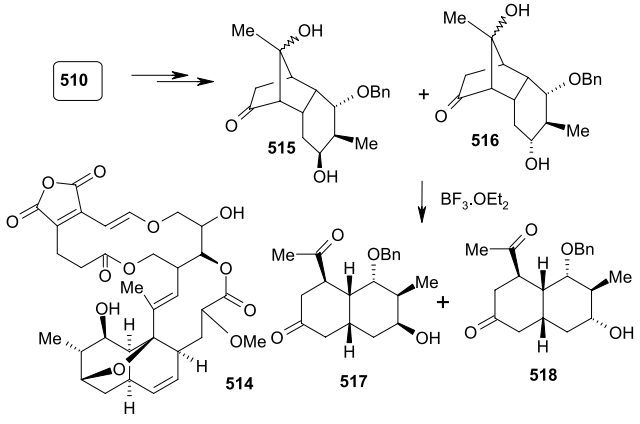
Gossinger and co-workers developed a methodology towards an oxygen-bridged decalin **513** in context with the synthesis of nodusmicin.[113a] Thus, the unsaturated 1,4-meso-diol **510** was elaborated into the enantiomerically pure tertiary alcohol **511**. Fragmentation of this tertiary alcohol **511** in the presence of camphorsulphonic acid and lithium perchlorate furnished the decalinone **512**. This decalinone was then elaborated into the oxygen-bridged

decalin **513**, an advanced intermediate in the synthesis of 18-deoxynargenicin (Scheme 120).



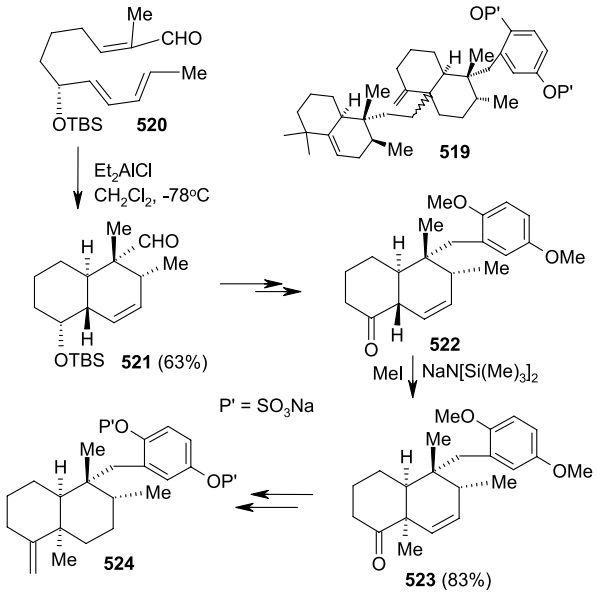
Scheme 120. Reagents and conditions: (i) camphorsulphonic acid, $LiClO_4$, Δ, 81%; (ii) KH, KO^{t}Bu, $FeCl_3$, DMF, 65%; (iii) $NaBH_4$, $CeCl_3\cdot 7H_2O$; iv, $Hg(OCOCF_3)_2$, THF, then $NaBH_4$, H_2O, 64%; (v) CrO_3, H_2SO_4, Me_2CO, 0 °C, 79%.

Gossinger and co-workers devised another route to the *cis*-decalin subunit in context with an approach towards coloradocin **514**, wherein the key fragmentation is carried out under much milder conditions.[113b] Thus, the unsaturated 1,4-meso-diol **510** was converted into the keto-alcohols **515** and **516**, which underwent fragmentation on treatment with $BF_3\cdot OEt_2$ to give the enantiomerically pure decalones **517** and **518** (Scheme 121).



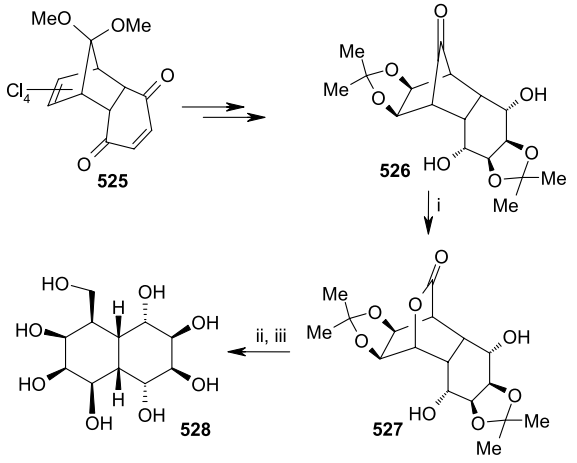
Scheme 121.

In order to establish the stereochemistry of the upper decalin part of the natural product, akaterpin **519**, Kobayashi and co-workers synthesised the *cis*-decalin **524** and its *trans* isomer and suggested that the upper decalin in akaterpin **519** has a cis-fused structure.[114] The synthesis of the *cis*-decalin **524** commenced with the triene **520**, which on intramolecular Diels–Alder reaction gave the *trans*-fused decalin **521**. The aldehyde **521** was then elaborated into the ketone **522**, which on methylation gave the *cis*-decalin **523**, which was transformed into **524** (Scheme 122). Further, a potential intermediate for the total synthesis of akaterpin was also synthesised, along with resolution of one of the intermediates.

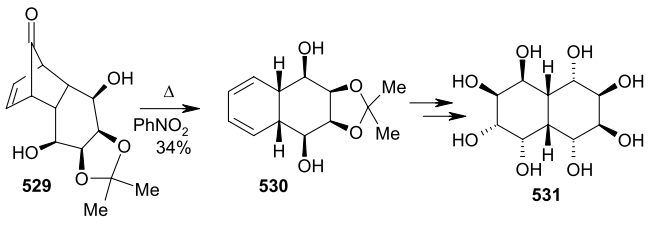


Scheme 122.

Mehta and co-workers reported a short and stereoselective synthesis of polyhydroxydecalins such as **528** (Scheme 123) with a view to find a potent glycomimic.[115a] Thus, the Diels–Alder adduct **525** was elaborated into the keto-diacetonide **526**. Baeyer–Villiger oxidation in **526** furnished the lactone **527** that, on reduction with lithium aluminium hydride, followed by hydrolysis, gave the polyhydroxy compound **528** (Scheme 123). Similarly, the ketone **529** was prepared from **525** and transformed into the polyhydroxy compound **531** via the diene **530** (Scheme 124).[115b]

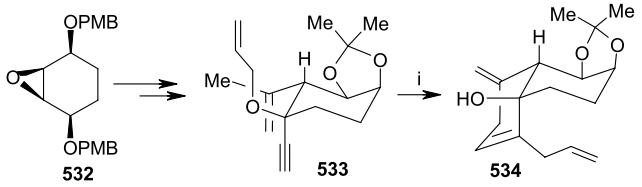


Scheme 123. Reagents and conditions: (i) *m*-CPBA, $NaHCO_3$, $CHCl_3$, 2 h, 43%; (ii) $LiAlH_4$, THF, 60%; (iii) CF_3CO_2H (30%), 90%.



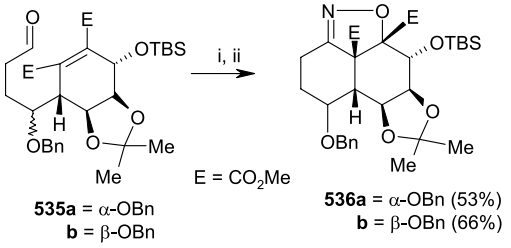
Scheme 124.

Recently, Barriault et al. reported a novel and stereoselective synthesis of the *cis*-decalin subunit of vinigrol via a tandem oxy-Cope/Claisen/ene reaction.[116] Thus, the epoxide **532**, readily available from 1,3-cyclohexadiene, was elaborated into the allyl ether **533** (Scheme 125). Microwave irradiation of **533** at 180 °C led to a tandem oxy-Cope/Claisen/ene reaction to give the *cis*-decalin **534** with high diastereoselectivity.



Scheme 125. Reagents and conditions: (i) 180 °C, PhMe, 80%.

Kozikowski and co-workers synthesised a highly oxygenated decalin derivative **536** as a possible intermediate towards forskolin involving an intramolecular nitrile oxide (3+2) cycloaddition.[117] Thus, the aldehyde **535** on conversion into its oxime and further treatment with sodium hypochloride underwent (3+2) cycloaddition to give the *cis*-fused isoxazoline **536**, in each case as a single isomer (Scheme 126).



Scheme 126. Reagents and conditions: (i) NH_2OH–HCl, Py; (ii) NaOCl, Δ.

3. Conclusions

The methods enumerated above demonstrate that there has been a renewed interest in the synthesis of *cis*-decalin and natural products containing the *cis*-decalin framework in their molecular architecture. The isolation of new natural products that contain a highly functionalised and substituted *cis*-decalin ring system from various sources and their associated biological properties have kindled this development. Emergence of new methodologies based on cyclisation, tandem reactions, ring-closing metathesis, cycloaddition of cyclohexadienones, and *o*-quinone ketals followed by 3,3-sigmatropic shifts, and cycloaddition of oxidopyrilium species, in addition to inter- and intramolecular Diels–Alder reactions, have enabled an efficacious and ready access to *cis*-decalin ring systems. Some methods have also been developed for the synthesis of enantiomerically pure decalins. The syntheses of many *cis*-decalin-based natural products, are, however, yet to be accomplished. The search for newer and efficient methods, especially for the asymmetric synthesis of decalins and the synthesis of natural products, will continue to be a sustained challenge for synthetic chemists.

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Efficient stereocontrolled synthesis of sphingadienine derivatives

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Abstract—Sphinga-4,8-dienines, principal long-chain bases of glycolipids in plants and fungi, were efficiently synthesized from L-serine. Hydrozirconation of pentadec-5-en-1-ynes followed by $ZnBr_2$-catalyzed addition to Garner's aldehyde afforded protected sphinga-4,8-dienines stereoselectively. The (2*S*,3*R*,4*E*,8*E*)-9-methyl-sphingadienine derivative was then coupled with 2(*R*)-acetoxypalmitic acid derivative prepared via asymmetric dihydroxylation to give a protected ceramide, which was converted into the corresponding glucocerebroside in two steps.

1. Introduction

Sphingolipids, for example, ceramides, sphingomyelin, cerebrosides, and gangliosides, are constituents of eukaryotic cellular membranes and play important roles in many physiological processes.[1] The common base component of these lipids is sphingosine: 2-amino-1,3-diol with a long-chain alkyl tail at C-3. Sphingoid bases show structural diversity in chain length (from 16 to 24 carbon atoms), degree of unsaturation (usually C4,5-*trans*-olefin), insertion of additional hydroxy group(s), and methyl branching. In mammalian tissues, the most common sphingoid base is D-*erythro*-C_{18}-sphingosine [(2*S*,3*R*,4*E*)-2-amino-octadec-4-ene-1,3-diol, (*E*)-sphing-4-enine], while the base composition in plants, fungi, or marine invertebrates is more variable. The major bases of cerebrosides in higher plants are sphing-8-enine, 4-hydroxy-sphing-8-enine, and sphinga-4,8-dienine, all of which have (*E*)- or (*Z*)-double bond between C8 and C9 in the hydrocarbon tail.[2] Fungi such as mushroom produce characteristic 9-methyl-branched sphinga-4,8-dienine[3] and some marine organisms such as sea star can produce 9-methyl-sphinga-4,8,10-trienine[4] in addition to sphingadienines. The presence of plural double bonds and/or a branched methyl group might be relevant for chilling and freezing tolerance.[5]

In recent years, it has been reported that simple glucocerebrosides isolated from fungi or plants exhibit significant activities such as anti-ulcerogenic activity,[6] Ca^{2+} ionophoretic property,[7] inhibitory activity against replicative DNA polymerases,[8] and elicitor activity in rice plants.[9] The major constituents of these cerebrosides were determined to be (2*S*,3*R*,4*E*,8*E*,2′*R*)-1-*O*-β-D-glucopyranosyl-2-(2′-hydroxyhexadecanoyl)amino-4,8-octadecadiene-1,3-diol (**1a**), its 9-methyl homologue (**1b**), and the (8*Z*)-isomer (**1c**). (Fig. 1) Several syntheses of **1a**, **1b**, **1c** as well as their sphingadienine moiety **2a**, **2b**, **2c** have been reported[10] due to the scarcity in natural sources. The interesting properties of **1** prompted us to investigate their synthesis, and we reported the synthesis of **1a** and **1c** using D-glucosamine as a chiral source of the sphingosine moiety.[11] However, the synthetic routes were rather lengthy.

In this paper, we report a more efficient approach to sphinga-4,8-dienines utilizing a diastereoselective addition of 1(*E*)-alkenyl zirconocenes to Garner's aldehyde,[12] a configurationally stable aldehyde prepared from L-serine in four steps.

2. Results and discussion

Recently we reported[13] a highly diastereoselective synthesis of both D-*erythro*- and L-*threo*-sphingosines from Garner's aldehyde with 1-alkenyl nucleophiles prepared via hydrozirconation[14] of terminal alkynes. As shown in Scheme 1, hydrozirconation of 1-pentadecyne (**3**) with zirconocene chloride hydride (Schwartz reagent)[15] (**4**) afforded 1(*E*)-pentadecenyl-zirconocene chloride (**5**-Zr) in a regio- and stereo-specific manner. Addition of **5**-Zr to Garner's aldehyde (**6**) in the presence of $ZnBr_2$ in THF[16] gave the

Keywords: Glycolipids; Sphingadienine; Garner's aldehyde; Hydrozirconation; Selective synthesis.
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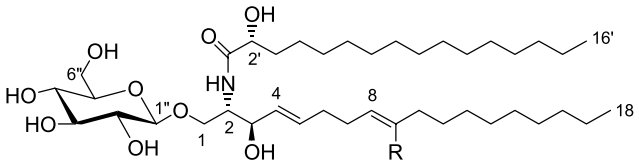
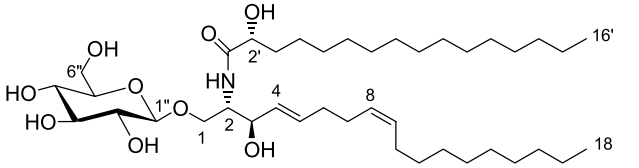
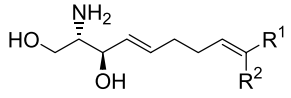


Glucocerebrosides **1a** (R = H)
1b (R = CH_3)



1c



2a (R^1 = *n*-C_9H_{19}, R^2 = H)
2b (R^1 = *n*-C_9H_{19}, R^2 = CH_3)
2c (R^1 = H, R^2 = *n*-C_9H_{19})

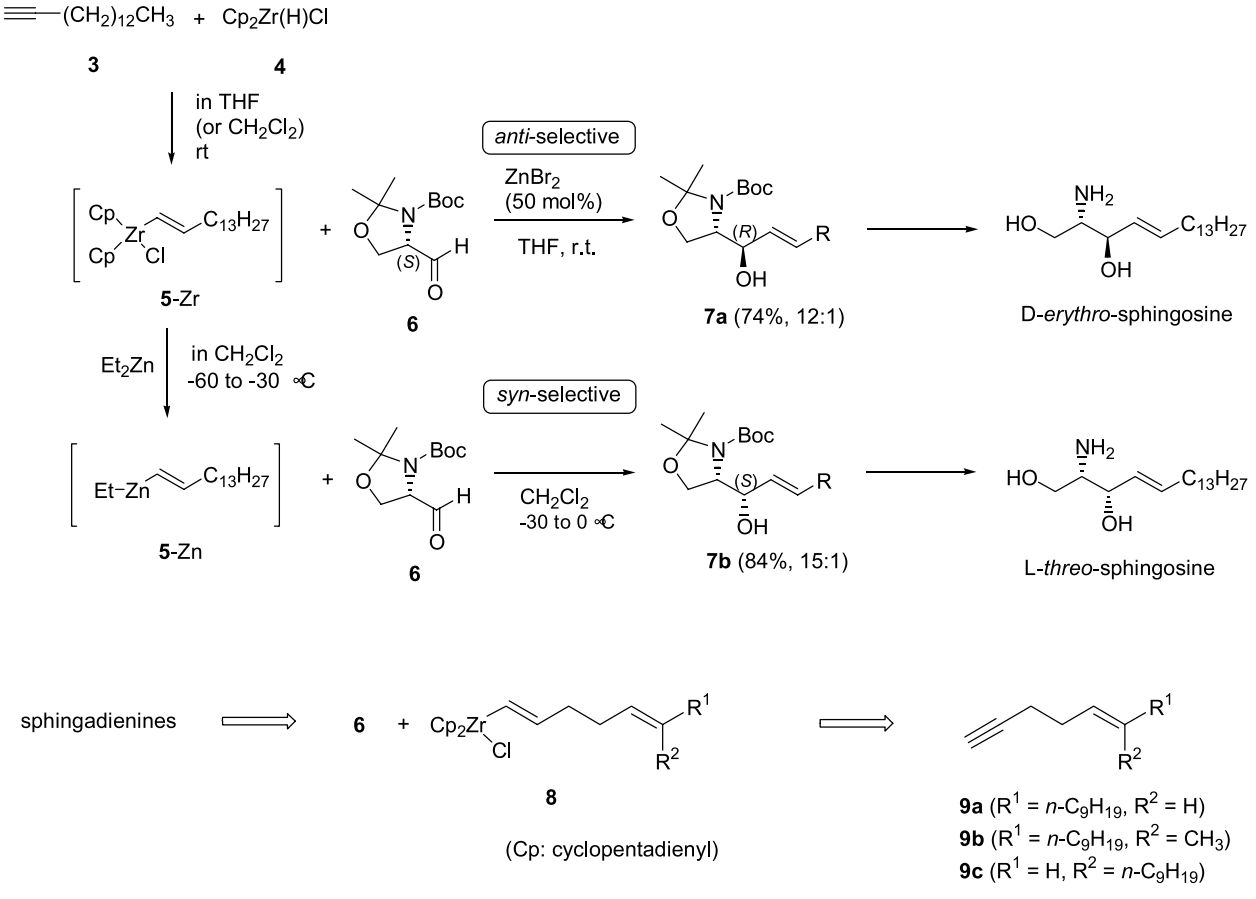
Figure 1.

natural *erythro*-(*anti*-) isomer (**7a**) with high diastereoselectivity (*anti*/*syn* = 12:1), whereas addition of 1-pentadecenyl-ethyl-zinc (**5**-Zn), prepared from **5**-Zr and Et_2Zn[17] in CH_2Cl_2, gave the unnatural *threo*-(*syn*-) isomer (**7b**) predominantly (*anti*/*syn* = 1:15).

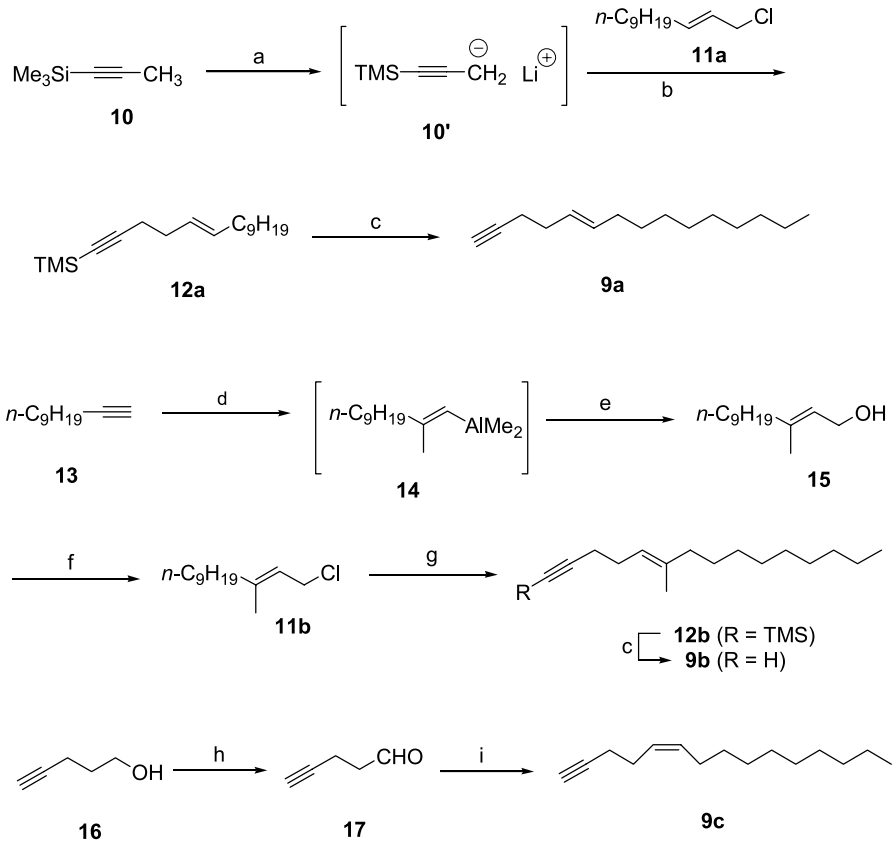
We planned to apply this protocol to the synthesis of sphingadienines. *N*,*O*-Protected C_{18}-sphingadienines should be prepared from **6** and pentadeca-1,5-dienyl-zirconocene derivatives **8**, which would be prepared by hydrozirconation of pentadec-5-en-1-ynes **9a**,**b**,**c**.

At the outset, we examined stereocontrolled syntheses of (*E*)-pentadec-5-en-1-yne **9a**, (*E*)-6-methylpentadec-5-en-1-yne **9b**, and (*Z*)-pentadec-5-en-1-yne **9c**. Although these en-ynes are known compounds,[10c,10h] we explored efficient methods of preparation. After several attempts, the following routes proved to be most suitable (Scheme 2). For **9a**, lithiated 1-trimethylsilyl (TMS)-1-propyne **10**′ was reacted with (*E*)-dodec-2-enyl chloride **11a**[11] according to the protocol of Lipshutz et al.[18] to give 1-TMS-pentadec-5-en-1-yne **12a** with a regio-controlled manner. The TMS group was removed with Bu_4NF to give **9a** in high yield.

For the synthesis of trisubstituted (*E*)-olefinic part of **9b**, Negishi's carboalumination protocol[19] was successfully applied. Thus, zirconocene dichloride-catalyzed methylalumination of 1-undecyne **13** with Me_3Al gave 2-methylundec-1-enyl-dimethyl-alane **14**, which was treated in situ with paraformaldehyde to afford (*E*)-3-methyldodec-2-en-1-ol



Scheme 1.



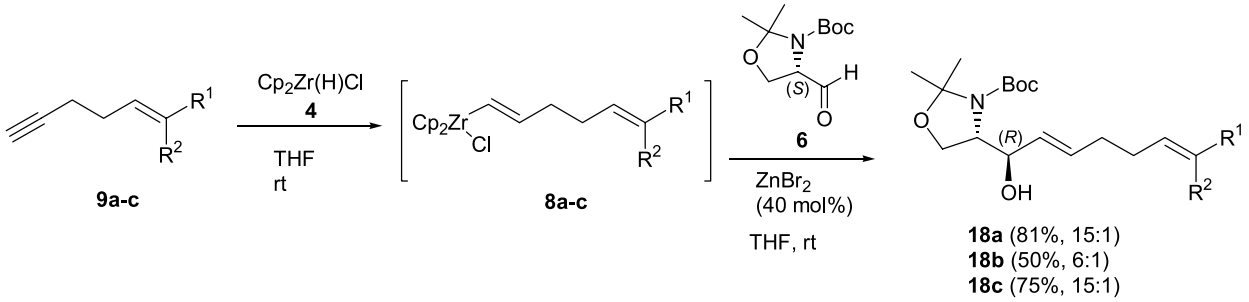
Scheme 2. Synthesis of pentadec-5-en-1-ynes. Reagents and conditions: (a) *n*-BuLi, THF, −40 to −20 °C; (b) in THF, −40 °C, 1 h (90%); (c) Bu_4NF, THF, 5 °C, 1 h (**9a**: 88%, **9b**: 96%); (d) Me_3Al, Cp_2ZrCl_2 (0.5 equiv), CH_2Cl_2, 5 °C to rt, 1 h; (e) $(HCHO)_n$, CH_2Cl_2, 5 °C to rt, 12 h (87%); (f) NCS, Ph_3P, THF, −20 °C; (g) **10′**, THF, −70–0 °C (77% from **15**); (h) PCC, Celite, CH_2Cl_2 (Ref. 20); (i) *n*-$C_{10}H_{21}PPh_3Br$, NaHMDS, THF, then **17**, −40–0 °C (55%).

15 in good yield with excellent stereoselectivity: no (*Z*)-isomer was detected by ^1H and ^{13}C NMR.[20] The alcohol was converted to the chloride by treatment with *N*-chlorosuccinimide (NCS) and Ph_3P. However, (*E*)-3-methyldodec-2-enyl chloride **11b** was found much less stable than **11a** and purification was difficult. Thus, the crude **11b** was treated with lithiated TMS-propyne **10′** to give (*E*)-1-TMS-6-methylpentadec-5-en-1-yne **12b** in 78% yield from **15**. Removal of the TMS group afforded **9b** in 64% overall yield from **13**.

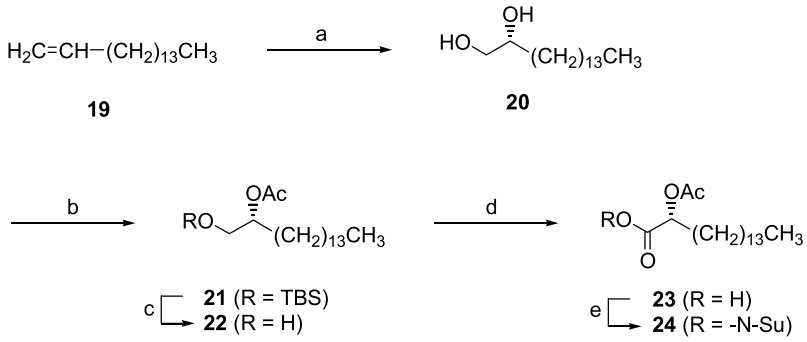
(*Z*)-Pentadec-5-en-1-yne **9c** was prepared in a straightforward manner via Wittig olefination. Thus, 4-pentyn-1-ol **16** was oxidized with pyridinium chlorochromate (PCC) to give 4-pentynal **17**,[21] which was treated with decylidenetriphenylphosphorane to give **9c** with high selectivity (*Z*/*E*≥12:1) in fair yield.

With the required terminal alkynes **9a**,**b**,**c** in hand, we examined one-pot hydrozirconation–addition reactions with Garner's aldehyde **6**. As shown in Scheme 3, hydrozirconation of **9a** with Schwartz reagent in THF gave (*E*,*E*)-pentadeca-1,5-dienyl-zirconocene chloride **8a**, which was treated in situ with **6** to afford protected (*E*,*E*)-sphingadienine derivative **18a** with high stereoselectivity (*anti*/*syn*=15:1). In a similar manner, (*E*,*Z*)-sphingadienine **18c** was prepared from **9c**. In the case of methyl-branched en-yne **9b**, the yield and the *anti*/*syn* ratio of the product **18b** were lower. Since the *anti*-isomer is slightly less polar than the *syn* on TLC, the minor *syn*-isomer can be removed by careful chromatography. These results confirmed that terminal alkynes are more reactive than internal alkenes toward hydrozirconation.

Next, preparation of (*R*)-2-hydroxypalmitic acid was



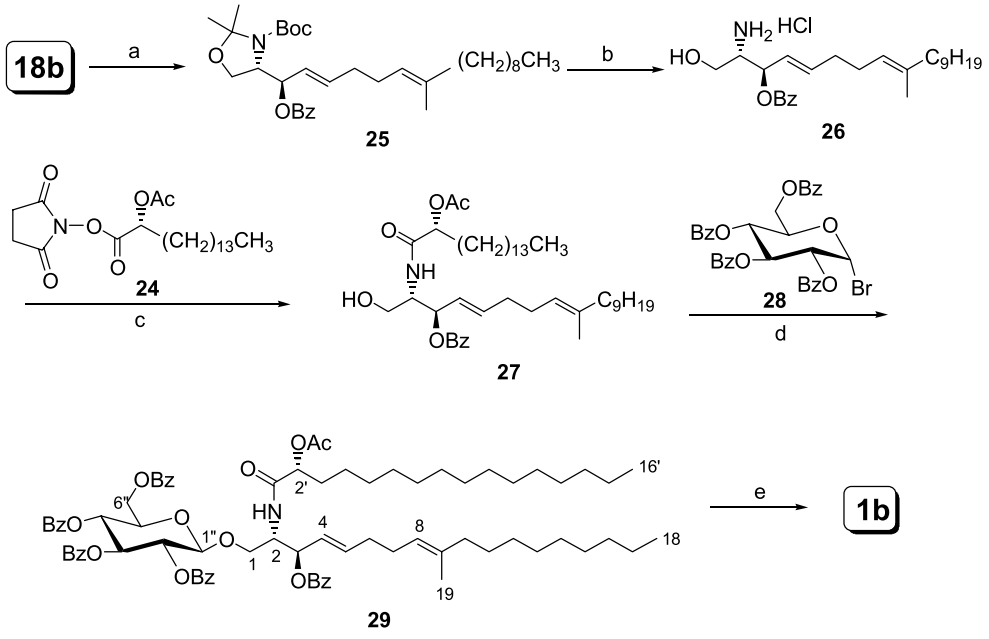
Scheme 3. One-pot hydrozirconation–addition reactions.



Scheme 4. Synthesis of (*R*)-acetoxypalmitic acid. Reagents and conditions: (a) AD-mix-β, *t*-BuOH–H_2O (Ref. 23b); (b) *t*-$BuMe_2SiCl$, pyridine, CH_2Cl_2, 5 °C to rt, 4 h, then Ac_2O, 5 °C to rt, 12 h (78%); (c) 1 M HCl, THF, rt, 5 h (83%); (d) $RuCl_3$ (cat), $NaIO_4$, CCl_4–CH_3CN–H_2O (2:2:3), rt, 2 h (83%); (e) *N*-hydroxysuccinimide, DCC, THF, 5 °C to rt, 5 h (97%).

examined. Previously we prepared a ceramide bearing (*R*)-acetoxypalmitic acid by simultaneous optical resolution and carboxyl-activation of racemic 2-acetoxypalmitic acid with (4*R*,5*S*)-4-methyl-5-phenyl-1,3-oxazolidine-2-thione derived from (−)-norephedrin.[22] However, racemic 2-hydroxypalmitic acid is not cheap and this method necessarily produces the other unwanted diastereomer. We explored a novel synthetic route via asymmetric dihydroxylation[23] (Scheme 4). According to the literature,[24] 1-hexadecene **19** was treated with AD-mix-β in *t*-BuOH–H_2O to give (*R*)-hexadecane-1,2-diol **20** in 64% yield with 85% ee, which was recrystallized from AcOEt to afford optically pure **20**. Selective protection of primary hydroxy group with *t*-butyldimethylsilyl (TBS) group followed by O-acetylation gave **21**. Acidic desilylation followed by oxidation of the primary alcohol with $RuCl_3$ and $NaIO_4$[25] afforded 2(*R*)-acetoxypalmitic acid **23**, whose optical rotation {$[\alpha]_D^{24}$+ 10.1 (*c* 1.0, $CHCl_3$)} agreed well with that reported {lit.[10a] $[\alpha]_D^{24}$+10.6 (*c* 0.52, $CHCl_3$)}.

With sphingadienine derivatives **18a–c** and 2(*R*)-acetoxypalmitic acid **23** in hand, we were in a position to complete the synthesis of glycolipid. Since **1a** and **1c** had been synthesized,[11] we focused on the synthesis of **1b**. For glycosylation of ceramide derivatives, protection of the C3–OH group is necessary. As shown in Scheme 5, **18b** was treated with benzoic acid and *N*,*N*′-dicyclohexylcarbodiimide (DCC) in the presence of 4-(dimethylamino)pyridine (DMAP) to give the 3-*O*-benzoate **25**. Removal of both the isopropylidene and Boc groups required harder conditions (aq HCl, 70 °C, 4 h) than usual, presumably due to the adjacent benzoyloxy group. This deprotection was also performed with TMSBr in CH_2Cl_2 at rt.[26] However, it should be noted that the latter method caused considerable isomerization of the trisubstituted double bond.[27] Attempts for the direct coupling of the crude amine HCl salt **26** and the acid **23** by DCC gave variable results. Condensation of **26** with active ester derivatives was then examined, and it was found that the succinimide ester **24** prepared from **23** by a standard manner reacted smoothly with **26** in the presence of Et_3N to furnish 3-*O*-benzoyl-ceramide **27**. Glycosylation with tetra-*O*-benzoylglucopyranosyl bromide **28** using silver triflate as a promoter afforded the desired β-glucoside **29** in 83% yield. Finally, **29** was deacylated with NaOMe in



Scheme 5. Synthesis of glycolipid. Reagents and conditions: (a) $PhCO_2H$, DCC, DMAP (cat), CH_2Cl_2, rt, 24 h (97%); (b) 2 M HCl, EtOH, 70 °C, 4 h; (c) Et_3N, THF, rt, 20 h (70% from **25**); (d) AgOTf, MS4A, CH_2Cl_2, −20–0 °C, 2 h (83%); (e) NaOMe, MeOH–THF, 5 °C, 2 h (86%).

methanol–THF to afford the glucocerebroside **1b**. The structure of **1b** was confirmed by the spectral data (^{1}H and ^{13}C NMR, FAB-MS), which were in good agreement with those reported.[2e,3,8,9,10a,10g]

3. Conclusion

We have developed efficient syntheses of sphinga-4,8-dienine derivatives from L-serine and a glucocerebroside containing 9-methyl-sphinga-(4*E*,8*E*)-dienine with 2(*R*)-hydroxypalmitoyl group. The synthesis has demonstrated the versatility of the one-pot preparation of (*E*)-allylic alcohols from terminal alkynes via hydro- or methylmetalation followed by addition to aldehydes: both the stereochemistry at C3 and the alkene geometries in sphingadienines have been successfully controlled.

4. Experimental

4.1. General

Air-/moisture-sensitive reactions were performed under a dry argon atmosphere. Melting points were determined with a Yanaco melting point apparatus MP-500D. Optical rotations were measured with a JASCO DIP-1000 polarimeter and $[\alpha]_D$ values are given in 10^{-1} degrees cm^2 g^{-1}. ^{1}H NMR spectra were recorded at 270 MHz on a JEOL JNM-GSX-270 spectrometer, and chemical shifts (δ) are reported in ppm relative to internal tetramethylsilane ($\delta=0.00$) or residual proton signal(s) of the solvent ($\delta=7.15$ for C_6D_6, $\delta=7.19$ for C_5D_5N). ^{13}C NMR spectra were recorded at 67.8 MHz and chemical shifts (δ) are reported in ppm relative to $CDCl_3$ ($\delta=77.0$), C_6D_6 ($\delta=128.0$), or C_5D_5N ($\delta=123.5$). Elemental analyses were performed in the analytical section in this institute (AIST). High-resolution mass (HRMS) and fast atom bombardment mass (FAB-MS) spectra were obtained on a Hitachi M80B and a JEOL MS600H mass spectrometer, respectively. Routine monitoring of reactions was carried out using Merck silica gel 60F$_{254}$ TLC plates. Column chromatography was performed with indicated solvents on silica gel (Kanto Chemicals, neutral, 100–210 μm, or Wakogel C-300, 45–75 μm). Organic solutions after extractive work-up were dried over anhydrous Na_2SO_4, and filtered through a cotton plug.

4.2. Synthesis of pentadec-5-en-1-ynes

4.2.1. (*E*)-1-Trimethylsilyl-pentadec-5-en-1-yne (12a). *n*-BuLi (4.5 mL, 1.5 M in hexane, 6.7 mmol) was added dropwise to dry THF (15 mL) at −40 °C. After a few minutes, a solution of 1-TMS-1-propyne **10** (750 mg, 6.7 mmol) in THF (5 mL) was added dropwise over 15 min, and the mixture was stirred for 15 min at this temperature and then for 20 min at −20 °C before being re-cooled to −40 °C. (*E*)-2-Dodecenyl chloride **11a** (700 mg, 3.4 mmol) in THF (5 mL) was added over 15 min, and the mixture was stirred for 1 h at −40 °C. The reaction was quenched by addition of aq NH_4Cl (1 mL), and the mixture was diluted with hexane (10 mL) and water (5 mL), and allowed to warm to 0 °C. The layers were separated, and the organic layer was successively washed with brine. The aqueous phase was extracted with hexane (2×10 mL), and the combined organic layers were dried and concentrated. The residue was purified by silica gel chromatography (eluting with hexane) to afford **12a** (865 mg, 90%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9H), 0.88 (t, $J=6.7$ Hz, 3H), 1.26 (s, 12H), 1.33 (m, 2H), 1.98 (q, $J=6.5$ Hz, 2H), 2.23 (m, 4H), 5.40 (dd, $J=5.0$, 15.4 Hz, 1H), 5.49 (dd, $J=5.6$, 15.1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.4, 22.7, 29.2, 29.4, 29.5, 29.6, 31.8, 31.9, 32.5, 84.6, 107.1, 128.0, 132.0; HRMS (EI) calcd for $C_{18}H_{34}Si$ (M^+) 278.2430, found 278.2423.

4.2.2. (*E*)-Pentadec-5-en-1-yne (9a). To an ice-cooled solution of **12a** (560 mg, 2.0 mmol) in THF (10 mL) was added a 1.0 M solution of Bu_4NF in THF (2.5 mL, 2.5 mmol), and the mixture was stirred for 1 h. The mixture was diluted with hexane and H_2O, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers were extracted with hexane. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography eluting with hexane to give **9a** (362 mg, 88%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, $J=6.7$ Hz, 3H), 1.26 (s, 12H), 1.33 (m, 2H), 1.95 (t, $J=2.4$ Hz), 1.99 (q, $J=6.7$ Hz, 2H), 2.22 (m, 4H), 5.42 (dd, $J=5.3$, 15.4 Hz, 1H), 5.51 (dd, $J=5.6$, 15.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.9, 22.7, 29.1, 29.3, 29.47, 29.52, 29.6, 31.6, 31.9, 32.5, 39.5, 68.3, 84.2, 127.9, 132.1; HRMS (EI) calcd for $C_{15}H_{26}$ (M^+) 206.2035, found 206.2090.

4.2.3. (*E*)-3-Methyldodec-2-en-1-ol (15). A 1.0 M solution of Me_3Al in hexane (4.0 mL, 4.0 mmol) was added to Cp_2ZrCl_2 (300 mg, 1.0 mmol) in a cooled flask with stirring, and the mixture was stirred for 10 min at rt. Most of the hexane was removed in vacuo and CH_2Cl_2 (4 mL) was added, and the mixture was cooled by an ice-water bath. To the resulting pale-yellow solution was added a solution of 1-undecyne **13** (308 mg, 2.0 mmol) in CH_2Cl_2 (1.0 mL), and the mixture was stirred for 1 h at rt. To this solution in an ice-water bath was added solid paraformaldehyde (125 mg, 4.0 mmol for the monomer) in 4 portions over 10 min, and stirring was continued while the mixture was allowed to warm to rt. The reaction mixture was diluted with AcOEt (15 mL) and aq potassium sodium tartrate (15 mL), and stirred for 10 min. The resulting suspension was filtered through a pad of Celite and washed thoroughly with AcOEt (10 mL). The combined filtrate and washings were transferred into a separatory funnel, and the layers were separated. The organic layer was then washed with brine, and the combined aqueous layers were extracted with AcOEt (2×20 mL). The combined organic extracts were dried and concentrated. The residue (445 mg) was purified by column chromatography eluting with hexane/AcOEt 6:1→5:1 to give **15** (345 mg, 87%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.87 (t, $J=6.5$ Hz, 3H), 1.26 (s, 12H), 1.39 (m, 2H), 1.50 (br, 1H), 1.65 (s, 3H), 2.04 (t, $J=7.4$ Hz, 2H), 4.13 (d, $J=6.8$ Hz, 2H), 5.39 (t, $J=6.7$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 16.1, 22.6, 27.7, 29.3, 29.50, 29.53, 31.9, 39.5, 59.3, 123.1, 140.1; HRMS (EI) calcd for $C_{13}H_{26}O$ (M^+) 198.1984, found 198.1986.

4.2.4. (*E*)-1-Trimethylsilyl-6-methyl-pentadec-5-en-1-yne (12b). To a stirred solution of methyldodecenol **15** (200 mg, 1.0 mmol) and Ph_3P (368 mg, 1.4 mmol) in THF (5 mL) was added *N*-chlorosuccinimide (188 mg, 1.4 mmol) in four portions at −30 °C. The resulting white suspension was allowed to warm to −20 °C, and diluted with hexane. The mixture was filtered and washed with hexane. The combined filtrate and washings were concentrated, and the residue was triturated with hexane (1 mL). The mixture was filtered and washed with a small amount of hexane. Removal of the solvent gave crude chloride **11b** (220 mg) as a colorless oil, which was used in the next step without further purification. In another flask, *n*-BuLi (1.4 mL, 1.5 M in hexane, 2.1 mmol) was added dropwise to dry THF (5 mL) at −50 °C. After a few minutes, a solution of 1-TMS-1-propyne **10** (225 mg, 2.0 mmol) in THF (1 mL) was added dropwise over 5 min, and the mixture was stirred for 20 min at this temperature and then for 20 min at −20 °C before being re-cooled to −70 °C. The crude (*E*)-3-methyl-2-dodecenyl chloride **11b** (220 mg) in THF (1.8 mL) was added over 10 min, and the mixture was allowed to warm to rt overnight. The reaction was quenched by addition of aq NH_4Cl (0.5 mL), and the mixture was purified as described for **12a** to give **12b** (225 mg, 77%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.14 (s, 9H), 0.88 (t, J=6.6 Hz, 3H), 1.26 (s, 12H), 1.37 (m, 2H), 1.60 (s, 3H), 1.97 (t, J=7.2 Hz, 2H), 2.22 (m, 4H), 5.14 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 0.13, 14.1, 16.0, 20.4, 22.7, 27.3, 27.9, 29.3, 29.4, 29.57, 29.60, 31.9, 39.7, 84.2, 107.5, 122.3, 137.0; HRMS (EI) calcd for $C_{19}H_{36}Si$ (M^+) 292.2586, found 292.2561.

4.2.5. (*E*)-6-Methyl-pentadec-5-en-1-yne (9b). This compound was prepared as described for **9a**, using **12b** (294 mg, 1.0 mmol) and Bu_4NF (1.2 mmol) in THF (6 mL). Chromatographic purification gave **9b** (212 mg, 96%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.7 Hz, 3H), 1.26 (s, 12H), 1.37 (m, 2H), 1.61 (s, 3H), 1.93 (t, J=2.4 Hz), 1.97 (t, J=7.1 Hz, 2H), 2.21 (m, 4H), 5.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.0, 19.0, 22.7, 27.2, 27.9, 29.3, 29.4, 29.59, 29.64, 31.9, 39.7, 68.1, 84.6, 122.3, 137.2; HRMS (EI) calcd for $C_{16}H_{28}$ (M^+) 220.2191, found 220.2149.

4.2.6. (*Z*)-Pentadec-5-en-1-yne (9c). To a stirred solution of decyltriphenylphosphonium bromide (1.50 g, 3.1 mmol) in THF (10 mL) at −40 °C was added sodium bis(trimethylsilyl)amide (600 mg, 3.2 mmol) in THF (3.5 mL) over 10 min. The resulting red-orange solution was allowed to warm to −20 °C, and was then cooled to −40 °C. To this solution was added a solution of 4-pentynal **17** (170 mg, 2.0 mmol) in THF (2.5 mL) over 10 min, and the mixture was allowed to warm to 0 °C. The resulting yellow solution was diluted with hexane (15 mL), and treated with saturated aq NH_4Cl (2 mL) and H_2O (10 mL). The layers were separated and the aqueous phase was extracted with hexane (2×15 mL). The organic layer was successively washed with H_2O and brine, dried, and concentrated. The residue was re-dissolved in hexane (3 mL) and triturated. The insoluble material was filtered off and washed with hexane. The filtrate was concentrated and the residual oil was chromatographed on a column eluting with hexane to give **9c** (226 mg, 55%) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.6 Hz, 3H), 1.27 (s, 14H), 1.95 (t, J=2.4 Hz), 2.04 (q, J=6.6 Hz, 2H), 2.25 (m, 4H), 5.39 (dd, J=6.3, 11.0 Hz, 1H), 5.48 (dd, J=6.6, 11.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 18.8, 22.7, 26.4, 27.3, 29.30, 29.32, 29.5, 29.6, 29.7, 31.9, 68.2, 84.2, 127.3, 131.7; HRMS (EI) calcd for $C_{15}H_{26}$ (M^+) 206.2035, found 206.2016.

4.3. General procedure for the synthesis of 18a–c from 9a–c

To a stirred suspension of $Cp_2Zr(H)Cl$ **4** (245 mg, 0.9 mmol) in THF (0.8 mL) on an ice-water bath was added a solution of pentadec-5-en-1-yne (**9a**, **9b**, or **9c**) (0.9 mmol) in THF (0.8 mL). The cooling bath was removed and the mixture was stirred at rt for 1 h, and then cooled to 0 °C. To the resulting yellow solution was added a solution of Garner's aldehyde **6** (116 mg, 0.5 mmol) in THF (1.0 mL) followed by $ZnBr_2$ (45 mg, 0.2 mmol), and the mixture was stirred for 30 min at 0 °C and then allowed to warm to rt. After being stirred for 16 h, the mixture was diluted with AcOEt (10 mL) and aq potassium sodium tartrate (10 mL), and stirred for 10 min. The resulting suspension was filtered through a pad of Celite and washed thoroughly with AcOEt (10 mL). The combined filtrate and washings were successively washed with H_2O and brine. The aqueous phase was extracted with AcOEt (2×20 mL), and the combined organic layers were dried over Na_2SO_4. After filtration and removal of the solvent, the residue was dissolved in THF (3 mL) and MeOH (1 mL), and treated with $NaBH_4$ (10 mg, 0.25 mmol). After 30 min, AcOH (20 mg, 0.33 mmol) was added, and the mixture was concentrated and purified by column chromatography (eluting with hexane/AcOEt mixture 7:1→5:1→4:1) to afford **18a–c**. The *anti*/*syn*-ratio was determined by the ^{1}H NMR integration of the diastereotopic (C-1′) protons [*anti* δ ca. 4.3 (br s) vs *syn* δ ca. 4.4 (t, J=7 Hz)].

4.3.1. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*,6*E*)-1-hydroxyhexadeca-2,6-dienyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (18a). This compound was obtained (177 mg, 81%) as a colorless oil containing a small amount of the *syn*-isomer (15:1). $[\alpha]_D^{25}$ −23.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 75 °C) δ 0.89 (t, J=6.7 Hz, 3H), 1.29 (s-like, 12H), 1.34 (m, 2H), 1.39 (s, 9H), 1.46 (s, 3H), 1.62 (s, 3H), 2.01 (m, 2H), 2.10 (m, 4H), 3.68 (dd, J=6.7, 8.9 Hz, 1H), 3.81 (dd, J=6.3, 9.0 Hz, 1H), 3.94 (m, 1H), 4.31 (m, 1H), 5.46 (m, 2H), 5.53 (dd, J=5.9, 15.1 Hz, 1H), 5.77 (dtd, J=1.5, 6.1, 15.4 Hz, 1H); ^{13}C NMR (C_6D_6, 75 °C) δ 14.1, 23.0, 24.4, 26.8, 28.5, 29.6, 29.7, 29.90, 29.95, 30.03, 32.2, 32.7, 32.90, 32.94, 62.7, 64.9, 73.6, 80.1, 94.6, 129.9, 130.6, 131.3, 132.0; HRMS (EI) calcd for $C_{22}H_{38}NO_3$ ($M-t$-BuO)$^+$ 364.2852, found 364.2847.

4.3.2. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*,6*E*)-1-hydroxy-7-methyl-hexadeca-2,6-dienyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (18b). This compound was obtained (113 mg, 50%) as a colorless oil containing a small amount of the *syn*-isomer (6:1). $[\alpha]_D^{24}$ −29.5 (*c* 1.1, $CHCl_3$); ^{1}H NMR (C_6D_6, 75 °C) δ 0.89 (t, J=6.7 Hz, 3H), 1.30 (s-like, 14H), 1.38 (s, 9H), 1.43 (s, 3H), 1.58 (s, 3H), 1.62 (s, 3H), 2.01 (t, J=7.3 Hz, 2H), 2.10 (m, 4H), 3.68 (dd, J=6.8, 9.0 Hz, 1H), 3.82 (br d, J=7.8 Hz, 1H), 3.94 (m, 1H), 4.31 (m, 1H), 5.22 (m, 1H), 5.54 (dd, J=5.9, 15.4 Hz, 1H), 5.79 (td, J=6.5,

15.4 Hz, 1H); ^{13}C NMR (C_6D_6, 75 °C) δ 14.1, 16.1, 23.0, 24.4, 26.8, 28.2, 28.45, 28.50, 29.69, 29.73, 29.95, 29.98, 32.2, 33.0, 40.1, 62.7, 64.9, 73.7, 80.1, 94.6, 124.2, 130.4, 132.2, 135.9, 153.4; HRMS (EI) calcd for $C_{27}H_{50}NO_4$ $(M+H)^+$ 452.3740, found 452.3772.

4.3.3. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*,6*Z*)-1-hydroxyhexadeca-2,6-dienyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (18c). This compound was obtained (164 mg, 75%) as a colorless oil containing a small amount of the *syn*-isomer (15:1). $[\alpha]_D^{25}$ −29.6 (*c* 2.0, $CHCl_3$); ^{1}H NMR (C_6D_6, 75 °C) δ 0.89 (t, J=6.7 Hz, 3H), 1.29 (s-like, 12H), 1.33 (m, 2H), 1.39 (s, 9H), 1.45 (s, 3H), 1.62 (s, 3H), 2.10 (m, 6H), 3.67 (dd, J=6.6, 9.0 Hz, 1H), 3.80 (dd, J=3.1, 8.9 Hz, 1H), 3.94 (m, 1H), 4.31 (m, 1H), 5.43 (m, 2H), 5.54 (tdd, J=1, 5.9, 15.4 Hz, 1H), 5.77 (dtd, J=1.2, 6.3, 15.4 Hz, 1H); ^{13}C NMR (C_6D_6, 75 °C) δ 14.1, 23.0, 24.5, 26.8, 27.5, 27.7, 28.5, 29.67, 29.69, 29.9, 30.1, 32.2, 32.9, 62.8, 64.9, 73.6, 80.1, 94.6, 129.3, 130.66, 130.72, 131.9; HRMS (EI) calcd for $C_{26}H_{48}NO_4$ $(M+H)^+$ 438.3583, found 438.3485.

4.4. Synthesis of palmitic acid derivatives

4.4.1. (*R*)-Hexadecane-1,2-diol (20). This compound was prepared according to Ref. 19b as a colorless solid. Mp 85–86 °C. $[\alpha]_D^{24}$ +4.3 (*c* 3.0, $CHCl_3$/MeOH 1:1) [lit.[19b] mp 83.2–84.0 °C; $[\alpha]_D^{25}$ +4.12 (*c* 2.7, $CHCl_3$/MeOH 1:1)].

4.4.2. (*R*)-1-*tert*-Butyldimethylsilyloxy-2-hexadecyl acetate (21). To an ice-cooled suspension of diol **20** (260 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) and pyridine (0.8 mL) was added a solution of *t*-butyldimethylchlorosilane (200 mg, 1.33 mmol) in CH_2Cl_2 (1 mL), and the mixture was allowed to stir at rt for 4 h. The reaction mixture was re-cooled by the ice-water bath and acetic anhydride (0.5 mL) was added dropwise, and the mixture was allowed to warm to rt overnight. The mixture was treated with MeOH (0.1 mL), and then diluted with hexane and H_2O. After extractive work-up, the organic layer was dried and concentrated. The residue was purified by column chromatography (eluting with hexane/AcOEt mixture 19:1) to give silyl-acetate **21** (325 mg, 78%) as a colorless oil. $[\alpha]_D^{25}$ +5.8 (*c* 1.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 6H), 0.87 (t, J=6.6 Hz, 3H), 0.88 (s, 9H), 1.25 (s, 24H), 1.55 (m, 2H), 2.04 (s, 3H), 3.62 (d, J=5.1 Hz), 4.88 (dq, J=7.5, 5.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ −5.4 (2C), 14.1, 18.2, 21.2, 22.7, 25.2, 25.8 (3C), 29.3, 29.48, 29.52, 29.55, 29.64, 29.65, 29.68, 30.5, 31.9, 64.3, 74.7, 170.7; HRMS (EI) calcd for $C_{24}H_{51}O_3Si$ $(M+H)^+$ 415.3607, found 415.3656.

4.4.3. (*R*)-1-Hydroxy-2-hexadecyl acetate (22). To a solution of **21** (208 mg, 0.5 mmol) in THF (4 mL) was added 1.0 M HCl aq (0.6 mL, 0.6 mmol), and the mixture was stirred at rt for 5 h. $NaHCO_3$ (50 mg, 0.6 mmol) was added and the mixture was diluted with AcOEt and H_2O, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers were extracted with AcOEt. The combined organic extracts were dried and concentrated to give a residue, which was purified by chromatography eluting with hexane/AcOEt 4:1→3:1 to give **22** (124 mg, 83%) as a colorless solid. Mp 38–40 °C. $[\alpha]_D^{25}$ −0.1 (*c* 3.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.6 Hz, 3H), 1.25 (s, 24H), 1.57 (m, 2H), 1.92 (br, 1H), 2.08 (s, 3H), 3.61 (dd, J=6.1, 12.0 Hz, 1H), 3.71 (dd, J=3.2, 12.0 Hz, 1H), 4.90 (dq, J=6.4, 3.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 21.2, 22.7, 25.3, 29.3, 29.4, 29.5, 29.60, 29.63, 29.65, 30.5, 31.9, 64.8, 75.7, 171.5. Anal. Calcd for $C_{18}H_{36}O_3$: C, 71.95; H, 12.08. Found: C, 72.10; H, 12.01.

4.4.4. (*R*)-2-Acetoxy-hexadecanoic acid (23). To a vigorously stirred mixture of alcohol **22** (152 mg, 0.50 mmol) in CCl_4 (1 mL)–CH_3CN (1 mL)–H_2O (1.5 mL) at rt was added $NaIO_4$ (325 mg, 1.5 mmol) and then $RuCl_3\cdot H_2O$ (5 mg, 0.02 mmol). The mixture was stirred for 2 h at rt, and then diluted with AcOEt and H_2O, and the layers were separated. The organic layer was washed with brine, and the combined aqueous layers were extracted with AcOEt. The combined organic extracts were dried and concentrated. The residual dark-brown oil was purified by chromatography eluting with hexane/AcOEt 2:1, then with heptane/AcOEt 2:1 with 1% AcOH to give **23** (130 mg, 83%) as a colorless solid. The analytical sample was recrystallized from hexane. Mp 59–61 °C. $[\alpha]_D^{25}$ +10.7 (*c* 1.0, $CHCl_3$) [lit.[9b] mp 61–62 °C; $[\alpha]_D^{22}$ +10.6 (*c* 0.52, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.6 Hz, 3H), 1.26 (s, 22H), 1.42 (m, 2H), 1.86 (m, 2H), 2.14 (s, 3H), 5.00 (t, J=6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.5, 22.7, 25.1, 29.1, 29.32, 29.34, 29.5, 29.59, 29.63, 29.66, 30.9, 31.9, 71.9, 170.6, 176.1. Anal. Calcd for $C_{18}H_{34}O_4$: C, 68.75; H, 10.90. Found: C, 68.73; H, 10.73.

4.4.5. (*R*)-2-Acetoxy-hexadecanoic acid *N*-hydroxysuccinimide ester (24). To an ice-cooled solution of **23** (98 mg, 0.31 mmol) and *N*-hydroxysuccinimide (42 mg, 0.36 mmol) in THF (2 mL) was added DCC (70 mg, 0.34 mmol), and the mixture was stirred at 5 °C for 1 h and at rt for 5 h. To the reaction mixture was added H_2O (20 mg), stirred for 1 h, and then diluted with hexane (5 mL). Dicyclohexylurea formed was filtered off and washed with hexane/AcOEt (10:1, 10 mL). The filtrate was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography (eluting with hexane/AcOEt mixture 3:1→2:1) to give **24** (120 mg, 97%) as a colorless solid. Mp 70–72 °C. $[\alpha]_D^{24}$ +21.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J=6.6 Hz, 3H), 1.26 (s, 20H), 1.31 (m, 2H), 1.49 (m, 2H), 1.99 (m, 2H), 2.16 (s, 3H), 2.84 (s, 4H), 5.31 (t, J=6.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.3, 22.7, 24.6, 25.6, 29.0, 29.27, 29.32, 29.5, 29.56, 29.62, 29.7, 31.3, 31.9, 70.3, 166.1, 168.4, 170.0.

4.5. Synthesis of glycolipid

4.5.1. *tert*-Butyl (4*S*)-4-[(1*R*,2*E*,6*E*)-1-benzoyloxy-7-methylhexadeca-2,6-dienyl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (25). Prior to reaction, the compound **18b** prepared above (6:1 mixture) was purified by flash chromatography eluting with hexane/AcOEt 6:1 to give purer **18b** (≥20:1). To an ice-cooled solution of **18b** (50 mg, 0.11 mmol), benzoic acid (24 mg, 0.20 mmol), DMAP (4 mg, 0.03 mmol) in CH_2Cl_2 (2 mL) was added DCC (41 mg, 0.20 mmol), and the mixture was stirred at rt for 24 h. To the reaction mixture was added MeOH (0.1 mL) dropwise, stirred for 15 min, and then diluted with hexane (5 mL). Dicyclohexylurea formed was filtered off and washed thoroughly with hexane/AcOEt (10:1, 10 mL). The filtrate was concentrated, and the residue was purified

by chromatography (eluting with hexane/AcOEt mixture 11:1→9:1) to afford **25** (60 mg, 97%) as a colorless oil. $[\alpha]_D^{25}$ −35.3 (*c* 1.2, $CHCl_3$); ^{1}H NMR (C_6D_6, 75 °C) δ 0.89 (t, *J*=6.7 Hz, 3H), 1.29 (s-like, 14H), 1.47 (s, 12H), 1.53 (s, 3H), 1.59 (s, 3H), 1.97 (m, 2H), 2.03 (m, 4H), 3.78 (dd, *J*=7.3, 8.3 Hz, 1H), 4.08 (m, 1H), 4.15 (d, *J*=8.8 Hz, 1H), 5.15 (m, 1H), 5.50 (dd, *J*=6.0, 15.3 Hz, 1H), 5.90 (td, *J*=6.6, 15.4 Hz, 1H), 6.29 (m, 1H), 7.11 (m, 3H), 8.22 (m, 2H); ^{13}C NMR (C_6D_6, 75 °C) δ 14.1, 16.1, 23.0, 24.4, 27.0, 27.8, 28.47, 28.50, 29.69, 29.74, 29.9, 30.0, 32.2, 32.9, 40.1, 60.7, 64.0, 73.3, 80.0, 123.7, 126.6, 128.5 (2C), 130.2 (2C), 131.5, 132.7, 135.1, 136.2, 152.3, 165.5; HRMS (EI) calcd for $C_{34}H_{53}NO_5$ (M^+) 555.3924, found 555.3949.

4.5.2. (2*S*,3*R*,4*E*,8*E*,2′*R*)-3-Benzoyloxy-2-(2′-acetoxyhexadecanoyl)amino-9-methyl-4,8-octadecadien-1-ol (27). To a stirred solution of benzoate **25** (40 mg, 0. 072 mmol) in EtOH (0.8 mL) was added a 2.0 M aq HCl (0.2 mL) and the mixture was stirred for 4 h at 70 °C. To this solution were added $CHCl_3$/MeOH 7:1 (10 mL) and H_2O (10 mL). The layers were separated and the aqueous phase was extracted with $CHCl_3$/MeOH 7:1 (2×10 mL). The combined organic extracts were dried and concentrated in vacuo to give crude 3-*O*-benzoyl-sphingadienine hydrochloride **26** (35 mg) as a colorless solid. This solid (35 mg) and (*R*)-acetoxypalmitate **24** (38 mg, 0.092 mmol) were dissolved in THF (1 mL). To this solution was added Et_3N (15 mg, 0.15 mmol) in THF (0.2 mL), and the mixture was stirred at rt for 20 h. The reaction mixture was diluted with AcOEt and H_2O, and extracted with AcOEt (3×10 mL). The combined organic layers were dried and concentrated to give a yellow oil, which was purified by preparative TLC with hexane/AcOEt 3:2 to give **27** (36 mg, 70%) as a colorless solid. R_f 0.27 (hexane/AcOEt 3:2); mp 56–58 °C. $[\alpha]_D^{24}$ +30.6 (*c* 0.70, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 6H), 1.25 (s-like, 38H), 1.55 (s, 3H), 1.81 (m, 2H), 1.92 (t, *J*=7.3 Hz, 2H), 2.08 (m, 4H), 2.15 (s, 3H), 2.82 (br, 1H), 3.69 (dd, *J*=3.2, 12.0 Hz, 1H), 3.76 (dd, *J*=3.7, 12.0 Hz, 1H), 4.24 (m, 1H), 5.07 (m, 1H), 5.17 (dd, *J*=4.7, 7.2 Hz, 1H), 5.60 (m, 2H), 5.90 (dt, *J*=14.4, 6.3 Hz, 1H), 6.80 (d, *J*=8.3 Hz, 1H), 7.46 (m, 2H), 7.60 (m, 1H), 8.04 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 16.0, 20.9, 22.7, 24.8, 27.2, 28.0, 29.29, 29.35, 29.41, 29.54, 29.62, 29.65, 29.69, 31.9, 32.5, 39.7, 53.5, 61.5, 74.1, 74.4, 122.8, 124.7, 128.5 (2C), 129.5, 129.8 (2C), 133.5, 136.3, 137.0, 166.6, 169.7, 170.2. Anal. Calcd for $C_{44}H_{73}NO_6$: C, 74.22; H, 10.33; N, 1.97. Found: C, 74.14; H, 10.48; N, 1.94.

4.5.3. (2*S*,3*R*,4*E*,8*E*,2′*R*)-2-(2′-Acetoxyhexadecanoyl) amino-3-*O*-benzoyl-1-*O*-(2″,3″,4″,6″-tetra-*O*-benzoyl-β-D-glucopyranosyl)-9-methyl-4,8-octadecadiene-1,3-diol (29). A solution of **27** (43 mg, 0.06 mmol), 2,3,4,6-tetra-*O*-benzoyl-α-D-glucosyl bromide **28** (68 mg, 0.10 mmol), oven-dried molecular sieves 4 Å (80 mg) in dichloromethane (2.5 mL) was stirred under argon at rt for 30 min before being cooled to −20 °C. To this suspension was added AgOTf (27 mg, 0.10 mmol) in toluene (0.5 mL), and the mixture was stirred at −20–0 °C for 2 h. The resulting suspension was diluted with AcOEt (10 mL), and the insoluble material was filtered off and washed thoroughly with AcOEt (15 mL). The filtrate was washed with aq $NaHCO_3$, H_2O, and brine (10 mL each). The combined aqueous layers were extracted with AcOEt (2×20 mL), and the organic extracts were dried and concentrated. The residue was purified by preparative TLC with hexane/AcOEt 5:2 to afford the glycoside **29** (65 mg, 83%) as a colorless solid. R_f 0.30 (hexane/AcOEt 5:2); $[\alpha]_D^{24}$ +16.8 (*c* 1.3, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, *J*=6.6 Hz, 6H, 18- and 16′-CH_3), 1.25 (s-like, 38H, 19×CH_2), 1.53 (s, 3H, branched CH_3), 1.70 (m, 2H, 3′-H_2), 1.90 (m, 2H, 10-H_2), 1.93 (s, 3H, CH_3CO), 2.00 (m, 4H, 6-H_2, 7-H_2), 3.74 (dd, *J*=4.3, 10.4 Hz, 1H, 1-Ha), 4.11 (m, 1H, 5″-H), 4.16 (dd, *J*=3.4, 10.4 Hz, 1H, 1-Hb), 4.33 (dd, *J*=4.9, 12.2 Hz, 1H, 6″-Hb), 4.48 (dd, *J*=3.2, 12.1 Hz, 1H, 6″-Ha), 4.50 (m, 1H, 2-H), 4.86 (d, *J*=7.8 Hz, 1H, 1″-H), 5.00 (dd, *J*=5.1, 6.8 Hz, 1H, 2′-H), 5.04 (m, 1H, 8-H), 5.50 (dd, *J*=7.8, 9.5 Hz, 1H, 2″-H), 5.52 (m, 1H, 3-H), 5.63 (t, *J*=9.8 Hz, 1H, 4′-H), 5.65 (m, 1H, 4-H), 5.85 (m, 1H, 5-H), 5.87 (t, *J*=9.6 Hz, 1H, 3″-H), 6.47 (d, *J*=9.0 Hz, 1H, NH), 7.22–7.56 (m, 15H), 7.80 (m, 2H), 7.87 (m, 2H), 7.92 (m, 2H), 7.95 (m, 2H), 7.99 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.1, 15.9, 20.6, 22.7, 24.6, 27.3, 28.0, 29.32, 29.35, 29.40, 29.53, 29.60, 29.63, 29.68, 31.78, 31.88, 31.89, 32.5, 39.6, 50.8, 62.9, 67.5, 69.5, 72.1, 72.4, 72.9, 73.9, 74.0, 100.8, 123.0, 124.7, 128.26, 128.29, 128.33, 128.35, 128.42, 128.8, 129.1, 129.5, 129.6, 129.7, 129.8, 130.1, 132.97, 133.01, 133.2, 133.3, 133.4, 136.1, 137.0, 165.0, 165.10, 165.15, 165.7, 165.9, 169.5, 169.6; FAB-MS (positive, NBA) *m/z* (%) 1313.3 ($[M+Na]^+$, 30), 1168.9 ($[M-PhCO_2]^+$, 42), 579.2 (62).

4.5.4. (2*S*,3*R*,4*E*,8*E*,2′*R*)-1-*O*-(β-D-Glucopyranosyl)-2-(2′-hydroxyhexadecanoyl)amino-9-methyl-4,8-octadecadiene-1,3-diol (1b). To a stirred solution of **29** (55 mg, 45 μmol) in MeOH (0.8 mL) and THF (0.8 mL) was added 1.0 M solution of NaOMe in MeOH (60 μL, 60 μmol), and the mixture was stirred for 2 h at 5–10 °C. Acetic acid (10 mg) was added and the solvent was removed. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH 9:1→7:1 to afford the cerebroside **1b** (28 mg, 86%) as a colorless amorphous solid. R_f 0.33 (CH_2Cl_2/MeOH 7:1). $[\alpha]_D^{24}$ +3.5 (*c* 0.56, $CHCl_3$/MeOH 1:1); {lit.[3e] $[\alpha]_D^{27}$ +5.1 (*c* 0.3, MeOH)}; ^{1}H NMR (pyridine-d_5 with 2% D_2O) δ 0.84 (t, 6H, *J*=6.6 Hz, 18- and 16′-CH_3), 1.23 (s-like, 36H, 18×CH_2), 1.35 (m, 2H, 11-H_2), 1.59 (s, 3H, 19-CH_3), 1.73 (br, 2H, 3′-H_2), 1.99 (t, *J*=7.3 Hz, 2H, 10-H_2), 2.12 (m, 4H, 6-H_2, 7-H_2), 3.87 (m, 1H, 5″-H), 4.00 (dd, *J*=7.6, 9.0 Hz, 1H, 2″-H), 4.18 (m, 3H, 1-Ha, 3″-H, 4″-H), 4.31 (dd, *J*=5.2, 11.8 Hz, 1H, 6″-Ha), 4.48 (dd, *J*=2.3, 11.5 Hz, 1H, 6″-Hb), 4.55 (dd, *J*=3.8, 7.9 Hz, 1H, 2′-H), 4.69 (dd, *J*=5.4, 10.7 Hz, 1H, 1-Hb), 4.73 (m, 1H, 3-H), 4.78 (m, 1H, 2-H), 4.88 (d, *J*=7.6 Hz, 1H, 1″-H), 5.22 (m, 1H, 8-H), 5.90 (br d, *J*=15.4 Hz, 1H, 5-H), 5.99 (dd, *J*=5.1, 15.4 Hz, 1H, 4-H), 8.34 (d, *J*=8.5 Hz, 1H, NH); ^{13}C NMR (pyridine-d_5) δ 14.2 (C-18 and 16′), 16.0 (C-19), 22.9 (C-17 and 15′), 25.8 (C-4′), 28.1 (C-7), 28.3 (C-11), 29.56, 29.59, 29.82, 29.85, 29.88, 29.95 (C-12–15 and 5′-13′), 32.1 (C-16 and 14′), 33.0 (C-6), 35.6 (C-3′), 39.9 (C-10), 54.5 (C-2), 62.5 (C-6″), 70.0 (C-1), 71.4 (C-4″), 72.2 (C-2′), 72.4 (C-3), 75.0 (C-2″), 78.3 (C-3″), 78.4 (C-5″), 105.5 (C-1″), 124.1 (C-8), 131.8 (C-4), 132.3 (C-5), 135.8 (C-9), 175.7 (C-1′); FAB-MS (positive, NBA) *m/z* (%) 750.6 ($[M+Na]^+$, 45), 710.6 ($[M-OH]^+$, 6), 548.6 ($[M-OH-Glc]^+$, 12), 320.3 (5), 276.4 (12).

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27. The isomerization was revealed by ^{13}C NMR spectrum of the *N*-acyl derivative of **26**. With TMSBr in CH_2Cl_2, however, no isomerizations were observed for the disubstituted (*E*)-olefins in **18a–c** and (*Z*)-olefin in **18c**.

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New potent cytotoxic lamellarin alkaloids from Indian ascidian *Didemnum obscurum*☆

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Abstract—Chemical investigations of the ascidian *Didemnum obscurum* has resulted in the isolation of four new lamellarin alkaloids, lamellarin-ζ (**1**), lamellarin-η (**2**), lamellarin-ϕ (**3**) and lamellarin-χ (**4**) along with seven known lamellarins, lamellarin-K (**5**), lamellarin-I (**6**), lamellarin-J (**7**), lamellarin-K triacetate (**8**), lamellarin-L triacetate (**9**), lamellarin-F (**10**) and lamellarin-T diacetate (**11**). The structures of the compounds **1**–**11** were established by detailed analysis of NMR spectral data. Cytotoxic activity of the isolates has been done against coloractal cancer cells.

1. Introduction

Ascidians (tunicates) are known to be a rich source of unique and biologically active secondary metabolites[1] viz. a cyclic depsipeptide didemnin-B,[2] eudistomin-C,[3] the lissoclinamides,[4] ascididemnin,[5] eilatin and the segolins.[6] The biomedical potential for ascidian secondary metabolites has resulted focused interest on these primitive chordates by several groups. The major secondary metabolites of ascidians are amino acid derived components,[7] and from the titled *Didemnum* species tyrosine and tryptophan amino acid derived compounds were isolated.[8]

Lamellarins are a group of DOPA (2-amino, 3-(3′,4′-dihydroxy phenyl)propionic acid) derived pyrrole hexacyclic alkaloids, which were first isolated from a prosobranch mollusc *Lamellaria* species by Faulkner and his co-workers in 1985.[9] Since that time a total of 38 lamellarins was isolated from different ascidisans.[10]

Lamellarins not only have an interesting structural feature, but also exhibit a wide array of significant biological activities; including cell division inhibition, cytotoxicity, HIV-I integrase inhibition, and immuno modulatory activity.[11] Lamellarin-I showed sensitizing effects to doxorubicin in multidrug resistant P_{388}/schabelcells at concentrations as low as 0.2 mm and showed full potentiation at a concentration 10 times lower than that of the prototype MDR inhibitor verapamil.[12]

2. Results and discussions

Previously from our group, we reported several lamellarins and their activities.[10b,11b,13] Our continuous interest in isolating the bioactive secondary metabolites from ascidians (tunicates),[10b,11b,13] we have collected a red colonial ascidian *Didemnum obscurum*, from Tiruchandur coast, Tamilnadu, India, during August-2002. The DCM–MeOH (1/1) extract of the ascidian was subjected to Sephadex LH-20 gel filtration chromatography and grouped into two fractions, Fraction-I and Fraction-II. Fraction-I was further subjected to silica-gel column chromatography, followed by reversed phase (C-18) HPLC column chromatography, using MeOH–H_2O (80/20) as eluent to afford two new lamellarins, lamellarin-ζ (**1**), and lamellarin-η (**2**) along with four known lamellarins, lamellarin-K (**5**),[14] lamellarin-I (**6**),[14] lamellarin-J (**7**),[15] and lamellarin-F (**10**).[14] Fraction-II was acetylated (Ac_2O/NaOAc) and purified sequentially on silica-gel column chromatography, and reversed phase (C-18) HPLC using MeOH–H_2O (60/40) as eluent, to afford two new lamellarins as acetates, lamellarin-ϕ triacetate (**3**), and lamellarin-χ triacetate (**4**) along with three known lamellarins as acetates, lamellarin-K triacetate (**8**),[10b] lamellarin-L

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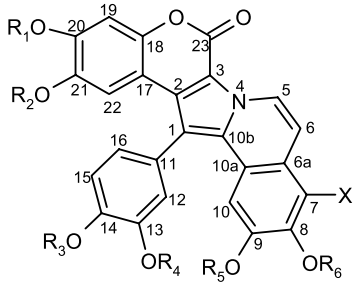
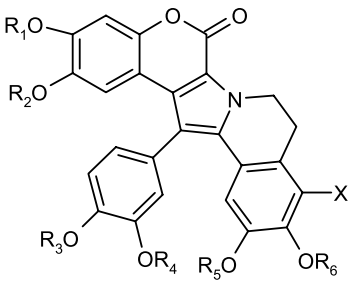
triacetate (**9**),[14] and lamellarin-T diacetate (**11**).[13]



1) R_1= H, R_2= Me, R_3=Me, R_4= Me, R_5= Me, R_6= Me, X = OMe.
2) R_1= H, R_2= Me, R_3=Me, R_4= Me, R_5= Me, R_6= Me, X = H.
3) R_1= Ac, R_2= Me, R_3=Ac, R_4= Me, R_5= Ac, R_6= Me, X = OMe.



4) R_1= Ac, R_2= Me, R_3=Ac, R_4=Me, R_5= Me, R_6= Ac, X = H.
5) R_1= H, R_2= Me, R_3= H, R_4= Me, R_5= Me, R_6= Me, X = OH.
6) R_1= H, R_2= Me, R_3=Me, R_4= Me, R_5= Me, R_6= Me, X = OMe.
7) R_1= H, R_2= Me, R_3=Me, R_4= Me, R_5= Me, R_6= Me, X = H.
8) R_1= Ac, R_2= Me, R_3= Ac, R_4= Me, R_5= Me, R_6= Me, X = OAc.
9) R_1= Ac, R_2= Me, R_3= Me, R_4=Ac, R_5= Me, R_6= Ac, X = H.
10) R_1= H, R_2= Me, R_3= Me, R_4= Me, R_5= Me, R_6= Me, X = OH.
11) R_1= Ac, R_2= Me, R_3=Me, R_4= Ac, R_5= Me, R_6= Me, X = OMe.

Lamellarin-ζ (**1**) was isolated as an optically inactive white solid and its molecular formula was deduced to be $C_{31}H_{27}NO_9$ from its HRFAB mass *m/z* 558.1760 and was supported by ^{13}C NMR, indicating the presence of 31 carbons. Its UV spectrum in methanol showed absorption maxima similar to those of lamellarins possessing a $\Delta^{5,6}$ double bond,[10b,11b,13] and its IR spectrum indicated the presence of phenolic and aromatic ester functionalities. Its ^1H NMR spectrum showed eight aromatic protons, of which three protons appeared as singlets at δ 6.64 (1H, s, H-22), 6.95 (1H, s, H-10), and 6.98 (1H, s, H-19), three protons were ascribed to an ABX pattern of 1,3,5-trisubstituted benzene ring, at δ 7.12, (1H, d, J=1.5 Hz, H-12), 7.18, (1H, dd, J=1.5, 8.0 Hz, H-16), and 7.14, (1H, d, J=8.0 Hz, H-15) and two *ortho*-coupled protons at δ 7.36 (1H, d, J=7.6 Hz, H-6), and δ 9.20 (1H, d, J=7.6 Hz, H-5) were assigned to the isoquinoline system. Further, its ^1H NMR spectrum displayed six methoxyl signals at δ 3.42 (3H, s, H-26), 3.47 (3H, s, H-29), 3.88 (3H, s, H-28), 3.92 (3H, s, H-25), 3.98 (3H, s, H-24), and 4.10 (3H, s, H-27); one D_2O exchangeable signal appeared at δ 5.80 as a broad singlet. Using the foregoing spectral data and a literature survey revealed that compound **1** belongs to lamellarin type of alkaloids, viz. lamellarin-B[1] and lamellarin-ε,[10b] which possess a $\Delta^{5,6}$double bond. The positions of the methoxyl signals on benzenoid rings were assigned by conventional HMQC, HMBC (Table 1) and NOESY correlations.

In the ^1H–^1H NOESY spectrum of lamellarin-ζ (**1**), the methoxyl signals at δ 3.47 (3H, s, H-29), 3.88 (3H, s, H-28), 4.10 (3H, s, H-27), and 3.42 (3H, s, H-26) showed correlations with the protons appearing at δ 6.64 (1H, s, H-22), 7.14 (1H, d, J=8.0 Hz, H-15), 7.12 (1H, d, J=1.5 Hz, H-12), and 6.95 (1H, s, H-10), respectively. The methoxyls at δ 3.92 (3H, s, H-25), and 3.98 (3H, s, H-24) did not show any cross peaks in the NOESY spectrum. In the HMBC spectrum of lamellarin-ζ, the H-22 proton signal at δ 6.64 (s) showed correlations with the carbons at δ 129.30 (C-2), 146.33 (C-18), 143.33 (C-20), and 147.01 (C-21); the H-19 aromatic signal at δ 6.98 (s) showed correlations with the carbons C-17 (δ 109.75), C-21 (δ 147.01), and C-20 (δ 143.33). Similarly, in the trisubstituted aromatic ring the proton at δ 7.14 (1H, d, J=8.0 Hz, H-15) showed correlations with the carbons C-13 (δ 149.89), and C-11 (δ 128.30); the proton at δ 7.18 (1H, dd, J=8.0, 1.5 Hz, H-16) showed correlation with the carbons C-2 (δ 129.30), C-1 (δ 111.64), C-12 (δ 114.24), and C-14 (δ 149.04) and the proton at δ 7.12 (1H, d, J=1.5 Hz, H-12) showed correlation peaks with the carbons C-1 (δ 111.64), C-16 (δ 124.02), and C-14 (δ 149.04). The proton at δ 6.95 (1H, s, H-10) showed correlation peaks with the carbons C-10b (δ

Table 1. Spectral data for lamellarin-ζ (**1**)

Position	^1H NMR multiplicity (J in Hz)[a]	^{13}C NMR[b]	HMBC (J in Hz)[c]
C-1	—	111.64	—
C-2	—	129.30	—
C-3	—	108.15	—
C-5	9.2, d, (7.6)	122.89	C-6a, C-10b, C-6
C-6	7.36, d, (7.6)	106.91	C-7, C-10a, C-5
C-6a	—	119.43	—
C-7	—	148.44	—
C-8	—	153.22	—
C-9	—	142.22	—
C-10	6.95, s	101.55	C-6a, C-8, C-10b, C-9
C-10a	—	121.26	—
C-10b	—	133.77	—
C-11	—	128.30	—
C-12	7.12, d, (1.5)	114.24	C-1, C-14, C-16
C-13	—	149.89	—
C-14	—	149.04	—
C-15	7.14, d, (8.0)	111.91	C-11, C-13
C-16	7.18, dd, (8.0, 1.5)	124.02	C-1, C-12, C-14, C-2
C-17	—	109.75	—
C-18	—	146.33	—
C-19	6.98, s	103.58	C-17, C-21, C-20
C-20	—	143.33	—
C-21	—	147.01	—
C-22	6.64, s	104.57	C-2, C-18, C-20, C-21
C-23	—	155.48	—
C-24	3.98, s	56.29	C-7
C-25	3.92, s	61.12	C-9
C-26	3.42, s	55.18	C-8
C-27	4.10, s	61.66	C-14
C-28	3.88, s	56.18	C-13
C-29	3.47, s	55.54	C-20

[a] Measured in $CDCl_3$, 600 MHz.
[b] Measured in $CDCl_3$, 150 MHz.
[c] Measured in $CDCl_3$, 600 MHz.

133.77), C-6a (δ 119.43), C-8 (δ 153.22), and C-9 (δ 142.22). The isoquinoline H-6 proton at δ 7.36 showed correlations with the carbons C-5 (δ 122.89), C-10a (δ 121.26), and C-7 (δ 148.44); the other isoquinoline H-5 at δ 9.2 showed correlation peaks with the carbons C-10b (δ 133.77), C-6 (δ 106.91), and C-6a (δ 119.43). The foregoing spectral data established the structure of lamellarin-ζ as **1**.

Lamellarin-η (**2**) was obtained as an optically inactive white solid, and its molecular formula was deduced to be $C_{30}H_{25}NO_8$ by HRFABMS *m/z* 528.1654 and was supported by ^{13}C NMR indicating the presence of 30 carbons. Its UV spectrum in methanol showed absorption maxima similar to those of lamellarin-ζ (**1**). Its IR spectrum indicated the presence of phenolic and ester functionalities.

The ^1H NMR spectrum showed nine aromatic protons of which four appeared as singlets at δ 6.68 (1H, s, H-22), 6.96 (1H, s, H-19), 7.14 (1H, s, H-10), and 7.05 (1H, s, H-7); three signals were ascribed to a 1,3,4 tri substituted benzene at δ 7.13 (1H, d, $J=1.8$ Hz, H-12), 7.138 (1H, d, $J=8.1$ Hz, H-15), and 7.20 (1H, dd, $J=8.1$, 1.8 Hz, H-16) and the two isoquinoline moiety protons at δ 9.18 (1H, d, $J=7.6$ Hz, H-5), and 7.00 (1H, d, $J=7.6$ Hz, H-6). Further, the ^1H NMR spectrum displayed five methoxyl groups at δ 3.48 (3H, s, H-28), 3.98 (3H, s, H-27), 3.87 (3H, s, H-26), 3.44 (3H, s, H-25), and 3.96 (3H, s, H-24). A literature survey revealed that compound **2** is closely related to lamellarin-α.[10b] The positions of methoxyl groups were deduced by its HMQC and HMBC (Table 2) and NOESY correlations.

Table 2. Spectral data of lamellarin-η (**2**)

Position	^1H NMR multiplicity (J in Hz)[a]	^{13}C NMR[b]	HMBC (J in Hz)[c]
C-1	—	110.71	—
C-2	—	129.41	—
C-3	—	107.75	—
C-5	9.18, d, (7.6)	123.28	C-6, C-6a, C-10b
C-6	7.00, d, (7.6)	112.24	C-7, C-10a, C-5
C-6a	—	124.79	—
C-7	7.05, s	107.36	C-6, C-10a, C-9, C-8
C-8	—	149.13	—
C-9	—	150.07	—
C-10	7.14, s	111.90	C-8, C-6a, C-10b, C-9
C-10a	—	119.02	—
C-10b	—	134.29	—
C-11	—	128.31	—
C-12	7.13, d, (1.8)	105.22	C-14, C-16, C-1, C-13
C-13	—	149.01	—
C-14	—	149.87	—
C-15	7.13, d, (8.0)	114.38	C-13, C-11, C-16
C-16	7.20, dd, (8.0, 1.8)	124.11	C-1, C-15
C-17	—	109.78	—
C-18	—	146.31	—
C-19	6.96, s	103.53	C-17, C-21, C-18, C-20
C-20	—	143.31	—
C-21	—	146.99	—
C-22	6.68, s	104.61	C-2, C-20, C-21, C-18
C-23	—	155.45	—
C-24	3.96, s	55.93	C-9
C-25	3.44, s	55.17	C-8
C-26	3.87, s	56.17	C-14
C-27	3.98, s	56.27	C-13
C-28	3.48, s	55.53	C-20

[a] Measured in$CDCl_3$ 600 MHz.
[b] Measured in $CDCl_3$, 150 MHz.
[c] Measured in $CDCl_3$, 600 MHz.

In its NOESY spectrum, the methoxyls at δ 3.48 (3H, s, H-28), 3.98 (3H, s, H-27), 3.87 (H-26), and 3.44 (H-25) showed correlations with the protons at δ 6.68 (1H, s, H-22), 7.138 (1H, d, $J=8.1$ Hz, H-15), 7.13 (1H, d, $J=1.8$ Hz, H-12), and 7.14 (1H, s, H-10), respectively. The methoxyl at δ 3.96 (3H, s, H-24) showed correlation with the proton at δ 7.05 (1H, s, H-7), which in turn showed correlation with the proton at δ 7.00 (1H, d, $J=7.6$ Hz, H-6).

The HMBC spectrum of lamellarin-η, revealed that the H-22 aromatic proton at δ 6.68 (1H, s) showed correlations with carbons C-2 (δ 129.41), C-17 (δ 109.78), and C-20 (δ 143.31). The H-19 aromatic signal at δ 6.96 (1H, s) showed correlations with carbons C-17 (δ 109.78), C-21 (δ 146.99), C-18 (δ 146.31), and C-20 (δ 143.31). The H-12 proton of trisubstituted benzene ring at δ 7.13 (1H, d, $J=1.8$ Hz) showed correlations with the carbons C-1 (δ 110.71), C-16 (δ 124.11), C-14 (δ 149.87), and C-13 (δ 149.01); the H-15 aromatic proton at δ 7.138 (1H, d, $J=8.1$ Hz, H-15) showed correlations with the carbons C-13 (δ 149.01), C-11 (δ 128.31), and C-16 (δ 124.11); and the proton H-16 at δ 7.20 (1H, dd, $J=8.1$, 1.8 Hz, H-16) showed correlations with the carbons C-1 (δ 110.71), and C-15 (δ 114.38). The H-10 aromatic signal at δ 7.14 showed correlations with the carbons C-10b (δ 134.29), C-6a (δ 124.79), C-8 (δ 149.13), and C-9 (δ 150.07); the aromatic H-7 proton appeared at δ 7.05 (1H, s) showed correlation with the carbons C-9 (δ 150.07), C-8 (δ 149.13), C-10a (δ 119.02), and C-6 (δ 112.24). One of the isoquinoline protons appeared at δ 7.00 (1H, d, $J=7.6$ Hz, H-6) and showed correlation with the carbons C-7 (δ 107.36), C-10a (δ 119.02), and C-5 (δ 123.28); while the other proton at δ 9.18 (1H, d, $J=7.6$ Hz) showed correlation with the carbons C-6 (δ 112.24), C-6a (δ 124.79), and C-10b (δ 134.29). Thus, the structure of lamellarin-η was established as **2**.

Lamellarin-ϕ (**3**) was obtained as an optically inactive white solid, and the molecular formula was established as $C_{35}H_{29}NO_{12}$, by HRFABMS, *m/z* 656.1762. Its UV spectrum is similar to those of lamellarin-ζ and lamellarin-η. Its ^1H NMR spectrum displayed eight aromatic protons, of which three appeared at δ 6.80 (1H, s, H-22), 7.15 (1H, s, H-10) and 7.1 (1H, s, H-19); three protons were attributed to the pendant 1,3,4-trisubstituted benzene at δ 7.18 (1H, d, $J=1.9$ Hz, H-12), 7.23 (1H, dd, $J=8.0$, 1.9 Hz, H-16), δ 7.28 (1H, d, $J=8.0$ Hz, H-15) and the remaining two were attributed to isoquinoline system at δ 9.25 (1H, d, $J=7.5$ Hz, H-5) and δ 7.08 (1H, d, $J=7.5$ Hz, H-6). Further, its ^1H NMR spectrum displayed signals for three acetyl groups at δ 2.32 (3H, s), 2.38 (3H, s), and 2.48 (3H, s) and four methoxyl groups at δ 3.45 (3H, s, H-31), 3.89 (3H, s, H-25), 3.488 (3H, s, H-24) and 3.82 (3H, s, H-28). A literature survey and the foregoing spectral data revealed that compound **3** is closely related to lamellarin-M[14] where 7-hydroxy and 9-methoxy of lamellarin-M were interchanged in compound **3**.

The positions of the methoxyl groups and thereby structure of lamellarin-ϕ was determined from the study of its NOESY spectrum. In its NOESY spectrum, the methoxyl at δ 3.45 (3H, s, 27-H), showed correlation with the proton at δ 6.80 (1H, s, H-22), which infers presence of a methoxyl at C-21. In the lamellarin group of alkaloids the H-10 and H-22 protons will appear upfield compared with the rest of the aromatic protons due to the shielding effect of the pendant benzene ring attached at C-1.[9] The methoxyl protons at δ 3.48 (3H, s, H-24) showed a correlation with the proton at δ 7.08 (1H, d, $J=7.5$ Hz, H-6), which in turn showed linear correlation (^{1}H–^{1}H COSY) with the proton at δ 9.24 (1H, d, $J=7.5$ Hz, H-5). Further, the methoxyl protons at δ 3.82 (3H, s, H-28) showed correlation with the proton appeared at δ 7.18 (1H, d, $J=1.9$ Hz, H-12). From the foregoing spectral data the structure of lamellarin-ϕ was established as **3**.

Lamellarin-χ (**4**) was obtained as an optically inactive white solid, and its molecular formula was deduced as $C_{34}H_{29}NO_{11}$ by HRFABMS. The ^{1}H NMR spectrum of lamellarin-χ showed seven aromatic signals out of which four appeared as singlets at δ 6.70 (1H, s, H-22), 6.80 (1H, s, H-10), 6.95 (1H, s, H-19), and 7.09 (1H, s, H-7); and the remaining three aromatic protons were ascribed to the pendant 1,3,4 tri substituted benzene ring at δ 7.10 (1H, d, $J=2.0$ Hz, H-12), 7.14 (1H, dd, $J=8.0$, 2.0 Hz, H-16), and 7.21 (1H, d, $J=8.0$ Hz, H-15). Further, its ^{1}H NMR spectrum displayed three methoxyl groups at δ 3.42 (3H, s, H-26), 3.81 (3H, s, H-27), and 3.33 (3H, s, H-30); three acetyl groups at δ 2.34 (3H, s), 2.30 (3H, s), and 2.28 (3H, s); and two linearly coupled methylene groups at δ 3.12 (2H, t, $J=6.3$ Hz, H-6), δ 4.77 (1H, quintet, $J=13.2$, 6.3 Hz, H-5a), and δ 4.88 (1H, quintet, $J=13.2$, 6.3 Hz, H-5b). The foregoing spectral data and a literature survey revealed that compound **4** is closely related to lamellarin-L[14] except for the hydroxyl and methoxy substitution being interchanged on the pendant benzene ring attached at C-1. The disposition of the methoxyl groups was deduced from the study of its NOESY spectral analysis. In its NOESY spectrum the methoxyl group at δ 3.33 (3H, s, H-30) showed correlation with the proton at δ 6.70 (1H, s, H-22), the methoxyl group at δ 3.42 (3H, s, H-26) showed correlation with the proton at δ 6.80 (1H, s, H-10) and the remaining methoxyl group at δ 3.81 (3H, s, H-27) showed correlation with the aromatic proton at δ 7.10 (1H, d, $J=2$ Hz, H-12), which belongs to the C-1 substituted aromatic ring. Hence, the structure of the lamellarin-χ was established as **4**.

As it was well demonstrated that lamellarin alkaloids exhibit cytotoxic activity, the isolates (**1**–**4**, **6**–**11**) were tested in vitro for their cytotoxic activity against coloractal cancer cells (COLO-205) and the IC_{50} values are given in Table 3.

Compounds **1**, **4**, **9** and **10** have shown excellent activity against test cancer cell lines. Further work is in progress.

3. Experimental

3.1. General experimental procedures

Melting points were obtained on a Mel-Temp apparatus and are uncorrected. The optical rotations were measured on a JASCO DIP-370 polarimeter. UV and IR spectra were recorded on Shimadzu-240 and Perkin-Elmer 240-C instruments, respectively. The ^{1}H and ^{13}C NMR was recorded on 600 MHz (Inova), 500 MHz (Bruker) instruments using TMS as internal standard. Chemical shifts are reported in δ (ppm) and coupling constants (J) are expressed in hertz. The MS were recorded on a VG Auto Spec-M instrument. Preparative scale HPLC was performed using a Supelcosil C_{18} column (60A°, 12 μm, 25 cm×21.2 mm).

Animal material. The ascidian *D. obscurum* F. Monnit, 1969 (Didemnidae) was collected from the Tiruchandur coast in the Gulf of Mannar, Tamilnadu, India, during August-2002. A voucher specimen (IIC-484) was deposited at the National Institute of Oceanography, Goa, India.

Extraction and isolation. The freshly collected ascidian specimens (2.5 kg wet weight) were soaked in methanol at the site of collection until workup. The initial methanol extract was decanted and the ascidian material was extracted with 1:1 dichloromethane/methanol (3×3 L) at room temperature. The combined extract including initial methanol extract was filtered, and the solvent was removed under reduced pressure to give predominantly an aqueous suspension, and it was extracted into ethyl acetate (3× 0.5 L), and was concentrated under reduced pressure to give a dark brown gummy mass (6.5 g). This crude extract was subjected to gel filtration chromatography (Sephadex LH-20, 1:1 CH_2Cl_2/MeOH, 35 mm×950 mm) by collecting a total of 25 continuous fractions (30 ml each). Following the TLC pattern, the 25 fractions were pooled into two fractions, Fraction-I and Fraction-II. Fraction-I was then subjected to silica-gel column chromatography, followed by reversed phase (C-18) HPLC column (Methanol/H_2O, 80: 20) at a flow rate of 5 ml per min to afford two new lamellarins, lamellarin-ζ (**1**), and Lamellarin-η (**2**) along with four known lamellarins, lamellarin-K (**5**),[14] lamellarin-I (**6**),[14] lamellarin-J (**7**),[15] and lamellarin-F (**10**).[14] Fraction-II was then acetylated (Ac_2O/NaOAc) and then subjected to silica-gel column chromatography, followed by reversed phase (C-18) HPLC using MeOH–H_2O (60/40) as eluent, to afford two new lamellarins as its acetates, lamellarin-ϕ triacetate (**3**), and lamellarin-χ triacetate (**4**) along with three known lamellarins as acetates, lamellarin-K triacetate (**8**),[10b] lamellarin-L triacetate (**9**),[14] and lamellarin-T diacetate (**11**).[13]

3.2. Biological assay

0.2 million cells in complete medium were seeded into a micro well plate. The cells were incubated in presence of

Table 3. IC_{50} values of lamellarins against COLO-205 cell lines

Compound	1	2	3	4	6	7	8	9	10	11
IC_{50} (μM)	0.0056	0.178	0.056	0.0002	0.025	0.05	0.7	0.00025	0.009	0.08

increasing concentrations of test compounds at 37 °C in a CO_2 incubator for 16 h. After 16 h the cells were centrifuged at 800×*g* for 10 min and the supernatant was discarded. The cells were re-suspended in 200 µl complete medium with 20 µl of 5 mg/ml of 3-(4,5-dimethylthiozol-3-yl)-2,5-diphenyl tetrazolium bromide (MTT) and incubated for 4 h at 37 °C in a CO_2 incubator. The cells were centrifuged at 800×g for 10 min, 100 µl of supernatant was discarded. The insoluble crystals formed due to the reduction of MTT by viable cells were dissolved in 0.1 M acidic isopropanol and quantified in a micro plate reader at 570 nm.[16] The percentage of inhibition of cell viability was computed with reference to the MTT reduction in control cells without test compound. The experimental measurements were made in triplicate and the average value was taken as percentage inhibition. The concentration of test compound required for 50% inhibition of cell viability (IC_{50}) was determined.

3.2.1. Lamellarin-ζ (1). White solid (4 mg), mp 268–272 °C, IR (KBr): ν_{max}: 3444.8, 1637, 1425, 1219, 772 cm^{-1}. UV (MeOH): λ_{max} (log ε): 230.0 (0.3626), 404.5 (0.0226) nm. ^1H NMR (600 MHz, $CDCl_3$): δ 9.20 (1H, d, J=7.6 Hz, H-5), 7.36 (1H, d, J=7.6 Hz, H-6), 7.18 (1H, dd, J=8.0, 1.5 Hz, H-16), 7.14 (1H, d, J=8.0 Hz, H-15), 7.12 (1H, J=1.5 Hz, H-12), 6.98 (1H, s, H-19), 6.95 (1H, s, H-10), 6.64 (1H, s, H-22), 4.10 (3H, s, H-27), 3.98 (3H, s, H-24), 3.92 (3H, s, H-25), 3.88 (3H, s, H-28), 3.47 (3H, s, H-29), 3.42 (3H, s, H-26). ^{13}C NMR: (150 MHz, $CDCl_3$): see Table 1. FABMS obsd *m/z* (%) 558 (M^++1, 25), 557 (M^+, 25), 464 (9), 391 (40), 329 (12), 307 (21), 279 (8), 228 (6), 176 (33), 154 (100), 136 (94), 107 (53), 69 (83), 57 (94). HRFABMS *m/z*: 558.1760; (calcd for $C_{31}H_{28}NO_9$, 558.1764; Δ 0.7 ppm).

3.2.2. Lamellarin-η (2). White solid (9 mg), mp 265–269 °C, IR (KBr): ν_{max}: 3441, 2928.3, 1669.7, 1424.1, 1266.3, 1223.9, 1049.6, 857.2, 760.2 cm^{-1}. UV (MeOH): λ_{max} (log ε): 236.5 (0.7618); 308 (0.5499); 392.5 (0.163), 412.0 (0.1945) nm. ^1H NMR (600 MHz, $CDCl_3$): δ 9.18 (1H, d, J=7.6 Hz, H-5), 7.20 (1H, dd, J=8.0, 1.8 Hz, H-16), 7.14 (1H, s, H-10), 7.13 (1H, d, J=8.0 Hz, H-15), 7.13 (1H, d, J=1.8 Hz, H-12), 7.05 (1H, s, H-7), 7.00 (1H, d, J=7.6 Hz, H-6), 6.96 (1H, s, H-19), 6.68 (1H, s, H-22), 5.79 (1H, br s, OH), 3.98 (3H, s, H-27), 3.96 (3H, s, H-24), 3.87 (3H, s, H-26), 3.48 (3H, s, H-28), 3.44 (3H, s, H-25). ^{13}C NMR: (150 MHz, $CDCl_3$): see Table 2. FABMS obsd *m/z* (%) 528 (M^++1, 22), 527 (M^+, 21), 467 (12), 439 (8), 391 (18), 367 (10), 176 (18), 154 (32), 137 (33), 109 (22), 81 (44), 69 (72), 55 (100). HRFABMS *m/z*: 528.1654; (calcd for $C_{30}H_{26}NO_8$, 528.1658; Δ 0.7 ppm).

3.2.3. Lamellarin-ϕ (3). White solid (4 mg), mp 276–279 °C, IR (KBr): ν_{max}: 1738, 1665, 1637, 1552, 772.1 cm^{-1}. UV (MeOH) λ_{max} (log ε): 224.5 (0.444), 298.0 (0.3169), 380 (0.0792), 399.5 (0.0983) nm. ^1H NMR (500 MHz, $CDCl_3$): δ 9.25 (1H, d, J=7.5 Hz, H-5), 7.28 (1H, d, J=8.0 Hz, H-15), 7.23 (1H, dd, J=8.0, 1.9 Hz, H-16), 7.18 (1H, d, J=1.9 Hz, H-12), 7.15 (1H, s, H-10), 7.10 (1H, s, H-19), 7.08 (1H, d, J=7.5 Hz, H-6), 6.80 (1H, s, H-22), 3.89 (3H, s, H-25), 3.82 (3H, s, H-28), 3.48 (3H, s, H-24), 3.45 (3H, s, H-31), 2.48 (3H, s), 2.38 (3H, s), 2.32 (3H, s); FABMS obsd *m/z* (%) 656 (M^++1, 32), 614 (8), 307 (23), 289 (16), 154 (92), 137 (100), 135 (92), 120 (19), 89 (26), 77 (32), 65 (12). HRFABMS *m/z*: 656.1762; (calcd for $C_{35}H_{30}NO_{12}$, 656.1768; Δ 0.9 ppm.).

3.2.4. Lamellarin-χ (4). White solid (5 mg), mp 164–166 °C, IR (KBr): ν_{max}: 1735, 1695, 1656, 1550, 1427, 1265, 1041, 858, and 758 cm^{-1}. UV (MeOH) λ_{max} (log ε): 208.0 (0.5547), 274.0 (0.3184), 313.0 (0.2745) nm. ^1H NMR (500 MHz, $CDCl_3$): δ 7.21 (1H, d, J=8.0 Hz, H-15), 7.14 (1H, dd, J=8.0, 2.0 Hz, H-16), 7.10 (1H, d, J=2.0 Hz, H-12), 7.09 (1H, s, H-7), 6.95 (1H, s, H-19), 6.80 (1H, s, H-10), 6.70 (1H, s, H-22), 4.88 (1H, quintet, J=13.2, 6.3 Hz, H-5b), 4.77 (1H, quintet, J=13.2, 6.3 Hz, H-5a), 3.81 (3H, s, H-27), 3.42 (3H, s, H-26), 3.33 (3H, s, H-30), 3.12 (2H, t, J=6.3 Hz, H-6), 2.34 (3H, s), 2.30 (3H, s), 2.28 (3H, s); FABMS obsd *m/z* (%) 628 (M^++1, 6), 586 (5), 544 (4), 340 (10), 308 (12), 290 (8), 155 (100), 138 (72), 122 (22), 108 (28), 91 (22), 81 (28), 69 (42), 55 (38). HRFABMS *m/z*: 628.192; (calcd for $C_{34}H_{30}NO_{11}$, 628.1818; Δ 16 ppm).

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Synthesis, X-ray crystallographic, and dynamic ^{1}H NMR studies of crown-tetrathia[3.3.3.3]metacyclophanes—conformational control by cooperative intramolecular C–H···π interaction both in solid state and in solution

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Abstract—Crown-tetrathia[3.3.3.3]metacyclophanes **3a–c** were synthesized via intermolcular coupling reaction in 22–30% yields. X-ray crystal analysis of **3b** revealed that it adopted a perpendicular conformation (**3b**-**B** or **3b**-**C**) in which two aromatic rings were inclined to be perpendicular to the opposite aromatic rings, driving two internal methyl groups into the π-cloud of the corresponding benzene rings. Furthermore, this perpendicular structural feature led to benzylic protons of thia-bridges being in close proximity to the adjacent aromatic rings. As a result, the induced upfield shifts for the two internal methyl protons and four benzylic protons were clearly observed in dynamic ^{1}H NMR spectra at low temperature, indicating that the intramolecular C–H···π interaction became increasingly important at low temperature. The energy barrier for inter-conversion between **3b**-**B** and **3b**-**C** was estimated to be 12.1 kcal mol^{-1} by using a coalescence method. The total stabilization enthalpy of the C–H···π interactions was quantitatively calculated to be 7.9 ± 0.8 kcal mol^{-1} by the dynamic NMR spectroscopy. In contrast, **3a** showed two non-interconvertible conformers at room temperature, which tended to interconvert at elevated temperature, however, many conformers co-existed at low temperature.

1. Introduction

The understanding of non-covalent weak interactions such as hydrogen-bonding, C–H···O/N, C–H···π, and N/O–H···π interactions, etc., is not only important in fundamental science, but also has implications for the development of various applications in crystal engineering and molecular design of materials.[1–7] Among these weak interactions, the C–H···π interaction, first explored by Nishio,[8–10] is considered as one of weak hydrogen bonds, in which the C–H and π-system acts as a soft acid and a soft base, respectively. The C–H···π interaction is of particular importance in influencing molecular recognition,[11–14] conformational preference,[15–24] biological processes, and the structure of biomacromolecules.[25–29] For example, Tsuzuki reported on the preferential conformation of crownophanes, which is determined by the co-effect of the C–H···π and C–H···O interactions.[15] Wilcox designed a sophisticated system to investigate the effect of the C–H···π interaction on molecular folding by using a 'slow rotation' strategy.[16–17] Ōki utilized the same strategy to take 1,9-disubstituted triptycenes as a model for the C–H···π interaction.[18–20] Additionally, many theoretical calculations[30–35] demonstrated that the C–H···π interaction is an attractive force in nature, and plays a role in stabilizing crystal packing.

The C–H and π-system in many organic molecules are in close proximity in crystalline state, however, it is sometime difficult to observe the C–H···π interaction in solution. This is because the mobility of a molecular structure usually results in conformationally averaged signals, for example, in the NMR spectra. Recently, as a parallel work of [*n*.3.3](1,2,6)cyclophanes,[36–37] we are focusing on the study of the synthesis, conformation, and complexation properties of [*n*.3.3](1,3,5)cycophanes.[38–39] Apart from the formation of cyclophanes as expected in the cyclization reaction, we isolated a dimeric product of a tetrathia[3.3.3.3]metacyclophane. X-ray single crystal analysis indicated that the intramolecular C–H···π interaction existed in solid state. Further dynamic NMR analysis revealed that cooperative intramolecular C–H···π (alkyl–aryl) interaction dominated

Keywords: Synthesis; Cyclophane; C–H···π Interaction; Conformation.
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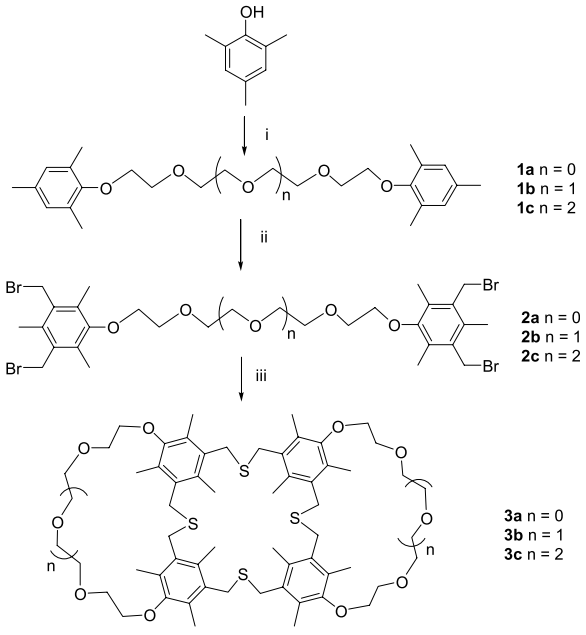
the conformation preference in solution, and its conformation at low temperature was similar to that in solid state. In the present paper, we report on their synthesis, X-ray structural characterization, and conformational behaviors of tetrathia[3.3.3.3]metacyclophanes.

2. Results and discussion

2.1. Synthesis of crown-tetrathia[3.3.3.3] metacyclophanes

The synthetic route leading to **3** is shown in Scheme 1. First, treatment of 2,4,6-trimethylphenol with a series of oligoethylene glycol dibromides in THF/NaOH solution afforded compounds **1a–c**. Bromomethylation of compounds **1a–c** in 47% hydrobromic acid/acetic acid and 1,3,5-trioxane using *N*,*N*,*N*-trimethyltetradecyl ammonium bromide as a phase transfer catalyst[40] was carried out to give tetrabromides **2a–c** in intermediate yields. As the reaction temperature was increased, the tribromide and tetrabromide gradually formed and their presence could be readily monitored by thin layer chromatography (TLC). Chromatography of the product mixture from the respective bromomethylation reactions gave **2a**, **2b**, and **2c** as white solids. In the ^{1}H NMR spectra of **2a**, **2b**, and **2c**, no aromatic proton signals were observed indicating that the aromatic positions in **1a**, **1b**, and **1c** were fully bromomethylated. When the tetrabromides **2a–c** were separately treated with 2 equiv of $Na_2S\cdot 9H_2O$ in 95% ethanol/benzene under high dilution conditions, a mixture of the intramolecularly coupled product[38] and the corresponding tetrathia[3.3.3.3]-metacyclophanes **3a–c** were obtained.

Taking the cyclization of **2b** as an example, the isolated product could in principle be any of **3b**, **4**, **5**, and **6**. The mass spectra of the compounds isolated from the cyclization of **2a–c** were determined using electrospray ionization (ESI) mass spectrometry. The isolated compound derived from **2a** showed molecular ions at 1027.5 ($[M+Na]^+$, 100). Similarly the compound derived from **2b** showed molecular ions at 1115.5 ($[M+Na]^+$, 30) and 1131.6 ($[M+K]^+$, 100) and that from **2c** at 1182.7 (M^+, 24), 1205.8 ($[M+Na]^+$, 14), and 1221.8 ($[M+K]^+$, 5). The above observation clearly confirmed that the corresponding compounds isolated were of dimeric nature. In the relatively simple ^{1}H NMR spectrum of **3b**, it appeared as three singlets at δ 2.47, 2.31, and 1.98 (integration ratio 1:1:1) corresponding to the three different pairs of methyl groups. This was further confirmed by a ^{13}C NMR DEPT experiment, which proved that there were three different types of methyl carbon signals at δ 14.86, 12.85, and 12.23, respectively, and two types of bridge carbon signals at δ 31.96 and 30.14. The above NMR data were collectively consistent with the structure of **3b** because the higher symmetry in **4**, **5**, or **6** should result in only two types of methyl protons or carbon signals. Although the ^{1}H NMR and ^{13}C NMR spectra of **3c** were very similar to those of **3b**, in particular the three types of protons and carbon NMR signals for the methyl groups, the spectra of **3a** were relatively more complicated. Compound **3a** showed six methyl protons signals in an integration ratio of 0.7:1:1:0.7:1:0.7 in CD_2Cl_2. This suggests the presence of two separate conformers that are non-interconverting in solution at room temperature. Additional evidence came from the 12 aromatic and four benzylic carbon signals observed in the ^{13}C NMR spectrum of the mixture (Fig. 1).



Scheme 1. The synthetic route for compounds **3a–c**. Reagents and conditions: (a) $Br(CH_2CH_2O)_nCH_2CH_2Br$, NaOH, THF; (b) 1,3,5-trioxane, HBr/HOAc, $C_{14}H_{29}N(CH_3)_3Br$; (c) Na_2S, Cs_2CO_3, C_2H_5OH/benzene.

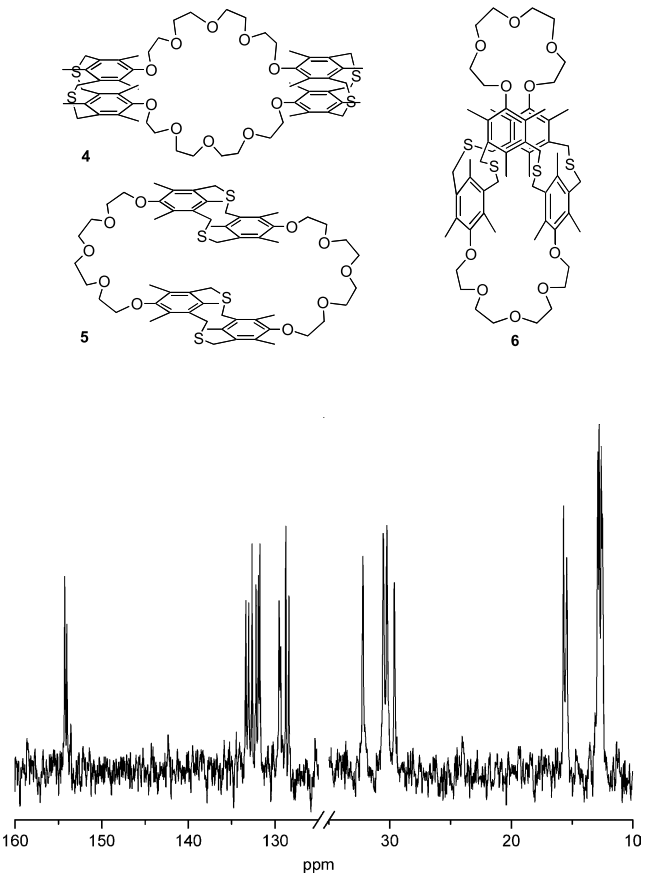
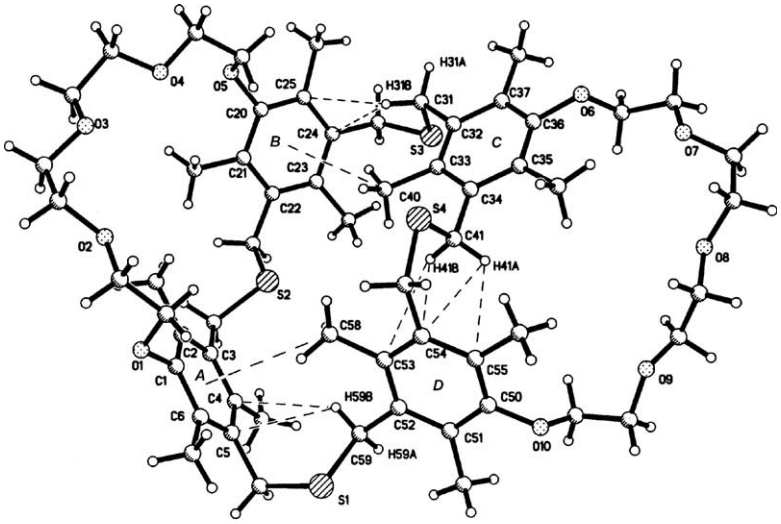
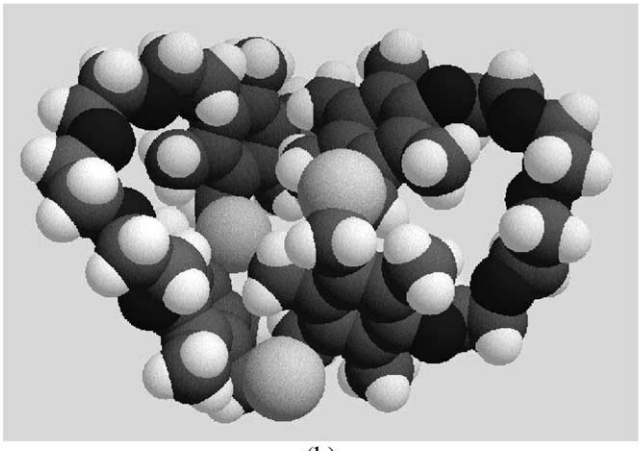


Figure 1. Part of ^{13}C NMR spectrum of compound **3a** in $CDCl_3$ at room temperature.



(a)



(b)

Figure 2. (a) ORTEP drawing of **3b** and (b) space-filling drawing of **3b** illustrating intramolecular close contacts.

2.2. X-ray crystallographic study of 3b

Single crystals of **3b** were grown by evaporative crystallization from a mixture of chloroform and acetonitrile solution, however, suitable crystals were not obtained for **3a** and **3c**. A drawing of the crystal structure of **3b** is shown in Figure 2. The four benzene rings (designated as A, B, C, and D in Fig. 2) in **3b** did not lie on the same plane as expected and each of them formed different dihedral angles (54.2° (ring B–ring A), 64.0° (ring C–ring D), 75.8° (ring B–ring C), and 71.7° (ring A–ring D)) with one another. The two oxa-crown macrorings were inclined to be approximately perpendicular to each other by bending the central thia-crown unit. Therefore, the whole molecule looked like an L-shape with two approximately perpendicular planes. In the crystal of **3b**, two internal methyl groups (C_{40} and C_{58}) were pointing toward the opposite aromatic rings B and A, respectively. The short distances (3.048 Å for C_{40}-ring A and 3.430 Å for C_{58}-ring B) between two internal methyl carbon atoms (C_{40} and C_{58}) and the geometrical centre of aryl rings (ring B and ring A) imply that they are subject to a C–H$\cdots\pi$ interaction (model a) as presented in Figure 3. Interestingly, four benzylic protons (H_{31B}, H_{41A}/H_{41B} and H_{59B}) are also in close proximity to the adjacent phenyl periphery (models b and c in Fig. 3). The distances between these benzylic protons concerned and C_{sp^2} of aromatic rings varied from 2.666 to 3.049 Å, being much shorter or approximately equal to that of van der Waals contact of H and C_{sp^2} (2.9–3.1 Å)[9] (Table 1). This type of C–H$\cdots\pi$ interaction is essentially comparable to the reported model,[33,41] in which the methylene group adopted a synclinal conformation, thus, leading to the methylene protons approaching the adjacent aromatic π-system.

It has been reported that the intramolecular edge–face aromatic interaction contributes to the stabilization of

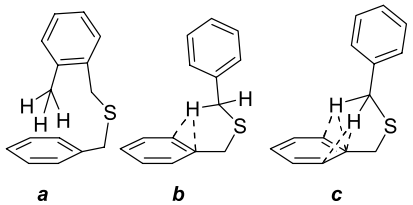


Figure 3. The intramolecular C–H$\cdots\pi$ interaction modes in **3b**.

Table 1. Non-bonded interatomic contacts (Å) and carbon···centroid distances in **3b**

Intramolecular contacts	Distance (Å)	Intramolecular contacts	Distance (Å)
H_{59B}–C_5	2.743	C_{59}–C_5	3.250
H_{59B}–C_4	2.764	C_{41}–C_{53}	3.545
H_{31B}–C_{24}	2.666	C_{41}–C_{54}	2.982
H_{31B}–C_{25}	2.713	C_{41}–C_{55}	3.459
H_{41A}–C_{55}	2.867	C_{31}–C_{24}	3.174
H_{41A}–C_{54}	2.795	C_{31}–C_{25}	3.451
H_{41B}–C_{54}	2.887	C_{40}–centroid	3.048[a]
H_{41B}–C_{53}	3.049	C_{58}–centroid	3.430[b]
C_{59}–C_4	3.545		

[a] The distances between C_{40} and geometric centre of ring A (C_1–C_2–C_3–C_4–C_5–C_6).
[b] The distance between C_{58} and geometric centre of ring B (C_{20}–C_{21}–C_{22}–C_{23}–C_{24}–C_{25}).

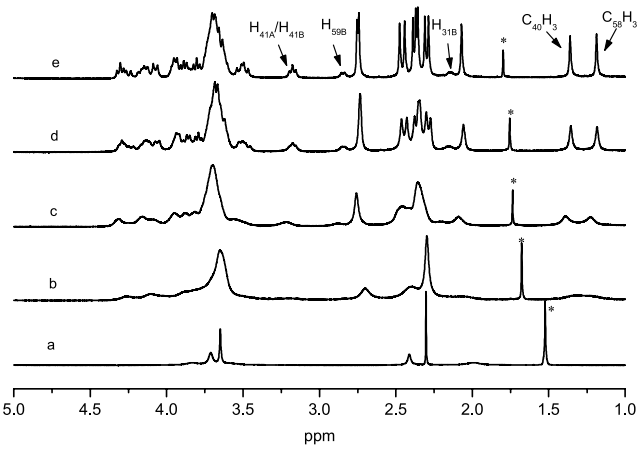


Figure 4. The variable-temperature ^{1}H NMR spectra of **3b** in CD_2Cl_2. (a) 298 K; (b) 253 K; (c) 243 K; (d) 233 K and (e) 223 K; *, residual water signal in CD_2Cl_2.

conformation of flexible molecules.[42] Similarly, intramolecular alkyl–aromatic interaction can perform the same role. This is because the methyl group possesses a three-fold axial symmetry and has more surface contact than aromatic edge–face interaction, which only has one interaction site. In fact the study of conformation population in the molecular folding reported by Wilcox has adduced the evidence that the intramolecular alkyl–aryl interaction has the same significance as the edge–face aromatic interaction in directing the conformation.[16–17] In general, intramolecular closeness between the C–H and π system results from the structural rigidity of a molecule, an attractive force between the C–H and π system or a consequence of crystal packing, which arises from the overall balance of interactions in a crystal structure. In the present case, the crowded structure of the C–H and the π system in **3b** does not come from intrinsic structural rigidity because **3b** can take non-congested conformations (see infra). The distances of C_{sp^2}–C_{sp^3} observed in **3b** was shorter than that of van der Waals contact for C_{sp^2}–C_{sp^3} by 4–19%. It seems persuasive that interactions (models a, b, and c in Fig. 3) are attributable to the stabilization of crystal packing. Taken together, these intramolecular cooperative C–H···π interactions would significantly exert a synergistic effect to force **3b** to take a perpendicular conformation in solid state.

2.3. Dynamic NMR spectroscopic study

Compound **3b**. As mentioned above, the close contacts between the C–H groups and π system in the solid state may stem from the attractive C–H···π interaction instead of crystal packing. However, in solution, if the C–H···π interaction observed functions effectively, **3b** is likely to prefer to a similar conformation to that in solid state when the effect of entropic factors on the conformation preference is reduced to an insignificant level at low temperature. For a flexible molecule, the conformation preference in solution is, however, pertinent to not only the enthalpic but also entropic factors due to the internal mobility[42] even though these C–H···π interactions are energetically attractive. Thus, in comparison with the conformation in solid state, **3b** was examined by ^{1}H NMR spectroscopy at 500 MHz over the temperature range of 298–223 K. (Fig. 4). At ambient temperature, the signals observed in ^{1}H NMR spectrum come from the averaged signals due to the dynamic equilibrium of all conformers. As the temperature decreased there were changes in their chemical shifts and they reappeared as four broad signals at δ 2.7, 2.4, 2.3, and 1.3, respectively. The signals began to sharpen at lower temperatures and at 223 K, 12 relatively sharp singlets with similar integration areas were observed for the methyl protons. It is particularly noteworthy that two substantially shifted signals emerged at δ 1.36 and 1.19. Meanwhile, three sets of signals at δ 3.17, 2.84, and 2.14 with an integration ratio of 2:1:1, which is very likely to correspond to benzylic protons namely H_{41A}/H_{41B}, H_{59B}, and H_{31B} (see Fig. 2a), respectively, were observed at the same temperature.

Considering the possible conformations with high symmetry, five different conformational structures of **3b** (Fig. 5) could correspond to that observed in the low temperature limit. These are **3b-A** (parallel), **3b-B** (perpendicular) or its mirror **3b-C**, **3b-D** (planar), and **3b-E** (stacked). The parallel conformer **3b-A** and planar conformer **3b-D** do not have any of its internal methyl groups lying within the shielding zone of another benzene ring and thus, should not have any significantly shielded methyl protons. Whereas a conformer like stacked **3b-E** is ruled out because it has all four internal methyl protons locating in the shielding zone of the opposite pair of aromatic rings. If the frozen conformation of **3b** were similar to that in the solid state as represented by perpendicular **3b-B** or **3b-C**, then there would be two shielded methyl proton signals that were consistent with what was observed. It was also observed that the three sets of benzylic signals were upfielded shift by ca. 0.47, 0.81, and 1.50 ppm[43] relative to that at room temperature. This concurs with the fact that the magnitude of upfield shifts observed correlates to the intra-atomic separation in solid state (H_{31B}–C_{sp^2} < H_{59B}–C_{sp^2} < H_{41A}(H_{41B})–C_{sp^2}), suggesting that the conformation in solution at low temperature agrees perfectly with that in solid state. Moreover, the ^{13}C NMR spectrum at 178 K might provide useful conformational information (Fig. 6). Two internal methyl carbons subjected to the C–H···π interaction downfielded shift by 0.45 and 1.57 ppm with respect to the chemical shifts at room temperature, while, another pair of internal methyl carbon without being

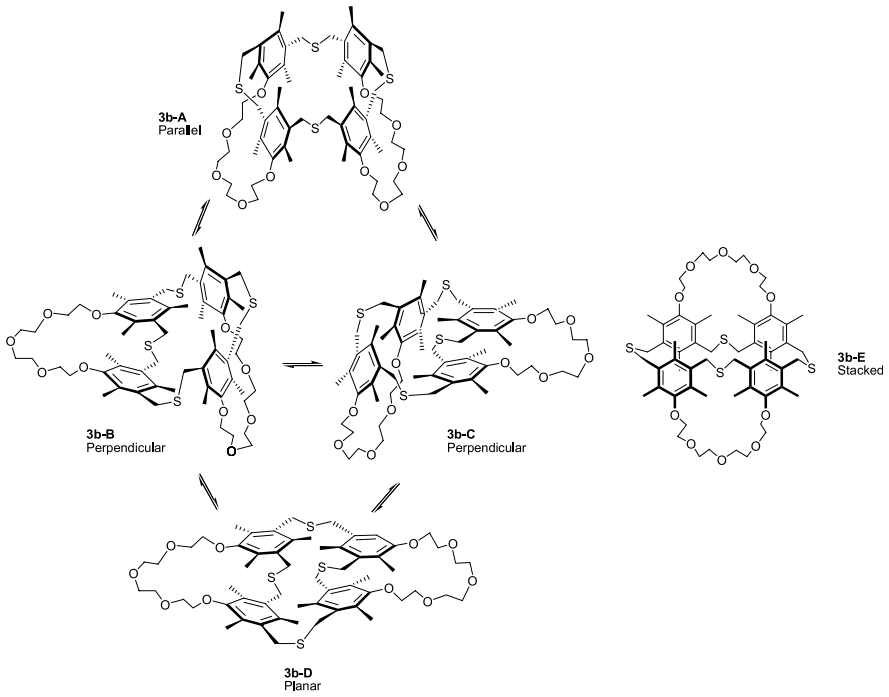


Figure 5. Possible conformation of **3b** in solution.

subjected to the C–H···π interaction experienced an upfielded shift of more than 1.57 ppm.

On the other hand, the inter-conversion between **3b**-**B** ⇔ **3b**-**C** would be established as the temperature was raised. The well-separated pair of significantly shielded methyl signals at high field served as the best probe in this conformational study. Using the Eyring equation,[44] the energy barrier ($\Delta G_c^{\neq}$) of inter-conversion between **3b**-**B** ⇔ **3c**-**C** was estimated to be about 12.1 kcal mol^{-1} (T_c=253 K, $\Delta\nu$=86 Hz).

As shown in Figure 4, all conformers convert rapidly on the NMR time scale at temperatures higher than 253 K. The chemical shifts of internal methyl protons are temperature dependent and are considered as weighted average signals, therefore, it is possible to estimate the enthalpy (ΔH°) and entropy (ΔS°) in terms of the following equations:[42,45]

$$\text{Observed internal methyl chemical shift} = P_1\delta_1 + 3(1-P_1)\delta_2$$

$$\text{Conformation with CH}-\pi\text{ interaction}\left(P_1\right) \overset{K}{\rightleftharpoons} \text{Conformation without CH}-\pi\text{ interaction}\left(1-P_1\right)$$

$$K = \frac{1-P_1}{P_1} = \exp\left[\frac{T\Delta S^\circ - \Delta H^\circ}{RT}\right]$$

Where P_1 is defined as the fractional population of conformers subject to C–H···π interaction and $1-P_1$ is the fractional population of conformers without C–H···π interaction. δ_1 and δ_2 represent the chemical shifts of internal methyl probe with or without C–H···π interaction, respectively. The calculated stabilization enthalpy and entropy are 7.9 ± 0.8 kcal mol^{-1} and 23 ± 3 cal mol^{-1}, respectively. The ΔH° is much larger than the contribution from a single C–H···π interaction (1.45 kcal mol^{-1})[31] and it is high enough to repel **3b** to take a complete perpendicular conformation as observed at low temperature at which the entropic effect was suppressed to a suitable low level. Therefore, we can conclude that in view of the enthalpy, the C–H···π interaction, which was amplified due to the cooperativity effect,[9–10,46] was responsible for the preferential conformation at low temperature.

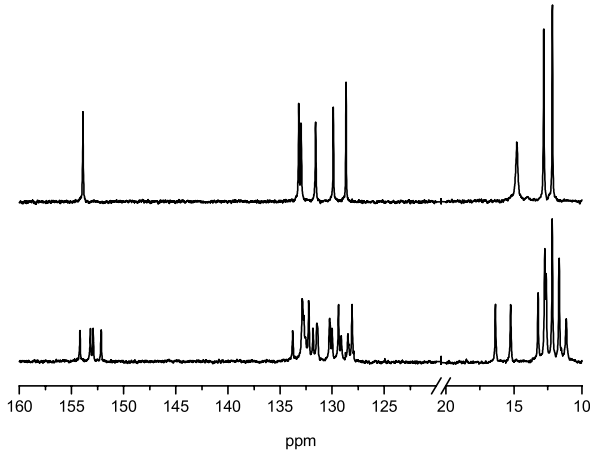


Figure 6. Part of the ^{13}C NMR spectrum of **3b** at 178 K. Top: 298 K and bottom: 178 K.

Compound **3a**. NMR analysis indicated two non inter-converting conformers of **3a** in solution at room temperature. It would thus, be interesting to determine whether they undergo inter-conversion at high temperature. The temperature-dependent ^{1}H NMR spectra of **3a** were measured in deuterated-nitrobenzene from room temperature to 393 K. As

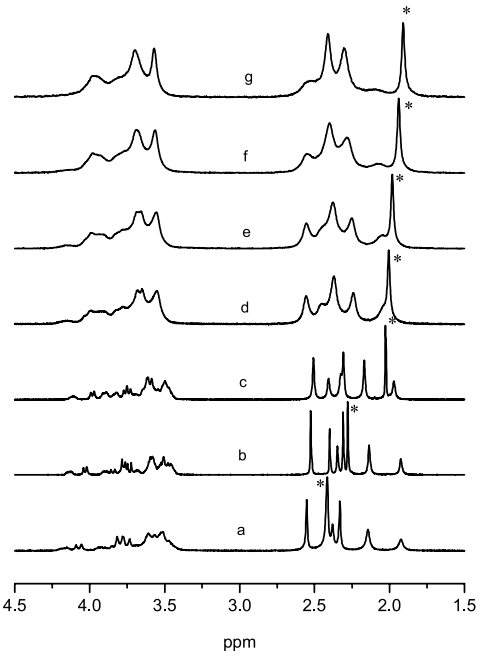


Figure 7. The variable-temperature ^{1}H NMR spectra of **3a** in deuterated nitrobenzene. (a) 300 K; (b) 315 K; (c) 352 K; (d) 368 K; (e) 373 K; (f) 383 and 393 K; *, residual water signal in deuterated nitrobenzene.

the temperature was raised to 393 K, the 12-methyl proton signals broadened and were partially overlapped to appear as four broad signals suggesting a possible inter-conversion between the two conformers or others (Fig. 7).

In contrast, the temperature-dependent ^{1}H NMR spectra of **3a** in CD_2Cl_2 were also determined down to the lower limit of 178 K (Fig. 8). At 300 K, the six methyl proton signals were resolved at δ 2.41, 2.31, 2.25, 2.13, 2.07, and 1.92, the last three being broad singlets. When the temperature was lowered, the three broad signals coalesced at about 273 K, and the other three began to broaden at about 253 K. At and below 233 K many new signals began to appear in the 'aromatic methyl proton' range. The spectra at the low temperature range were rather complicated and no peak

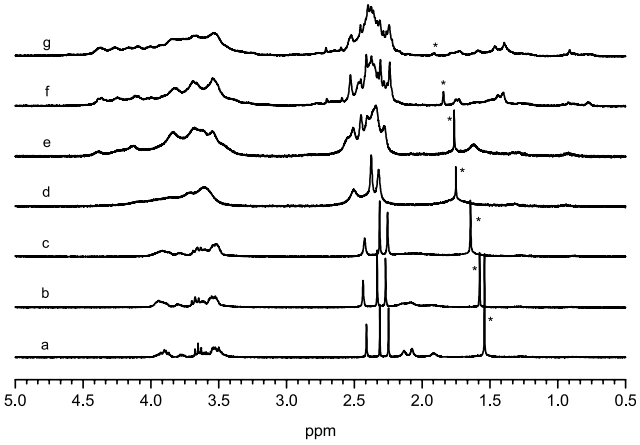


Figure 8. The variable-temperature ^{1}H NMR spectra of **3a** in CD_2Cl_2. (a) 298 K; (b) 283 K; (c) 273 K; (d) 253 K; (e) 233 K; (f) 193 K and (g) 178 K; *, residual water signal in CD_2Cl_2.

assignment or structural feature could be deduced, but the broad peaks around δ 1.40 in the NMR spectra at low temperature gave us an indication that the C–H$\cdots\pi$ interaction exists. The observation in general also indicated that the molecule **3a** could adopt many possible conformations at the low temperature limit but at room temperature two major conformers were present with a relatively high conformational barrier to inter-conversion.

3. Conclusions

In summary, crown-tetrathia[3.3.3.3]metacyclophanes were synthesized via cesium carbonate-assisted high dilution method with intermediate yields. X-ray crystallographic analysis of **3b** demonstrated that one pair of internal methyl groups was in close proximity to the opposite aromatic rings and, meanwhile, four benzylic protons approached the periphery of adjacent aromatic rings. The variable temperature NMR spectroscopic experiments showed that the chemical shifts of one pair of methyl groups and four benzylic protons were upfielded shift at low temperature. The change in chemical shifts intimated that the conformation in solution at low temperature was congruent to that observed in solid state. The correspondence in conformation between solid state and solution as well as the determination of total stabilization enthalpy of the C–H$\cdots\pi$ interaction revealed that the intramolecular cooperative C–H$\cdots\pi$ interaction dominated the preferential conformation both in solid state and in solution.

4. Experimental

4.1. General

All melting points were determined with a Sybron/Thermolyne MP-12615 melting point apparatus and were uncorrected. The ^{1}H NMR spectra were determined using $CDCl_3$ (unless otherwise stated) as solvent at room temperature on a Bruker ACF (300 MHz) or on a Bruker AMX (500 MHz) Fourier transform nuclear magnetic resonance spectrometer. All chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. All ^{13}C NMR were determined in $CDCl_3$ at room temperature on a Bruker ACF (300 MHz) spectrometer. Infrared spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer. Mass spectra were determined on a VG Micromass 7035 mass spectrometer at 70 eV with electron impact or on a Finnegan TSQ mass spectrometer with electrospraying ionization. Relative intensities are given in parenthesis. Microanalysis was performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore.

4.2. Preparation of compounds 1

General procedure. Sodium hydroxide (1.76 g, 44 mmol) was added to a solution of 2,4,6-trimethylphenol (6.0 g, 44 mmol) in THF (100 mL) to form the corresponding phenoxide ion. Oligoethylene glycol dibromide (22 mmol) was then added, and the mixture was stirred and refluxed overnight. After the reaction was complete, the THF in

mixture was removed under the reduced pressure, and then the residue was then poured into water and the product was extracted with dichloromethane. The organic layer was washed, dried, and evaporated. The crude product mixture was chromatographed on silica gel using ethyl acetate/hexane as eluent to give the desired product.

4.2.1. 1,8-Bis(2,4,6-trimethylphenoxyl)-3,6-dioxaoctane (1a). Yield: 64%; white solid: mp 98.5–100 °C; IR (KBr) 3005, 2923, 2895, 2874, 2857, 1486, 1453, 1365, 1322, 1307, 1275, 1236, 1215, 1135, 1041, 955, 904, 858, 783, 595 cm^{-1}. ^1H NMR δ 2.22 (6H, s, CH_3), 2.25 (12H, s, CH_3), 3.79 (4H, s, oxyethylene), 3.82–3.87 (4H, m, oxyethylene), 3.91–3.95 (4H, m, oxyethylene), 6.81 (4H, s, aromatic); MS (EI) *m/z* 386 (M^+, 69). Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.58; H, 8.87. Found: C, 74.28; H, 9.10.

4.2.2. 1,11-Bis(2,4,6-trimethylphenoxyl)-3,6,9-trioxaundecane (1b). Yield: 83%; colorless oil; IR (neat) 3004, 2920, 2870, 2733, 1485, 1460, 1375, 1352, 1308, 1217, 1132, 1060, 1036, 955, 898, 855, 781 cm^{-1}. ^1H NMR δ 2.23 (6H, s, CH_3), 2.25 (12H, s, CH_3), 3.69–3.77 (8H, m, oxyethylene), 3.79–3.86 (4H, m, oxyethylene), 3.89–3.95 (4H, m, oxyethylene), 6.80 (4H, s, aromatic); MS (EI) *m/z* 430 (M^+, 58). Anal. Calcd for $C_{26}H_{38}O_5$: C, 72.53; H, 8.90. Found: C, 72.40; H, 8.74.

4.2.3. 1,14-Bis(2,4,6-trimethylphenoxyl)-3,6,9,12-tetraoxatetradecane (1c). Yield: 38%; pale yellowish oil; IR (neat) 3004, 2920, 2869, 1485, 1460, 1375, 1352, 1308, 1217, 1130, 1060, 955, 898, 855, 782 cm^{-1}. ^1H NMR δ 2.23 (6H, s, CH_3), 2.25 (6H, s, CH_3), 2.26 (6H, s, CH_3), 3.68–3.76 (12H, m, oxyethylene), 3.80–3.84 (4H, m, oxyethylene), 3.89–3.94 (4H, m, oxyethylene), 6.80 (4H, s, aromatic); MS (EI) *m/z* 474 (M^+, 62). Anal. Calcd for $C_{28}H_{42}O_6$: C, 70.86; H, 8.92. Found: C, 70.88; H, 8.79.

4.3. Preparation of compounds 2

General procedure. Compound **1** (7 mmol) was added to a mixture of 47% aq HBr (15 mL) and glacial acetic acid (100 mL), followed by 1,3,5-trioxane (4.8 g, 56 mmol) and tetradecyltrimethyl ammonium bromide (0.60 g). The mixture was warmed up and maintained at a temperature of 70 °C for 2 h followed by heating at 95–97 °C for 5 h (TLC was carefully performed to monitor the completeness of the reaction). After the reaction was complete, the reaction mixture was cooled to room temperature. The mixture was poured into ice-water and extracted with CH_2Cl_2. CH_2Cl_2 was washed with 5% $NaHCO_3$ and water, dried, and filtered. The organic solvent was removed under the reduced pressure and the residue was chromatographed on silica gel using ethyl acetate/hexane as eluent to afford **2**.

4.3.1. 1,8-Bis(2,4,6-trimethyl-3,5-dibromomethylphenoxyl)-3,6-dioxaoctane (2a). Yield: 54%; white solid: mp 147–149 °C; IR (KBr) 2923, 2874, 1457, 1309, 1263, 1208, 1109, 1052, 1020, 928, 873, 835, 628, 554 cm^{-1}. ^1H NMR δ 2.37 (12H, s, CH_3), 2.41 (6H, s, CH_3), 3.79 (4H, s, oxyethylene), 3.86 (8H, s, oxyethylene), 4.56 (8H, s, CH_2Br); MS (EI) *m/z* 754 (M^+, 0.3). Anal. Calcd for $C_{28}H_{38}Br_4O_4$: C, 44.35; H, 5.05. Found: C, 44.60; H, 4.79.

4.3.2. 1,11-Bis(2,4,6-trimethyl-3,5-dibromomethylphenoxyl)-3,6,9-trioxaundecane (2b). Yield: 68%; white solid: mp 131–134 °C; IR (KBr) 3004, 2925, 2870, 1456, 1417, 1379, 1346, 1308, 1263, 1208, 1138, 1105, 1051, 1017, 927, 871, 836, 792, 761, 704, 680, 628, 593, 570, 551, 467 cm^{-1}. ^1H NMR δ 2.36 (12H, s, CH_3), 2.40 (6H, s, CH_3), 3.75 (8H, s, oxyethylene), 3.85 (8H, m, oxyethylene), 4.55 (8H, s, CH_2Br); MS (EI) *m/z* 642 ($M^+ - 2^{79}Br$, 1). Anal. Calcd for $C_{30}H_{42}Br_4O_5$: C, 44.91; H, 5.28. Found: C, 45.30; H, 5.24.

4.3.3. 1,14-Bis(2,4,6-trimethyl-3,5-dibromomethylphenoxyl)-3,6,9,12-tetraoxatetradecane (2c). Yield: 59%; white solid: mp 114–116 °C; IR (KBr) 3005, 2949, 2874, 1455, 1420, 1377, 1348, 1309, 1263, 1208, 1141, 1118, 1108, 1072, 1052, 946, 872, 629, 553, 568, 468 cm^{-1}. ^1H NMR δ 2.36 (12H, s, CH_3), 2.40 (6H, s, CH_3), 3.70 (4H, s, oxyethylene), 3.71–3.77 (8H, m, oxyethylene), 3.80–3.88 (8H, m, oxyethylene), 4.55 (8H, s, CH_2Br); MS (EI) *m/z* 688 ($M^+ - 2Br$, 0.5). Anal. Calcd for $C_{32}H_{46}Br_4O_6$: C, 45.41; H, 5.48. Found: C, 45.42; H, 5.61.

4.4. Preparation of compounds 3

General procedure. A solution of 95% sodium sulfide nonahydrate (480 mg, 2.0 mmol) in 95% ethanol (300 mL) and a solution of tetrabromide **2** (1.0 mmol) in benzene (300 mL) in separate rotaflow dropping funnels were added dropwise simultaneously at the same rate to nitrogen purged 95% ethanol (1 L). After the addition the mixture was stirred for overnight and the bulk of the solvent was removed under reduced pressure. Water and dichloromethane were added to the residue, and the mixture was stirred until all solids dissolved. The organic layer was separated, dried, and evaporated. The residue was chromatographed on silica gel using ethyl acetate/hexane as eluent to give **3**.

4.4.1. 3,11,19,27-Tetrathia-7,15,23,31-biscrown-4-6,8,14,16,22,24,30,32,33,34,35,36,-dodecamethyl-[3.3.3.3]metacyclophane (3a). Yield: 22%; white solid: mp > 300 °C; IR (KBr) 2923, 2873, 1458, 1414, 1372, 1349, 1307, 1259, 1213, 1094, 933 cm^{-1}. ^1H NMR δ 1.91 (br s, CH_3), 2.10 (br s, CH_3), 2.13 (br s, CH_3), 2.26 (s, CH_3), 2.32 (s, CH_3), 2.39 (s, total integration for the six signals 36H with the relative intensities of the first, third, and fifth to the others being 0.7:1), 3.3–4.0 (m, 40H, CH_2S and oxyethylene); ^{13}C NMR δ 12.51, 12.61, 12.77, 12.90, 15.44, 15.71, 29.64, 30.24, 30.55, 32.24, 69.63, 70.41, 71.98, 72.14, 128.44, 128.77, 129.37, 129.55, 131.76, 131.93, 132.21, 132.67, 133.06, 133.39, 154.01, 154.26; MS (ESI) *m/z* 1005.5 ($[M+H]^+$, 15), 1027.5 ($[M+Na]^+$, 100). Anal. Calcd for $C_{56}H_{76}O_8S_4$: C, 66.89; H, 7.62. Found: C, 67.21; H, 7.90.

4.4.2. 3,11,19,27-Tetrathia-7,15,23,31-biscrown-5-6,8,14,16,22,24,30,32,33,34,35,36-dodecamethyl-[3.3.3.3]metacyclophane (3b). Yield: 30%; colorless crystal: mp 146–149 °C; IR (KBr) 2920, 2872, 1458, 1375, 1351, 1308, 1260, 1225, 1100, 936, 875, 731 cm^{-1}. ^1H NMR δ 1.98 (12H, br s, CH_3), 2.31 (12H, s, CH_3), 2.47 (12H, s, CH_3), 3.4–4.0 (48H, br m, CH_2S and oxyethylene); ^{13}C NMR δ 12.23, 12.85, 14.86, 30.14, 31.96, 70.25, 70.48, 70.93, 72.25, 128.75, 129.96, 131.66, 133.03, 133.26, 153.94; MS (ESI) *m/z* 1093.5 ([M+

H]$^+$, 4), 1131.6 ([M+K]$^+$, 100). Anal. Calcd for $C_{60}H_{84}O_{10}S_4$: C, 65.90; H, 7.74. Found: C, 65.63; H, 7.99.

4.4.3. 3,11,19,27-Tetrathia-7,15,23,31-biscrown-6-6,8,14,16,22,24,30,32,33,34,35,36,-dodecamethyl-[3.3.3.3]metacyclophane (3c). Yield: 30%; white solid: mp 194–197 °C; IR (KBr) 2916, 2868, 1458, 1420, 1373, 1351, 1309, 1260, 1242, 1100, 937, 877, 839 cm^{-1}. ^{1}H NMR δ 2.02 (12H, s, CH_3), 2.31 (12H, s, CH_3), 2.46 (12H, s, CH_3), 3.62–3.78 (56H, m, CH_2S and oxyethylene); ^{13}C NMR δ 12.00, 12.69, 14.61, 30.14, 31.93, 70.26, 70.70, 70.92, 71.16, 71.45, 72.02, 128.90, 129.67, 131.80, 132.78, 133.13, 153.43; MS (ESI) *m/z* 1181.7 ([M+H]$^+$, 35), 1203.7 ([M+Na]$^+$, 42). Anal. Calcd for $C_{64}H_{92}O_{12}S_4$: C, 65.05; H, 7.85. Found: C, 65.35; H, 8.00.

5. Supporting materials

Crystallographic data (excluding structure factors) for the structure in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 186822 (**3b**). 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].

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Synthesis of thiazino[6,5-*b*]indole derivatives, analogues of the phytoalexin cyclobrassinin. A new method for preparation of 3-aminomethylindole

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Abstract—An efficient non-reductive synthesis of 3-aminomethylindole (**6**) was developed from gramine (**1**) via 3-phthalimidomethylindole (**2**). The reactions of amine **6** with substituted methyl dithiobenzoates gave 3-(arylthiocarbonylaminomethyl)indoles. The Hugerschoff ring-closure reactions of the thiobenzamide intermediates (**11a–f**) with phenyltrimethylammonium tribromide and subsequent basic treatment furnished 2-arylthiazino[6,5-*b*]indole derivatives (**14a–f**). By use of the latter bromine source, the phytoalexin cyclobrassinin (**8**) was prepared in a considerably higher yield than described previously. The structures of the novel products were elucidated by IR, ^{1}H and ^{13}C NMR spectroscopy, including 2D-HMQC, 2D-HMBC and DEPT measurements.

1. Introduction

The phytoalexins are a group of structurally diverse, low molecular weight, generally lipophilic antimicrobial substances formed in plants.[1] They are not present in healthy plant tissue and are synthesized in response to pathogen attack or physical or chemical stress, probably as a result of the de novo synthesis of enzymes. The accumulation of phytoalexins is one of an array of induced defence responses associated with plant disease resistance.[2]

Numerous phytoalexins are known in cruciferous plants that are important from economic and dietary aspects.[3] Brassinin has been identified as a constituent of cabbage. Some of the *cruciferae* species that have been examined accumulate a novel series of specific indole-sulfur compounds. The basic structures are characterized by an indole ring variably substituted at positions 2 and/or 3 with nitrogen- and sulfur-containing substituents.[4]

Among these compounds, brassinin (**7**) and cyclobrassinin (**8**) exhibit antitumour activity,[5] and brassinin also exerts an antiproliferative effect in human acute T-lymphoblastic leukaemia cells.[6] These compounds can serve as lead compounds for the generation of more efficient analogues.[7] As a continuation of our earlier work on the chemistry of sulfur- and nitrogen-containing condensed-skeleton heterocycles,[8–10] our present aim was the preparation and structural characterization of thiazino[6,5-*b*]indole derivatives, analogues of cyclobrassinin (**8**).

2. Results and discussion

For the synthesis of the above phytoalexins, the key intermediate is usually 3-aminomethylindole (**6**).[11] In the present work too this amine was the first choice as intermediate for the preparation of **7** and **8** and their aryl analogues.

Compound **6** was earlier obtained by the reduction of oxime **3** (Scheme 1),[5,12–15] although some of the reduction procedures (metallic sodium in ethanol,[12] lithium aluminium hydride,[13] and Devarda's alloy[14]) have been reported to be difficult to reproduce and gave low yields.[14–16]

Keywords: Phytoalexins; 3-Aminomethylindole; Thiazino[6,5-*b*]indole; Hugerschoff reaction.
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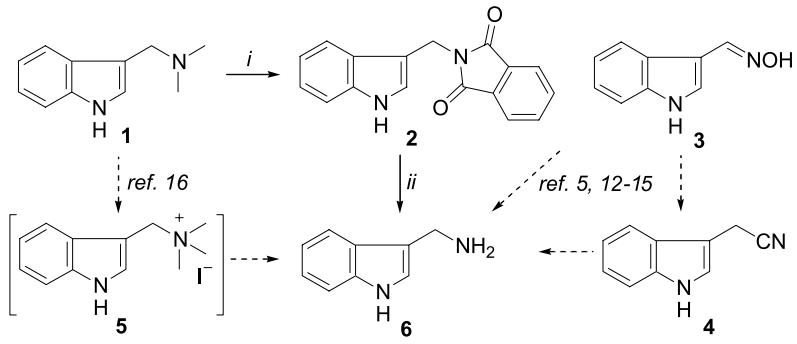


Scheme 1. (i) Phthalimide, neat, 2 h, vacuum; (ii) hydrazine hydrate, EtOH, Δ.

Good yields were obtained by nickel bromide-catalysed reduction with sodium borohydride and subsequent purification by column chromatography[15] and by catalytic hydrogenation with Raney nickel,[5] though amine **6** was not isolated in the latter case.

Another possible route to **6** is the catalytic reduction of the 3-cyano compound **4**.[17] A milligram-scale non-reductive procedure has been reported, starting with the quaternization of gramine (**1**) and subsequent treatment with concentrated ammonia solution. In this case, bis(indolylmethylamine) was formed as a by-product in 13% yield.[16] 3-Aminomethylindole was found to be rather unstable as the free base, and air and light accelerated its decomposition.

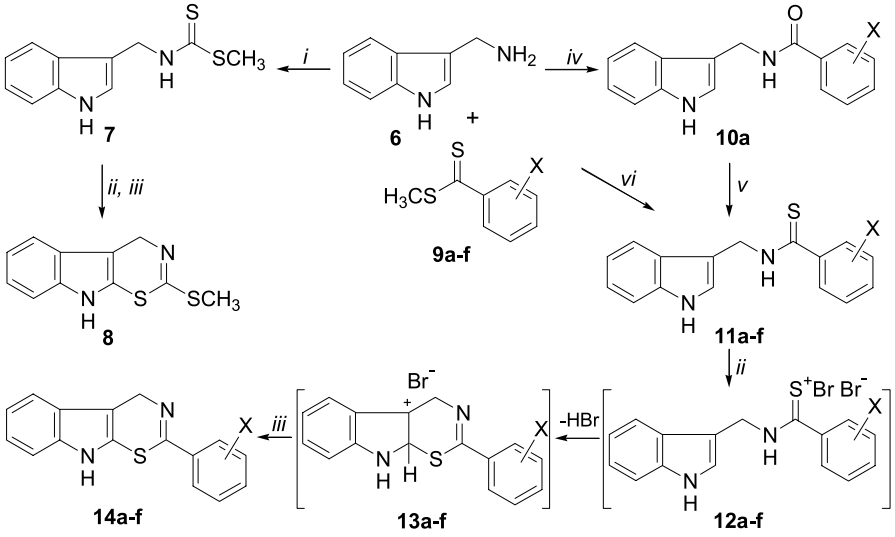
After unsuccessful attemps to reproduce the literature procedures,[13,14] we set out to develop a new method for the gram-scale preparation of **6**. Our attention turned to the phthalimido derivative **2**[18] and an effective, non-reductive method has been developed starting from gramine (**1**). To the best of our knowledge, the preparation of **6** from **2** has not been described previously.

The phthalimide derivative **2** was obtained by a literature procedure.[18] For the splitting-off of the phthalimido group, several reaction conditions were investigated. Finally, this step was performed with hydrazine hydrate under very strict reaction conditions (reflux, 10 min), resulting in **6** in good yield (Scheme 1).

Starting from amine **6**, brassinin (**7**) was prepared in 71% yield by a slight modification of a literature procedure,[19] using chloroform as solvent and triethylamine and catalytic 4-dimethylaminopyridine as base (Scheme 2).

As solid compounds, quaternary ammonium perhalogenides constitute convenient halogen sources. For the ring-closure reaction of brassinin, pyridinium tribromide (yield 35%),[19] *N*-bromosuccinimide (yield 34%)[5] and dioxane dibromide (yield 47%)[20] have been applied earlier. We used phenyltrimethylammonium tribromide. This has been stated to be a selective brominating reagent for arylalkyl ketones, ketones and ketals, which contain double bonds or activated aromatic nuclei, which would be attacked by bromine.[21] We found that a selective Hugerschoff ring-closure reaction with phenyltrimethylammonium tribromide gives cyclobrassinin (**8**) in higher yield (59%) than reported previously (Scheme 2).

The reactions of amine **6** in dichloromethane at rt with



X: H (**a**), 2-Cl (**b**), 4-Cl (**c**), 4-F (**d**), 4-Me (**e**), 2,4-diCl (**f**)

Scheme 2. (i) $CHCl_3$, Et_3N, DMAP, CS_2, MeI; (ii) CH_2Cl_2, $PhMe_3NBr_3$; (iii) Et_3N; (iv) toluene, 5% NaOH, PhCOCl; (v) Lawesson's reagent, THF, rt; (vi) CH_2Cl_2, Et_3N, DMAP.

substituted methyl dithiobenzoates (**9a–f**) furnished 3-(arylthiocarbonylaminomethyl)indoles (**11a–f**). Alternatively, **11a** was prepared by sulfurization from the corresponding benzamide **10a**, using Lawesson's reagent in tetrahydrofuran.

The Hugerschoff reactions of thiobenzamides **11a–f** were also performed with phenyl-trimethylammonium tribromide, affording moderate to good yields. The bromine-mediated cyclization process most probably involves electrophilic addition to the thiocarbonyl moiety, to furnish **12** as a transient intermediate, which is then attacked by the π-electron system of the aromatic ring to give **13**, followed by the rapid formation of **14a–f** in the presence of base (Scheme 2).[22]

3. Structure

The structures of the new compounds follow straightforwardly from the IR, ^{1}H and ^{13}C NMR data. Only a few additional remarks are necessary.

The ring closure of **11**-type thioamides to thiazines was proved by the characteristic changes in the spectra:

(1) Instead of the characteristic[23a] downfield line of the thiocarbonyls (194.3–197.5 ppm for compounds **7** and **11a–f**), the C=N bond of the thiazines gives a ^{13}C NMR line in the interval 150.0–152.0 ppm in the spectra of **8** and **14a–f**.
(2) In consequence of the $-I$ effect of the neighbouring thioimino moiety in the thiazines, the line of the methylene carbon is shifted downfield (48.8–49.3 ppm) as compared with that for the thioamides, where the electron-donating NH group is attached to the methylene carbon (42.0–43.1 ppm). The analogous change was also be observed in the ^{1}H NMR shifts, which are about 5.10 and 5.33 ppm for compounds in the series of types **11** and **14**.
(3) The β effect[23b] of the S substitution on C-9a leads to a significant upfield shift of the C-4a line in the ^{13}C NMR specra of thiazines (from ∼110.7 to ∼99.5 ppm).

The ^{1}H and ^{13}C NMR chemical shifts of the condensed benzene ring are not sensitive to ring closure because of the isolating function of the 9-NH group, which has an electron reservoir nature. Similarly, the aryl substituent does not have a significant influence on the spectral data of the other moieties of these molecules as a consequence of the equalizing role of the thioamide or thioimine groups. The spectroscopic characteristics, IR frequencies, ^{1}H and ^{13}C NMR chemical shifts, intensities, multiplicities and coupling constants are all in accord with those expected for the various aryl groups.

It is worthy of mention that the acidity of 9-NH is slightly stronger in the thiazines, due to the electron-withdrawing effect of the condensed hetero ring: the NH signal is downfield-shifted by ∼0.5 ppm relative to that for the thioamides, from ∼11.0 to ∼11.5 ppm.

4. Experimental

4.1. General

Melting points were determined on a Kofler apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F_{254} plates were used for TLC; the eluent was dichloromethane–*n*-hexane 9/1. Gramine was prepared from indole, 35% formaldehyde solution and a 40% aqueous solution of dimethylamine.[24] Compounds **9a–f** were prepared from substituted benzyl halides and sulfur in the presence of triethylamine by the method of Thiel and Mayer.[25]

IR spectra were recorded in KBr pellets with a Bruker IFS 55 FT-spectrometer. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 solution in 5 mm tubes at rt, on a Bruker DRX 500 spectrometer at 500 (^{1}H) or 125 (^{13}C) MHz, using TMS ($\delta_{TMS}=0$ ppm) as internal reference, with the deuterium signal of the solvent as the lock. Assignments were supported by DEPT, HMQC (except for **14d**,**e**) and HMBC (except for **14d–f**) mesaurements. DEPT spectra were run in a standard manner, using only the $\Theta=135°$ pulse to separate CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. 2D-HMQC and 2D-HMBC spectra were obtained by using the standard Bruker pulse programs INV4GS and INV4GSLPLRND, respectively.

4.2. 3-Aminomethylindole (6)

To a suspension of 3-phthalimidomethylindole[18,26] (**2**) (6.4 g, 23 mmol) in 27 mL of dry ethanol, 85% hydrazine hydrate (10.0 g, 170 mmol) was added and the mixture was intensively stirred on a preheated oil bath at 120 °C for 10 min (after ∼1.5 min, **8** has dissolved and after 4 min, a white precipitate has formed). The reaction mixture was then poured into a mixture of ice-water (120 g) and diethyl ether (100 mL). The mixture was shaken in an ice-bath, while 20% NaOH solution (40 mL) was added. The white precipitate partially dissolved and the aqueous phase was extracted with diethyl ether carefully in a separation funel. The extraction was repeated with diethyl ether (2× 100 mL). The combined organic phase was extracted in turn with 10% NaOH (50 mL) and with water (100 mL) and dried (Na_2SO_4), and the organic solvent was evaporated off (water bath <50 °C). The residue was coevaporated with toluene (2×20 mL; water bath <60 °C) and it was taken up in *n*-hexane and filtered. The crystalline residue was purified by recrystallization from diisopropyl ether and ethyl acetate. After standing at −18 °C, a white crystalline powder was obtained (2.2 g; yield 65%; mp 101–102 °C), lit.[14] mp 103–105 °C. Anal. Calcd for $C_9H_{10}N_2$ (146.19): C, 73.94; H, 6.89; N, 19.16. Found: C, 73.67; H, 7.02; N, 19.24.

4.2.1. 3-(*S*-Methyldithiocarbamoylaminomethyl)indole (7, brassinin). To a stirred solution of 3-aminomethylindole (**5**) (1.0 g, 6.9 mmol) in chloroform (20 mL), triethylamine (0.96 mL, 6.9 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added. Carbon disulfide (0.46 mL, 7.59 mmol) was next added dropwise under ice cooling and the mixture was stirred at the same temperature for 2 h. Methyl iodide (0.44 mL, 6.9 mmol) in chloroform (5 mL)

was then added dropwise to the solution and it was stirred for 5 h at rt. The organic phase was extracted in turn with 3% hydrochloric acid (10 mL) and with water (10 mL), dried (Na_2SO_4) and evaporated. Diisopropyl ether was added to the residue to give **1** as a crystalline powder. White crystals, mp 133–135 °C (lit.[19] mp 132–133 °C), yield 71% (from dichloromethane, *n*-hexane). Anal. Calcd for $C_{11}H_{12}N_2S_2$ (236.36): C, 55.90; H, 5.12; N, 11.85; S, 27.37. Found: C, 55.65; H, 5.24; N, 11.62; S, 27.40; ν_{max} (KBr disc) 3392, 3302, 1480, 1073, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.99 (1H, s, N*H*CH), 10.21 (1H, s, N*H*CH_2), 7.62 (1H, dd, H-4), 7.38 (1H, dd, H-7), 7.34 (1H, s, H-2), 7.10 (1H, dt, H-6), 7.01 (1H, dt, H-5), 4.98 (2H, d, $J=5$ Hz, CH_2), 2.53 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 197.3 (NCSS), 137.0 (C-7a), 127.4 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.6 (C-4 and C-5, overlapping lines), 112.4 (C-7), 111.0 (C-3), 43.1 (*C*H_2), 18.2 (*C*H_3).

4.2.2. 4,9-Dihydro-2-methylthio-1,3-thiazino[6,5-*b*]indole (8, cyclobrassinin). To an intensively stirred solution of brassinin **7** (0.20 g, 0.85 mmol) in dichloromethane (10 mL) at rt, phenyltrimethylammonium tribromide (0.32 g, 0.85 mmol) was added in one portion. After stirring for 45 s, triethylamine (0.24 mL, 1.7 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was purified by column chromatography, using dichloromethane–*n*-hexane (1/1, followed by 2/1) as eluent, to give **8** after evaporation as a crystalline powder (0.12 g). White crystals, mp 135–136 °C (lit.[19] mp 136–137 °C), yield 59%. Anal. Calcd for $C_{11}H_{10}N_2S_2$ (234.34): C, 56.38; H, 4.30; N, 11.95; S, 27.37. Found: C, 56.21; H, 4.42; N, 12.02; S, 27.42; ν_{max} (KBr disc) 3370, 1602, 765 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.43 (1H, s, N*H*), 7.48 (1H, dd, H-5), 7.34 (1H, dd, H-8), 7.09 (1H, dt, H-7), 7.03 (1H, dt, H-6), 5.06 (2H, s, CH_2), ~2.50 (3H, s, CH_3 overlapped by the light isotope signal of the solvent); δ_C (126 MHz, DMSO-d_6) 151.7 (C-2), 137.4 (C-8a), 125.4 (C-4b), 122.3* (C-9a), 122.2* (C-7), 120.2 (C-6), 117.8 (C-5), 111.9 (C-8), 102.5 (C-4a), 48.9 (C-4), 15.5 (*C*H_3), *interchangeable assignments.

4.2.3. 3-(Benzoylaminomethyl)indole (10a). Amine **6** (0.72 g, 3.50 mmol) was dissolved in toluene (25 mL). To this solution, sodium hydroxide (0.62 g, 15.40 mmol) dissolved in water (10 mL) was added. After the addition of benzoyl chloride (0.42 g, 3.85 mmol), the reaction mixture was shaken intensively for 20 min. The crystals that separated out were filtered off and washed in turn with water and with toluene and dried. The white crystalline benzamide was recrystallized from diisopropyl ether. White powder, mp 157–159 °C, 0.82 g, yield 85%. Anal. Calcd for $C_{16}H_{14}N_2O$ (250.30): C, 76.78; H, 5.64; N, 11.19. Found: C, 76.92; H, 5.81; N, 11.29; ν_{max} (KBr disc) 3416, 3302, 1628, 738, 695 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 10.90 (1H, s, N*H*CH), 8.80 (1H, s, N*H*CH_2), 7.87 (2H, H2′,6′), 7.66 (1H, dd, H-4), 7.45 (1H, H-4′), 7.43 (2H, H-3′,5′), 7.36 (1H, dd, H-7), 7.29 (1H, d, H-2), 7.07 (1H, dt, H-6), 6.98 (1H, dt, H-5), 4.64 (2H, d, $J=5.6$ Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 166.9 (CO), 137.2 (C-7a), 134.5 (C-1′), 131.9 (C-4′), 129.1 (C-3′,5′), 128.1 (C-2′,6′), 127.4 (C-3a), 124.8 (C-2), 122.0 (C-6), 119.7 (C-4), 119.4 (C-5), 113.5 (C-3), 112.3 (C-7), 35.5 (*C*H_2).

4.2.4. 3-(Thiobenzoylaminomethyl)indole (11a) from benzamide 10a. To a solution of 3-(benzoylaminomethyl)-indole (**10a**) (0.2 g, 0.8 mmol) in tetrahydrofuran (15 mL), Lawesson's reagent (0.32 g, 0.8 mmol) was added in one portion. The reaction mixture was stirred at rt for 24 h. After evaporation the residue was purified by column chromatography using dichloromethane–*n*-hexane as eluent to give **11a** as a pale-yellow crystalline powder (analytical data identical to those given above).

4.3. General procedure for 3-(arylthiocarbonylaminomethyl)indoles (11a–f) from 6 and methyl dithiobenzoates (9a–f)

Amine **6** (0.52 g, 2.53 mmol) was dissolved in dichloromethane (20 mL). To this solution, triethylamine (0.50 g, 11.12 mmol) and 4-dimethylaminopyridine (0.06 g, 0.5 mmol) were added. After the addition of the appropriate methyl dithiobenzoate (**9a–f**) (2.78 mmol), the reaction mixture was left at rt in a good hood for 2-3 days. After evaporation, the residue was dissolved in dichloromethane (30 mL). The organic phase was extracted in turn with 3% hydrochloric acid (10 mL), 3% sodium hydroxide (10 mL) and water (10 mL), dried (Na_2SO_4) and evaporated. Trituration of the residue with diisopropyl ether gave **11a–f** as crystalline powders.

4.3.1. 3-(Thiobenzoylaminomethyl)indole (11a). Pale-yellow crystals, mp 145–146 °C (from dichloromethane, *n*-hexane), yield 74%. Anal. Calcd for $C_{16}H_{14}N_2S$ (266.36): C, 72.15; H, 5.30; N, 10.52; S, 12.04. Found: C, 72.35; H, 5.51; N, 10.32; S, 12.30; ν_{max} (KBr disc) 3359, 3268, 1480, 1233, 775, s750, 690 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.59 (1H, s, N*H*CH_2), 7.72–7.73 (3H, m, H-4 and H2′,6′, overlapping signals), 7.38–7.45 (5H, m, H-2, H-7, H-3′,5′ and H-4′, overlapping signals), 7.12 (1H, dt, H-6), 7.03 (1H, dt, H-5), 5.14 (2H, d, $J=$ 4.2 Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 197.5 (*C*S), 142.3 (C-1′), 137.1 (C-7a), 131.3 (C-4′), 128.7 (C-3′,5′), 128.2 (C-2′,6′), 127.6 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.6 (C-4 and C-5, two overlapping lines), 112.4 (C-7), 111.1 (C-3), 43.1 (*C*H_2).

4.3.2. 3-(2-Chlorothiobenzoylaminomethyl)indole (11b). White crystals, mp 113–115 °C (from dichloromethane, *n*-hexane), yield 62%. Anal. Calcd for $C_{16}H_{13}ClN_2S$ (300.81): C, 63.89; H, 4.36; N, 9.31; S, 10.66. Found: C, 63.59; H, 4.32; N, 9.50; S, 10.82; ν_{max} (KBr disc) 3411, 3309, 1456, 1240, 756, 741 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.80 (1H, s, N*H*CH_2), ~7.4 (3H, m, H-2, H-7, H-6′, overlapping signals), ~7.32 (3H, m, H-3′,5′ and H-4′, overlapping signals), 7.69 (1H, dd, H-4), 7.12 (1H, dt, H-6), 7.04 (1H, dt, H-5), 5.05 (2H, d, $J=$ 5.0 Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 195.5 (*C*S), 143.5 (C-1′), 137.1 (C-7a), 130.4* (C-4′), 130.1 (C-6′), 129.5* (C-3′), 129.1 (C-2′), 127.7* (C-5′), 127.5 (C-3a), 125.8 (C-2), 122.2 (C-6), 119.7 (C-4), 119.6 (C-5), 112.4 (C-7), 110.4 (C-3), 42.0 (*C*H_2). *interchangeable assignments.

4.3.3. 3-(4-Chlorothiobenzoylaminomethyl)indole (11c). Yellow crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 65%. Anal. Calcd for $C_{16}H_{13}ClN_2S$ (300.81): C, 63.89; H, 4.36; N, 9.31; S, 10.66. Found: C,

63.78; H, 4.50; N, 9.22; S, 10.82; ν_{max} (KBr disc) 3359, 3262, 1447, 1233, 839, 813, 751 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.03 (1H, s, N*H*CH), 10.66 (1H, s, N*H*CH_2), 7.74 (2H, H-2′,6′), 7.68 (1H, dd, H-4), 7.45 (2H, m, H-3′,5′), 7.42 (1H, s, H-2), 7.40 (1H, dd, H-7), 7.11 (1H, dt, H-6), 7.02 (1H, dt, H-5), 5.11 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 195.9 (*C*S), 140.8 (C-1′), 137.1 (C-7a), 136.1 (C-4′), 130.0 (C-2′,6′), 128.7 (C-3′,5′), 127.6 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.7 (C-5), 119.6 (C-4), 112.4 (C-7), 110.8 (C-3), 42.8 (*C*H_2).

4.3.4. 3-(4-Fluorothiobenzoylaminomethyl)indole (11d). Yellow crystals, mp 125–127 °C (from dichloromethane, *n*-hexane), yield 57%. Anal. Calcd for $C_{16}H_{13}FN_2S$ (284.35): C, 67.58; H, 4.61; N, 9.85; S, 11.28. Found: C, 67.36; H, 4.82; N, 10.02; S, 11.10; ν_{max} (KBr disc) 3390, 3252, 1456, 840, 742 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.02 (1H, s, N*H*CH), 10.60 (1H, s, N*H*CH_2), 7.72 (2H, H-2′,6′), 7.68 (1H, dd, H-4), 7.41 (1H, s, H-2), 7.39 (1H, dd, H-7), 7.22 (2H, H-3′,5′), 7.10 (1H, dt, H-6), 7.01 (1H, dt, H-5), 5.10 (2H, d, $J=5.3$ Hz, CH_2); δ_C* (126 MHz, DMSO-d_6) 196.0 (*C*S), 164.3 (C-4′), 138.6 (C-1′), 137.1 (C-7a), 130.7 (C-2′,6′), 127.5 (C-3a), 125.8 (C-2), 122.1 (C-6), 119.63 (C-4), 119.58 (C-5), 115.5 (C-3′,5′), 112.4 (C-7), 110.9 (C-3), 42.8 (*C*H_2), *due to F,C-couplings, the signals of the aryl group are doublets, ^1J(F,C): 248.4 Hz, ^2J(F,C): 22.8 Hz, ^3J(F,C): 9.2 Hz, ^4J(F,C): 2.7 Hz.

4.3.5. 3-(4-Methylthiobenzoylaminomethyl)indole (11e). Yellow crystals, mp 133–135 °C (from dichloromethane, *n*-hexane), yield 55%. Anal. Calcd for $C_{17}H_{16}N_2S$ (280.39): C, 72.82; H, 5.75; N, 9.99; S, 11.44. Found: C, 72.96; H, 5.92; N, 10.18; S, 11.25; ν_{max} (KBr disc) 3302, 3250, 1456, 1278, 844, 737 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.00 (1H, s, N*H*CH), 10.47 (1H, s, N*H*CH_2), 7.70 (1H, dd, H-4), 7.66 (2H, H-2′,6′), 7.40 (1H, s, H-2), 7.39 (1H, dd, H-7), 7.19 (2H, m, H-3′,5′), 7.11 (1H, dt, H-6), 7.01 (1H, dt, H-5), 5.12 (2H, d, $J=5.3$ Hz, CH_2), 2.31 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 197.1 (*C*S), 141.3 (C-4′), 139.4 (C-1′), 137.1 (C-7a), 129.2 (C-3′,5′), 128.3 (C-2′,6′), 127.6 (C-3a), 125.7 (C-2), 122.1 (C-6), 119.66 (C-4), 119.59 (C-5), 112.4 (C-7), 111.2 (C-3), 42.6 (*C*H_2), 21.7 (*C*H_3).

4.3.6. 3-(2,4-Dichlorothiobenzoylaminomethyl)indole (11f). White crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 71%. Anal. Calcd for $C_{16}H_{12}Cl_2N_2S$ (335.25): C, 57.32; H, 3.61; N, 8.36; S, 9.56. Found: C, 57.18; H, 3.78; N, 8.28; S, 10.15; ν_{max} (KBr disc) 3302, 3248, 1456, 1281, 819, 801*, 758 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.04 (1H, s, N*H*CH), 10.84 (1H, s, N*H*CH_2), 7.69 (1H, dd, H-4), 7.59 (1H, s, H-3′), 7.30–7.40 (4H, m, H-2, H-7, H-5′, H-2′,6′, overlapping signals), 7.12 (1H, dt, H-6), 7.04 (1H, dt, H-5), 5.05 (2H, d, $J=4.5$ Hz, CH_2); δ_C (126 MHz, DMSO-d_6) 194.3 (*C*S), 142.3 (C-1′), 137.1 (C-7a), 134.1 (C-4′), 130.8 (C-6′), 130.3 (C-2′), 129.5 (C-3′), 128.0 (C-5′), 127.5 (C-3a), 125.9 (C-2), 122.2 (C-6), 119.6 (C-4 and C-5, two overlapping lines), 112.4 (C-7), 110.2 (C-3), 42.1 (*C*H_2).

4.4. General procedure for 4,9-dihydro-2-aryl-1,3-thiazino[6,5-*b*]indole (14a–f) from 3-(arylthiocarbonylaminomethyl)indoles (11a–f)

To an intensively stirred solution of thiocarboxamide **11a–f** (0.85 mmol) in dichloromethane (10 mL) at rt phenyltrimethylammonium tribromide (0.32 g, 0.85 mmol) was added in small portions during 1 min. After stirring for 5 min, triethylamine (0.24 mL, 1.7 mmol) was added in one portion. The mixture was evaporated (water bath <50 °C) and the residue was purified by column chromatography, using first dichloromethane–*n*-hexane (1/1, followed by 2/1) as eluent to give **14a–f** as a crystalline powder.

4.4.1. 4,9-Dihydro-2-phenyl-1,3-thiazino[6,5-*b*]indole (14a). Orange crystals, mp 132–135 °C (ethanol), yield 51%. Anal. Calcd for $C_{16}H_{12}N_2S$ (264.35): C, 72.70; H, 4.58; N, 10.60; S, 12.13. Found: C, 72.62; H, 4.74; N, 10.81; S, 12.02; ν_{max} (KBr disc) 3390, 1620, 761, 737, 698 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.53 (1H, s, N*H*), 7.89 (2H, H-2′,6′), 7.55 (1H, H-4′), ~7.50 (3H, m, H-5 and H-3′,5′, overlapping signals), 7.37 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.32 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 152.0 (C-2), 138.2 (C-1′), 137.5 (C-8a), 132.1 (C-4′), 129.7 (C-3′,5′), 127.5 (C-2′,6′), 125.3 (C-4b), 123.0 (C-9a), 122.1 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.7 (C-4a), 49.0 (C-4).

4.4.2. 4,9-Dihydro-2-(2-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14b). Brown crystals, mp 143–145 °C (ethanol), yield 64%. Anal. Calcd for $C_{16}H_{11}ClN_2S$ (298.79): C, 64.32; H, 3.71; N, 9.38; S, 10.73. Found: C, 64.15; H, 3.92; N, 9.45; S, 10.75; ν_{max} (KBr disc) 3500–2000, 1630, 759, 745 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.49 (1H, s, N*H*), 7.58 (1H, H-6′), ~7.50 (3H, m, H-5 and H-3′,5′, overlapping signals), 7.45 (1H, H-4′), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.07 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 150.7 (C-2), 138.6 (C-2′), 137.4 (C-8a), 132.2 (C-5′), 131.4 (C-1′), 130.8 (C-6′), 130.4 (C-3′), 128.5 (C-4′), 125.3 (C-4b), 122.9 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.2 (C-4a), 49.3 (C-4).

4.4.3. 4,9-Dihydro-2-(4-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14c). Light-brown crystals, mp 147–149 °C (ethanol), yield 61%. Anal. Calcd for $C_{16}H_{11}ClN_2S$ (298.79): C, 64.32; H, 3.71; N, 9.38; S, 10.73. Found: C, 64.11; H, 3.80; N, 9.56; S, 10.85; ν_{max} (KBr disc) 3500–2000, 1624, 834, 748 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.54 (1H, s, N*H*), 7.89 (2H, H-2′,6′), 7.56 (2H, H-3′,5′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 151.0 (C-2), 137.5 (C-8a), 136.9 (C-1′), 136.8 (C-4′), 129.8 (C-3′,5′), 129.2 (C-2′,6′), 125.2 (C-4b), 122.5 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.7 (C-4a), 49.0 (C-4).

4.4.4. 4,9-Dihydro-2-(4-fluorophenyl)-1,3-thiazino[6,5-*b*]indole (14d). Brown crystals, mp 144–149 °C (ethanol), yield 54%. Anal. Calcd for $C_{16}H_{11}FN_2S$ (282.33): C, 68.06; H, 3.93; N, 9.92; S, 11.36. Found: C, 67.70; H, 4.11; N, 10.1; S, 11.46; ν_{max} (KBr disc) 3397, 1633, 1247, 842, 740 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.53 (1H, s, N*H*), 7.94 (2H, H-2′,6′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.34 (2H, H-3′,5′), 7.11 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.33 (2H, s, CH_2); δ_C* (126 MHz, DMSO-d_6) 164.7 (C-4′), 150.9 (C-2), 137.5 (C-8a), 134.7 (C-1′), 129.9 (C-2′,6′), 125.3 (C-4b), 122.7 (C-9a), 122.2 (C-7), 120.3 (C-6), 118.8

(C-5), 116.7 (C-3′,5′), 111.8 (C-8), 99.7 (C-4a), 48.9 (C-4), *due to F,C-couplings, the signals of the aryl group are doublets, ^{1}J(F,C): 249.3 Hz, ^{2}J(F,C): 22.0 Hz, ^{3}J(F,C): 9.2 Hz, ^{4}J(F,C): 2.7 Hz.

4.4.5. 4,9-Dihydro-2-(4-methylphenyl)-1,3-thiazino[6,5-*b*]indole (14e). Light-brown crystals, mp 148–150 °C (from dichloromethane, *n*-hexane), yield 71%. Anal. Calcd for $C_{17}H_{14}N_2S$ (278.37): C, 73.35; H, 5.07; N, 10.06; S, 11.52. Found: C, 73.52; H, 5.12; N, 10.27; S, 11.61; ν_{max} (KBr disc) 3400, 1633, 842, 736 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.51 (1H, s, N*H*), 7.78 (2H, H-2′,6′), 7.49 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.29 (2H, H-3′,5′), 7.10 (1H, dt, H-7), 7.05 (1H, dt, H-6), 5.31 (2H, s, CH_2), 2.35 (3H, s, CH_3); δ_C (126 MHz, DMSO-d_6) 151.8 (C-2), 142.0 (C-4′), 137.4 (C-8a), 135.5 (C-1′), 130.2 (C-3′,5′), 127.4 (C-2′,6′), 125.3 (C-4b), 123.1 (C-9a), 122.1 (C-7), 120.2 (C-6), 117.9 (C-5), 111.7 (C-8), 99.8 (C-4a), 48.8 (C-4), 21.8 (*C*H_3).

4.4.6. 4,9-Dihydro-2-(2,4-chlorophenyl)-1,3-thiazino[6,5-*b*]indole (14f). Brown crystals, mp 157–160 °C (ethanol), yield 42%. Anal. Calcd for $C_{16}H_{10}Cl_2N_2S$ (333.24): C, 57.67; H, 3.02; N, 8.41; S, 9.56. Found: C, 57.82; H, 3.15; N, 8.53; S, 9.44; ν_{max} (KBr disc) 3366, 824, 753 cm^{-1}; δ_H (500 MHz, DMSO-d_6) 11.50 (1H, s, N*H*), 7.75 (1H, H-3′), 7.57 (1H, H-6′), 7.53 (1H, H-5′), 7.50 (1H, dd, H-5), 7.36 (1H, dd, H-8), 7.11 (1H, dt, H-7), 7.06 (1H, dt, H-6), 5.34 (2H, s, CH_2); δ_C (126 MHz, DMSO-d_6) 150.0 (C-2), 137.40* (C-4′), 137.38* (C-8a), 136.0 (C-2′), 132.7 (C-1′), 131.8 (C-6′), 130.5 (C-3′), 128.7 (C-5′), 125.3 (C-4b), 122.5 (C-9a), 122.3 (C-7), 120.3 (C-6), 118.0 (C-5), 111.8 (C-8), 99.2 (C-4a), 49.3 (C-4), *interchangeable assignments.

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New approach to λ^5-phosphinines

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Abstract—A novel approach to λ^5-phosphinines has been discovered. Phosphonium salts bearing an alkyl group and the residue of β-dialkylaminocrotonic acid react with DMADMF affording λ^5-phosphinines. A plausible mechanism of the reaction is offered.

1. Introduction

Over 40 years ago the first representatives of λ^5-phosphinines, a hitherto unknown class of heterocyclic compounds, were synthesized, thus starting a thorough study of them in the following years.[1] Various methods for their synthesis have been offered, but in general almost all known methods start from λ^3-phosphinines or dihydrophosphinines.[2] So far, synthesis by oxidative addition starting from trivalent phosphinine derivatives is the most common method. Synthetic approaches to λ^3-phosphinines are summarized in review by Markl.[3] The properties of these compounds were studied thoroughly and they have been shown to be a valuable class of organophosphorus compounds. Recently, λ^3-phosphinines have been demonstrated to act as superior ligands compared to conventional phosphines in rhodium catalyzed hydroformylation of alkenes.[4] It was also shown that λ^5-phosphinines are quite stable and could survive relatively harsh reaction conditions.[5] A comprehensive review on their synthesis and properties has shown that despite available methods, the phosphinines remain poorly accessible compounds.[2] This lack of a convenient method for their synthesis hampers their further use.

Continuing our study directed at phosphorylated enamines[6] we have discovered a very simple method for the synthesis of the λ^5-phoshinines starting from linear phosphorylated enamines.

2. Results and discussion

It has already been shown by us that push–pull enamines are readily phosphorylated with diphenylchlorophosphine giving stable phosphine derivatives.[6] Continuing our systematic research on phosphorylation of push–pull enamines we found that enamine **1** is readily phosphorylated with phosphorus trichloride in the presence of bases, giving derivative **2**. The dichlorophosphine **2** is a thermally unstable compound, which we failed to isolate in analytically pure state. However, the dichlorophosphine **2** exists for a quite a long time in solution and owing to high selectivity of the reaction it is convenient to use its benzene solution for further transformations. The dichlorophosphine **2** was transformed into diamide derivative **3** followed by treatment with a set of alkylating agents, thus affording phosphonium salts **4a–c** (Scheme 1).

These salts are stable compounds, although hydroscopic in some cases (**4b**,**c** and **5a**,**b**). Analogously, phosphonium salts **5a–c** were prepared,[6a] purified and characterized. The phosphonium salts **4**, **5** were treated with DMADMF in order to prepare dienamine derivatives of type **9**. It is well known that the enamine bearing an alkyl group at the α-position and strong electron-accepting substituents at the β-position have a sufficiently acidic methyl (methylene) group that reacts quite readily with DMADMF.[7] Unexpectedly, upon treatment of phosphonium salts **4**, **5** with DMADMF λ^5-phosphinine derivatives **6**, **7** formed, with no linear products being registered at all (Scheme 1). The yields of the phosphinines were not optimized, but in all cases ^{31}P NMR spectra of the reaction mixture exhibited only phosphinine signal. The compounds proved to be very stable, surviving aqueous alkaline work-up and chromatographic separation.

The structure of the λ^5-phosphinines obtained was

Keywords: λ^5-Phosphinines; Phosphonium salts; Phosphorylated enamines; DMADMF.
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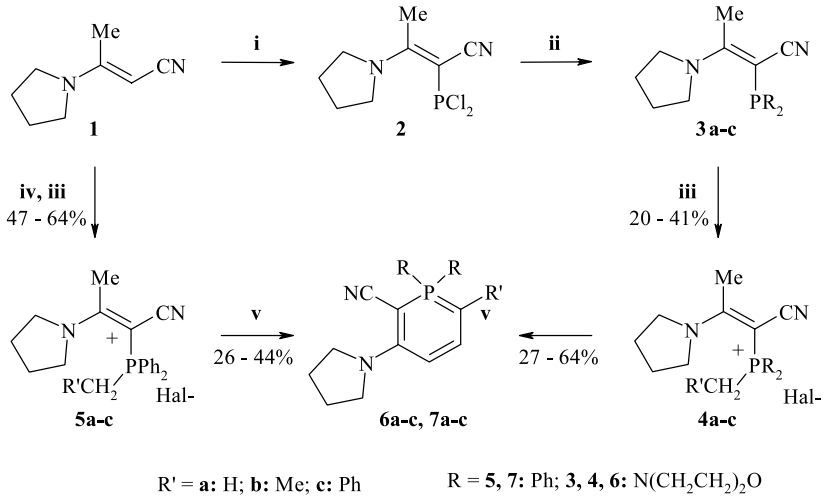


Scheme 1. Reagents and conditions: (i) PCl_3, C_6H_6, $(i\text{-Pr})_2NEt$; (ii) $HN(CH_2CH_2)_2O$, C_6H_6, $(i\text{-Pr})_2NEt$; (iii) C_6H_6, 80 °C, for a: MeI, for b: EtI, for c: BnBr; (iv), Ph_2PBr, C_6H_6, $(i\text{-Pr})_2NEt$; (v) DMADMF, 120 °C.

confirmed by ^1H (Table 1), ^{13}C (Table 2), ^{31}P NMR spectroscopy, mass spectrometry, and elemental analysis. Characteristic features for λ^5-phosphinine ring in the ^1H NMR spectra are spin–spin coupling interactions between the phosphorus atom and protons of the ring and in ^{13}C NMR spectra signal of carbon atoms with characteristic C–P coupling constants (Fig. 1).

To rationalize the reaction, we can consider two possible reaction pathways. Thus, the phosphonium salts bearing two active methyl (methylene) groups, namely P–CH_2–R and Me group at the α-carbon atom of the enamines are capable of reacting with DMADMF.[7,8]

In order to check the proposed mechanism of the reaction where the first step is the introduction of dimethylaminomethylene group at the Me group at the α-carbon atom of the enamines, we embarked on the synthesis of the linear dienamine derivatives bearing a phosphonium substituent. Unfortunately, all our attempts to carry out the reaction under milder conditions, or use equivalent amounts of reagents always resulted in the final phosphinines, with no linear products being registered. To synthesize these compounds we have used another approach. We have prepared linear dienamine derivatives bearing a pentavalent phosphorus group without an alkyl group. Thus, pentavalent derivatives **8a–c** readily reacted with DMADMF affording phosphorylated linear dienamines **9a–c** in high yields. Unfortunately, we failed to carry out reduction of phosphineoxide **9a**[9] or phosphinethioxide **9b**[10] to the corresponding phosphine **10**. The reagent of choice appeared to be the selenide derivative.[11] The phosphine selenide **9c** was treated with hexamethylphosphorus triamide affording in high yield phosphine **10**, which was further transformed into phosphonium salts **11** upon treatment with alkyl halides (Scheme 2).

We have also synthesized another model dienamine **14**. Enamine **1** reacted readily with dichloromethylphosphine giving chlorophosphine, which in turn, was subjected to the

Table 1. ^1H NMR data of compounds **6**, **7**, **19**

N	^1H NMR (300 MHz), δ (ppm), J (Hz)				
	$NAlk_2$	R	R′	C(4)H or C(4)–CHO	C(5)H
6a[a]	1.92 (4H, br m), 3.55 (4H, br m)	3.12 (8H, br m), 3.69 (8H, br m)	4.01 (1H, dd, $^3J_{HH}$= 11.1 Hz, $^2J_{PH}$=11.1 Hz)	4.72 (1H, d, $^3J_{HH}$= 8.1 Hz)	7.09 (1H, ddd, $^3J_{HH}$= 11.1 Hz, $^3J_{HH}$=8.1 Hz, $^3J_{PH}$=44.4 Hz)
6b[a]	1.37 (4H, br m), 3.45 (4H, br m)	2.87 (8H, br m), 3.45 (8H, br m)	1.64 (3H, d, $^3J_{PH}$= 12.3 Hz)	4.76 (1H, d, $^3J_{HH}$= 8.0 Hz)	6.91 (1H, dd, $^3J_{HH}$= 8.0 Hz, $^3J_{PH}$=40.5 Hz)
6c[a]	1.92–1.99 (4H, m), 3.51–3.69 (4H, m)	3.05–3.21 (8H, m), 3.51–3.69 (8H, m)	7.13 (1H, t, $^3J_{HH}$= 6.6 Hz), 7.24–7.33 (4H, m)	4.90 (1H, dd, $^3J_{HH}$= 9.3 Hz, $^4J_{PH}$=1.8 Hz)	7.26 (1H, dd, $^3J_{HH}$= 9.3 Hz, $^3J_{PH}$=39 Hz)
7a[a]	1.25 (4H, m, $^3J_{HH}$= 6.6 Hz), 3.42 (4H, t, $^3J_{HH}$=6.6 Hz)	7.00–7.08 (6H, m), 7.68–7.77 (4H, m)	4.05 (1H, dd, $^3J_{HH}$= 11.1 Hz, $^2J_{PH}$=20.1 Hz)	4.72 (1H, d, $^3J_{HH}$=9 Hz)	7.15 (1H, ddd, $^3J_{HH}$= 11.1 Hz, $^3J_{HH}$=9 Hz, $^3J_{PH}$=39 Hz)
7b[a]	1.28 (4H, m, $^3J_{HH}$= 6.6 Hz), 3.45 (4H, t, $^3J_{HH}$=6.6 Hz)	7.00–7.14 (6H, m), 7.64–7.80 (4H, m)	1.72 (3H, d, $^3J_{PH}$= 13.2 Hz)	4.66 (1H, d, $^3J_{HH}$= 8.4 Hz)	6.96 (1H, dd, $^3J_{HH}$= 8.4 Hz, $^3J_{PH}$=36.9 Hz)
7c[a]	1.19 (4H, m, $^3J_{HH}$= 6.6 Hz), 3.38 (4H, t, $^3J_{HH}$=6.6 Hz)	6.97–7.03 (6H, m), 7.88–7.97 (4H, m)	6.82 (1H, t, $^3J_{HH}$= 7.5 Hz), 6.98 (2H, t, $^3J_{HH}$=7.5 Hz), 7.23 (2H, d, $^3J_{HH}$=7.5 Hz)	4.89 (1H, dd, $^3J_{HH}$= 9.3 Hz, $^4J_{PH}$=1.5 Hz)	7.58 (1H, dd, $^3J_{HH}$= 9.3 Hz, $^3J_{PH}$=33.6 Hz)
19[b]	2.06 (4H, br), 3.56 (4H, br)	7.55–7.78 (10H, m)	5.59 (1H, dd, $^3J_{HH}$= 11.4 Hz, $^2J_{PH}$=24 Hz)	8.37 (1H, s)	8.06 (1H, dd, $^3J_{HH}$= 11.4 Hz, $^3J_{PH}$=38.1 Hz)

[a] C_6D_6.
[b] $CDCl_3$.

Table 2. ^{13}C NMR data of compounds **6**, **7**, **19**

N	^{13}C NMR (75 MHz), δ (ppm), J (Hz)								
	$NAlk_2$	R	R′ or CHO	C(2)	C(3)	C(4)	C(5)	C(6)	CN
6a[a]	25.7, 50.6	45.2, 67.1 ($^3J_{CP}$=6.2 Hz)	—	44.9 ($^1J_{CP}$=136.3 Hz)	157.3 ($^2J_{CP}$=12.7 Hz)	87.9 ($^3J_{CP}$=13.9 Hz)	143.7 ($^2J_{CP}$=9.7 Hz)	66.8 ($^1J_{CP}$=128.4 Hz)	122.4
6b[a]	25.7, 50.5	45.7, 67.1 ($^3J_{CP}$=5.7 Hz)	16.7 ($^2J_{CP}$=7.8 Hz)	43.7 ($^1J_{CP}$=139.3 Hz)	155.6 ($^2J_{CP}$=12.7 Hz)	86.0 ($^3J_{CP}$=12.3 Hz)	144.7 ($^2J_{CP}$=16.1 Hz)	78.2 ($^1J_{CP}$=123.7 Hz)	122.7
6c[a]	25.6, 50.4	45.6, 66.7 ($^3J_{CP}$=5.5 Hz)	124.6, 126.3 ($^3J_{CP}$=6.4 Hz), 128.6, 139.1 ($^2J_{CP}$=9.7 Hz)	44.2 ($^1J_{CP}$=139.6 Hz)	156.4 ($^2J_{CP}$=12.4 Hz)	88.4 ($^3J_{CP}$=11.5 Hz)	142.0 ($^2J_{CP}$=15.0 Hz)	82.2 ($^1J_{CP}$=127.0 Hz)	122.8 ($^2J_{CP}$=3.5 Hz)
7a[a]	25.6, 50.4	128.8 ($^2J_{CP}$=11.4 Hz), 131.4 ($^4J_{CP}$=2.6 Hz), 132.3 ($^3J_{CP}$=10.7 Hz), 132.6 ($^1J_{CP}$=90.9 Hz)	—	36.5 ($^1J_{CP}$=117.3 Hz)	156.0 ($^2J_{CP}$=11.7 Hz)	86.6 ($^3J_{CP}$=13.4 Hz)	143.8 ($^2J_{CP}$=3.9 Hz)	61.9 ($^1J_{CP}$=99.5 Hz)	123.1 ($^2J_{CP}$=7.3 Hz)
7b[a]	25.6, 50.2	128.8 ($^2J_{CP}$=11.1 Hz), 131.5 ($^4J_{CP}$=2.4 Hz), 132.8 ($^3J_{CP}$=9.7 Hz), 128.5 ($^1J_{CP}$=90 Hz)	17.4 ($^2J_{CP}$=12.4 Hz)	34.9 ($^1J_{CP}$=116.8 Hz)	154.0 ($^2J_{CP}$=10.9 Hz)	84.7 ($^3J_{CP}$=11.6 Hz)	144.9 ($^2J_{CP}$=10.2 Hz)	70.3 ($^1J_{CP}$=92.7 Hz)	123.0 ($^2J_{CP}$=7.5 Hz)
7c[a]	25.5, 50.3	128.9 ($^2J_{CP}$=12.7 Hz), 131.9 ($^4J_{CP}$=3.2 Hz), 132.3 ($^3J_{CP}$=10.7 Hz), 129.4 ($^1J_{CP}$=90.4 Hz)	123.9, 126.0 ($^3J_{CP}$=5.9 Hz), 128.6, 140.4 ($^2J_{CP}$=11.5 Hz)	39.7 ($^1J_{CP}$=118.3 Hz)	155.4 ($^2J_{CP}$=9.9 Hz)	89.2 ($^3J_{CP}$=10.8 Hz)	141.9 ($^2J_{CP}$=11.5 Hz)	73.8 ($^1J_{CP}$=99.7 Hz)	122.7 ($^2J_{CP}$=9.3 Hz)
19[b]	26.0, 53.9 (b)	123.6 ($^1J_{PC}$=92.5 Hz), 129.7 ($^2J_{PC}$=13.8 Hz), 132.7 (b), 134.1	159.3	48.7 ($^1J_{PC}$=112.5 Hz)	151.9 (b)	100.2 ($^3J_{PC}$=15 Hz)	133.5 (b)	86.1 ($^1J_{PC}$=92.5 Hz)	118.9 ($^2J_{PC}$=7.5 Hz)

[a] C_6D_6.
[b] $CDCl_3$.

reaction with morpholine followed by oxidation with sulfur affording enamine **12**. The phosphorylated enamine **12** reacted with DMADMF giving dienamine **13**, which readily reacted with methyl iodide resulting in phosphonium salt **14** (Scheme 3).

Heating of the salts **11** or **14** in benzonitrile or DMF instead of DMADMF did not afford the expected phosphinines **7** or **16**, respectively. In the case of the salt **14**, dealkylation occurred, giving dienamine **13**, while the salts **11** remained without changes at all. It should be noted that we have also failed to obtain phosphinine **16** using another synthetic pathway. Thus, compound **12** was transformed into phosphonium salt **15** by alkylation at sulfur. Unfortunately, the salt **15** upon treatment with DMADMF also dealkylated and underwent insertion of dimethylaminomethylene group affording again the dienamine **13** (Scheme 3). These experiments clearly showed that heating of salts **11** and **14** does not lead to the phosphinines via a thermal cyclization.

We decided to explore another assumption that DMADMF acted in the reaction both as reagent and as a base. We treated these salts with a strong base such as DBU.[12] Thus, on heating the salts **11a–c** at 130 °C in DMF with 2 equiv of DBU in all three cases phosphinines **7a–c** formed. Benzyl salt **11c** formed for 30 min in almost 70% yield. Under the same conditions, the methyl salt **7a** after 4 h yielded only 50% of the corresponding phosphinine **11a**. The ethyl salt **11b** reacted under prolonged heating with the lowest yield. Thus, after 10 h it yielded traces of the phosphinine **7b** along with a lot of admixtures. Thus, one can conclude that the reaction of the salts **11** proceeds through electrocyclization of intermediate ylides **17** (Scheme 4). A recent publication devoted to studies on electrocyclizations of 1-amino-1,3,5-hexatrienes clearly showed that electron-withdrawing groups at positions 2 and 4 substantially decreased activation barriers of electrocyclic ring closures.[13] We have a good analogy with our results. The intermediate compounds **17** have nitrile group at 4-position and H, Me, Ph groups at 6-position, respectively. The experiments corroborate with these findings. Cyclization proceeds most readily with the salt **11c** bearing phenyl group at 6-position.

Unfortunately, treatment of the phosphonium salt **14** with DBU gave a complex mixture of products. Although PMR spectrum of the solid separated from the reaction mixture revealed the presence of the targeted phosphinine **16**, we were unable to separate it in analytically pure form. Use of other bases and change of conditions did not help.

Thus, we can draw a conclusion that in the reaction with salts **4**, **5**, DMADMF acts both as reagent and a base. This assumption was supported by the work where it was shown that at elevated temperatures DMADMF undergoes disproportionation. These results were rationalized by the mechanism where compounds of this type dissociate via $(R'O)_2CHNR_2$, $(R'O)CH(NR_2)_2$, and $CH(NR_2)_3$, where such strong bases as RO^- and R_2N^- took part. Thus, the reaction media acted as a strong base.[14]

To verify this further, we subjected the salts **11** under the same conditions in which the phosphinine **7** were prepared starting from the salts **5**, that is, heating in DMADMF. To

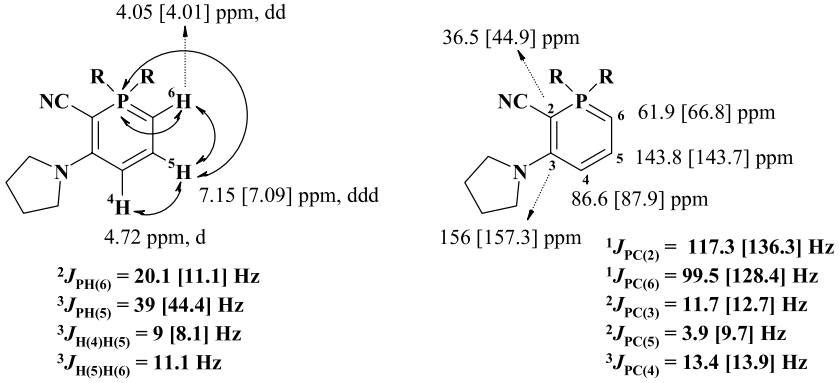
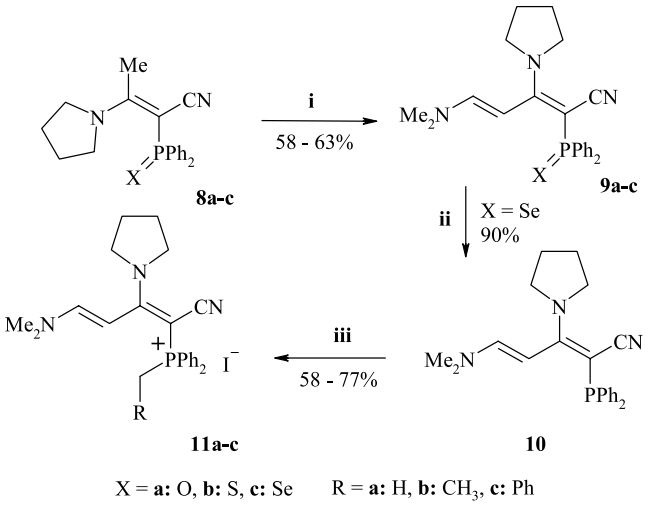


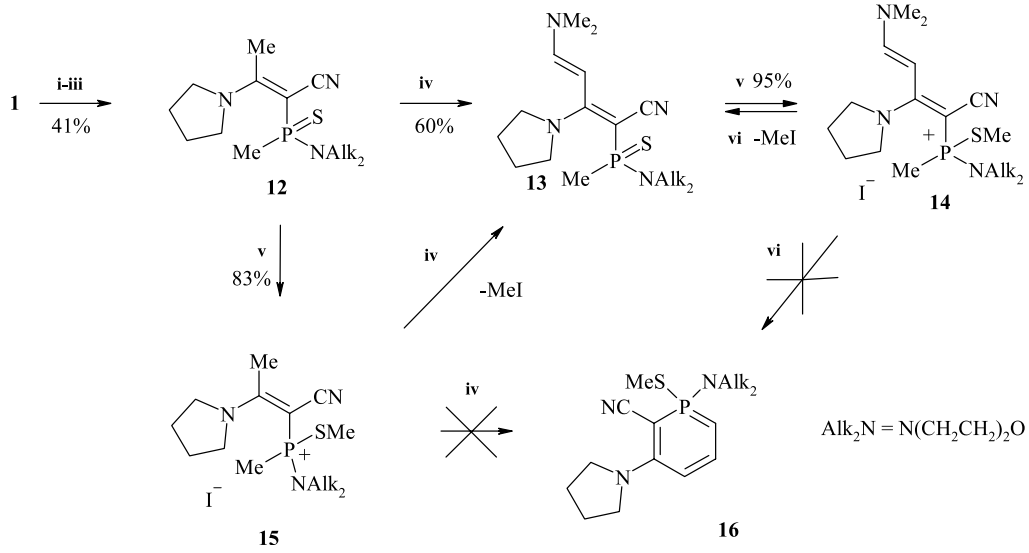
Figure 1. Significant ^{1}H (obtained according to H–H COSY and ^{1}H{^{31}P} experiments) and ^{13}C NMR data of 1,1-diphenyl-1λ^5-phosphinine **7a** [1,1-dimorpholin-4-yl-1λ^5-phosphinine **6a**].



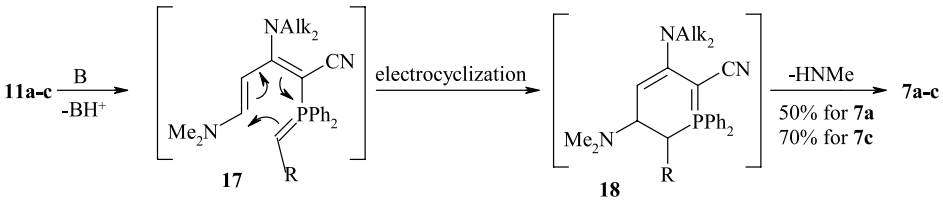
Scheme 2. Reagents and conditions: (i) DMADMF, 110 °C for a: 10 h, for b: 2 days, for c: 7 days; (ii) $P(NMe_2)_3$, C_6H_6; (iii) for a: MeI, for b: EtI, for c: BnBr.

our surprise, behavior of these salts was quite different. Thus, the salt **11c** after heating it for 4 h afforded phosphinine **7c** in almost 55% yield. In transition to ethyl derivative **11b**, heating for 5 days resulted in trace amounts of the phosphinine **7b** with decomposition of the starting salt. Finally, the reaction with the methyl salt derivative **11a** revealed that two products formed almost in equal amounts, with the predominant one being the phosphinine **7a**. The second product was found to be formylated derivative **19** (Scheme 5).

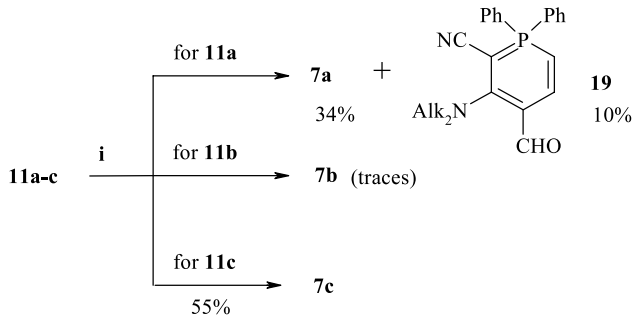
These results decisively refute the assumption that the reaction of the salts **4**, **5** with DMADMF proceeds via the salts **11**. In these reactions, we always identified only phosphinine even in the reaction mixtures by ^{31}P NMR spectroscopy. Formation of the formylated product **19** could be rationalized by the reaction scheme where the insertion of dimethylaminomethylene group proceeds at the methyl group attached to the phosphorus. It should be noted that in the reaction mixture we identified product **22** (δ_P= 14.5 ppm), which hydrolyzed to formyl derivative **19** (Scheme 6).



Scheme 3. Reagents and conditions: (i) $MePCl_2$, C_6H_6, Et_3N; (ii) $HN(CH_2CH_2)_2O$, C_6H_6, Et_3N; (iii) S, C_6H_6; (iv) DMADMF, 110 °C; (v) MeI, reflux; (vi) 100–150 °C.



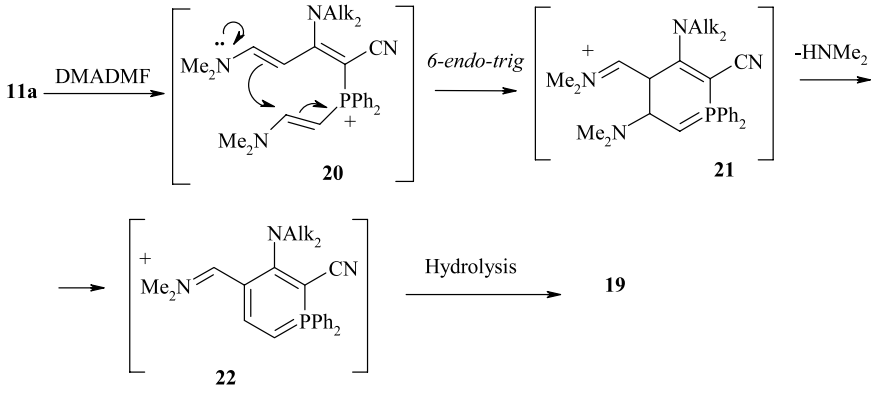
Scheme 4. Reagents and conditions: DMF, DBU, 130 °C.



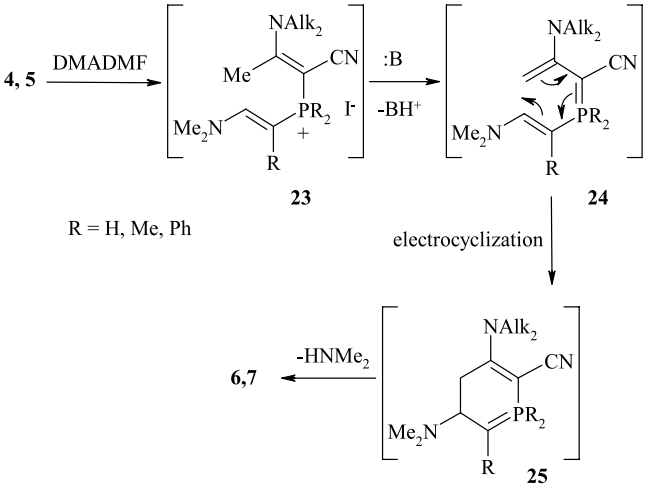
Scheme 5. Reagents and conditions: (i) DMADMF, 110 °C.

Taking into account all these results one can draw the conclusion that formation of phosphinine **6**, **7** proceeds initially via insertion of dimethylaminomethylene group at the methyl group attached to the phosphorus atom followed by dehydrohalogenation, electrocyclization, and finally elimination of dimethylamine (Scheme 7).

We undertook the research directed at synthesis of the intermediates **23**. Treatment of the salts **4**, **5** with 2-bromo-1,1-diethoxyethane or 3-bromoprop-1-yne with this end in view failed. The reagents yielded complex mixtures. Although we were unable to synthesize the intermediate **23** to prove the offered reaction pathway, the investigation



Scheme 6. Possible mechanism for the formation of **19**.



Scheme 7. Proposed mechanism for the formation of phosphinines **6**, **7**.

presented above allowed us to assume that formation of the phosphinines proceeds by the Scheme 7.

Further investigations are in progress and will be reported in due course.

3. Conclusion

In conclusion, we have found a convenient and simple method for the synthesis of λ^5-phosphinines. The starting materials are readily available push–pull enamines. Most probably, the first step of the reaction is the insertion of dimethylaminomethylene group at the methyl (methylene) group attached to the phosphorus atom of the enamines affording phosphorylated dienamine derivatives, which undergo cyclization induced by a base. The method makes easily accessible various λ^5-phosphinines.

4. Experimental

4.1. General

All procedures with compounds sensitive to hydrolysis and oxidation were carried out in an atmosphere of dry argon. All solvents were purified and dried by standard methods. NMR spectra were recorded on a Varian VXR-300 spectrometer: ^{1}H and ^{13}C (300 and 75.4 MHz, respectively), C_6D_6 and $CDCl_3$ as solvents with TMS as an internal standard; ^{31}P (121 MHz) with 85% H_3PO_4 as an external standard, in $CHCl_3$. IR spectra were recorded on a Nexus-470 spectrometer for samples in KBr discs. Mass spectra were obtained on a 'HEWLETT-PACKARD' HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet for substances 6, 7, on VG 70-70EQ, VG ANALYTICAL (FAB) for phosphonium salts or a MX-1321 instrument (EI, 70 eV) by direct inlet for other substances. Microanalyses were performed in the Microanalytical Laboratory of the Institute of Organic Chemistry, National Academy of Sciences of Ukraine. Melting points are uncorrected. Yields refer to pure isolated products. The starting enamines were prepared according to the literature.[15]

4.2. General procedures for phosphonium salts

Procedure A. To a stirred solution of PCl_3 (1.01 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1** (1 g, 7.3 mmol) and $(i\text{-Pr})_2NEt$ (1.23 g, 9.4 mmol) in benzene (20 mL) was added dropwise. After 12 h, to the stirred solution obtained, a solution of morpholine (1.28 g, 14.6 mmol) and $(i\text{-Pr})_2NEt$ (1.89 g, 14.6 mmol) in benzene (20 mL) was added dropwise. After 3 h the reaction mixture was filtered and an appropriate alkyl halide (11 mmol) was added to the mother liquor. The reaction mixture was heated at 80 °C under argon for 8 h. After cooling the precipitated solid was collected by filtration and recrystallized from an appropriate solvent.

Procedure B. To a stirred solution of Ph_2PBr (1.93 g, 7.3 mmol) in benzene (20 mL) under dry argon, a solution of enamine **1** (1 g, 7.3 mmol) and $(i\text{-Pr})_2NEt$ (1.23 g, 9.4 mmol) in benzene (20 mL) was added dropwise. After 24 h precipitated salts were filtered off and an appropriate alkyl halide (11 mmol) was added to the mother liquor. The reaction mixture was heated at 80 °C under argon for 8 h. After cooling the precipitated solid was collected by filtration and recrystallized from an appropriate solvent.

Procedure C. To a suspension of dienamine **9c** (1 g, 2.2 mmol) in benzene (20 mL) $P(NMe_2)_3$ (0.39 g, 2.4 mmol) was added, and the reaction mixture was boiled at 80 °C till complete dissolution. After cooling the corresponding alkyl halide (3.3 mmol) was added. After 2 h the precipitated solid was collected by filtration and washed with benzene.

4.2.1. [1-Cyano-2-pyrrolidin-1-ylprop-1-enyl](methyl) dimorpholin-4-ylphosphonium iodide (4a). Procedure A was applied. White solid (1.44 g, 41%). Mp 230–232 °C (MeOH). ^{31}P NMR δ 57.5. ^{1}H NMR ($CDCl_3$) δ 2.03–2.21 (4H, m, CH_2), 2.45 (3H, s, CH_3), 2.59 (3H, d, $^{2}J_{PH}$= 12.6 Hz, PCH_3), 3.33 (8H, br m, $PNCH_2$), 3.79 (10H, br m, OCH_2(8H), NCH_2), 3.98 (2H, t, $^{3}J_{HH}$=6.6 Hz, NCH_2). ^{13}C NMR ($CDCl_3$) δ 12.1 ($^{1}J_{CP}$=96.1 Hz, PCH_3), 22.4 (C(3)), 26.0 (CH_2), 44.8 ($PNCH_2$), 50.1 ($^{1}J_{CP}$=157.8 Hz, C(1)), 53.3 (NCH_2), 54.8 (NCH_2), 66.5 ($^{3}J_{CP}$=5.5 Hz, OCH_2), 121.2 ($^{2}J_{CP}$=11.5 Hz, CN), 169.2 ($^{2}J_{CP}$=14.6 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2975, 2954, 2929, 2890, 2854, 2173, 1625, 1540, 1448, 1398, 1346, 1265, 1155, 1110, 970, 773, 528. MS FAB, *m/z* (%): 353 (M^+, 100). Anal. Calcd for $C_{17}H_{30}N_4O_2PI$: C 42.51; H 6.30; N 11.66; P 6.45; I 26.42. Found: C 42.57; H 6.31; N 11.64; P 6.41; I 26.40.

4.2.2. [1-Cyano-2-pyrrolidin-1-ylprop-1-enyl](ethyl) dimorpholin-4-ylphosphonium iodide (4b). Procedure A was applied. Yellow solid (0.72 g, 20%). Mp 178–182 °C (*i*-PrOH/toluene ~ 1:1). ^{31}P NMR δ 55.5. ^{1}H NMR ($CDCl_3$) δ 1.21–1.44 (3H, m, PCH_2CH_3), 2.03–2.19 (2H, m, CH_2), 2.45 (3H, s, CH_3), 2.87–3.15 (2H, m, PCH_2), 3.35 (10H, br m, $PNCH_2$(8H), CH_2), 3.80 (10H, br m, OCH_2(8H), NCH_2), 3.86 (1H, t, $^{3}J_{HH}$=6.9 Hz, NCH_2), 3.97 (1H, t, $^{3}J_{HH}$= 6.9 Hz, NCH_2). ^{13}C NMR ($CDCl_3$) δ 6.3 ($^{2}J_{CP}$=6.3 Hz, PCH_2CH_3), 17.2 ($^{1}J_{CP}$=103.1 Hz, PCH_2), 23.4 (C(3)), 24.7 (CH_2), 25.8 (CH_2), 45.7 ($PNCH_2$), 48.6 ($^{1}J_{CP}$=161.0 Hz, C(1)), 53.5 (NCH_2), 54.3 (NCH_2), 66.7 (OCH_2), 118.9 ($^{2}J_{CP}$=7.5 Hz, CN), 169.1 ($^{2}J_{CP}$=17.6 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2970, 2956, 2919, 2861, 2173, 1550, 1450, 1403, 1340, 1261, 1151, 1110, 968, 912. MS FAB, *m/z* (%): 367 (M^+, 100). Anal. Calcd for $C_{18}H_{32}N_4O_2PI$: C 43.73; H 6.52; N 11.33; P 6.27; I 25.67. Found: C 43.65; H 6.54; N 11.13; P 6.21; I 25.81.

4.2.3. Benzyl(1-cyano-2-pyrrolidin-1-ylprop-1-enyl) dimorpholin-4-ylphosphonium bromide (4c). Procedure A was applied, recrystallized from *i*-PrOH/heptane ~ 1:2. Amorphous solid (1.11 g, 30%). ^{31}P NMR δ 57.1. ^{1}H NMR ($CDCl_3$) δ 1.96–2.10 (4H, m, CH_2), 2.11 (3H, s, CH_3), 3.32 (8H, br m, $PNCH_2$), 3.72 (8H, br m, OCH_2), 3.91 (2H, t, $^{3}J_{HH}$=6.9 Hz, NCH_2), 4.01 (2H, t, $^{3}J_{HH}$=6.9 Hz, NCH_2), 4.63 (2H, d, $^{2}J_{PH}$=15.0 Hz, PCH_2), 7.35 (3H, br m, Ph), 7.47 (2H, br m, Ph). ^{13}C NMR ($CDCl_3$) δ 22.5 (C(3)), 24.5 (CH_2), 25.6 (CH_2), 31.4 ($^{1}J_{CP}$=87.2 Hz, PCH_2) 46.1 ($PNCH_2$), 49.2 ($^{1}J_{CP}$=160.9 Hz, C(1)), 52.8 (NCH_2), 54.4 (NCH_2), 66.3 (OCH_2), 118.4 ($^{2}J_{CP}$=10.9 Hz, CN), 128.3 (Ph), 128.8 ($^{2}J_{CP}$=6.9 Hz, Ph), 129.1 (Ph), 128.6 ($^{4}J_{CP}$= 6.3 Hz, Ph), 170.1 ($^{2}J_{CP}$=17.8 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2966, 2919, 2859, 2175, 1540, 1452, 1396, 1348, 1263, 1112, 968. MS FAB, *m/z* (%): 429 (M^+, 100). Anal. Calcd for $C_{23}H_{34}N_4O_2PBr$: C 54.23; H 6.73; N 11.00; P 6.08; Br 15.68. Found: C 54.03; H 6.73; N 10.88; P 6.05; Br 15.53.

4.2.4. (1-Cyano-2-pyrrolidin-1-ylprop-1-enyl)(methyl) diphenylphosphonium iodide (5a). Procedure B was applied, recrystallized from *i*-PrOH. Amorphous solid (2.16 g, 64%). ^{31}P NMR δ 21.8 (q, $^{2}J_{PH}$=12.6 Hz). ^{1}H NMR ($CDCl_3$) δ 2.01–2.11 (2H, m, CH_2), 2.14 (3H, s, CH_3), 2.14–2.21 (2H, m, CH_2), 2.76 (3H, d, $^{2}J_{PH}$=12.6 Hz, PCH_2), 3.79 (2H, br m, NCH_2), 4.05 (2H, br m, NCH_2), 7.61–7.95 (10H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 14.3 ($^{1}J_{CP}$=62.3 Hz, PCH_3), 24.1 (CH_2), 24.3 ($^{3}J_{CP}$=4.6 Hz, C(3)), 25.2 (CH_2), 48.1 ($^{1}J_{CP}$=124.2 Hz, C(1)), 53.2 (NCH_2), 117.8 ($^{2}J_{CP}$=13.3 Hz, CN), 120.6 ($^{1}J_{CP}$= 89.6 Hz, PPh_2), 130.0 ($^{2}J_{CP}$=14.2 Hz, PPh_2), 132.1 ($^{3}J_{CP}$=10.8 Hz, PPh_2), 134.1 ($^{4}J_{CP}$=1.9 Hz, PPh_2), 167.4 ($^{2}J_{CP}$=15.9 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2969, 2950, 2871,

2171, 1548, 1436, 1400, 1346, 110, 912, 748, 690. MS FAB, *m/z* (%): 335 (M^+, 100). Anal. Calcd for $C_{21}H_{24}N_2PI$: C 54.56; H 5.23; N 6.06; P 6.70; I 27.45. Found: C 54.54; H 5.25; N 6.00; P 6.78; I 27.29.

4.2.5. (1-Cyano-2-pyrrolidin-1-ylprop-1-enyl)(ethyl) diphenylphosphonium iodide (5b). Procedure B was applied. Yellow solid (1.64 g, 47%). Mp 160–163 °C (benzene). ^{31}P NMR δ 24.6 (m). ^1H NMR ($CDCl_3$) δ 1.29 (3H, dt, $^3J_{HH}=7.5$ Hz, $^3J_{PH}=19.8$ Hz, PCH_2CH_3), 2.07 (3H, s, CH_3), 2.07–2.13 (2H, m, CH_2), 2.21–2.28 (2H, m, CH_2), 2.94 (2H, dq, $^3J_{HH}=7.5$ Hz, $^2J_{PH}=12$ Hz, PCH_2), 3.88 (2H, t, $^3J_{HH}=6.9$ Hz, NCH_2), 4.14 (2H, t, $^3J_{HH}=6.9$ Hz, NCH_2), 7.72–7.83 (6H, m, PPh_2), 7.86–7.97 (4H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 6.8 (PCH_2CH_3), 21.1 ($^1J_{CP}=57.2$ Hz, PCH_2), 24.4 (CH_2), 24.5 (CH_2), 24.6 ($^3J_{CP}=4.3$ Hz, C(3)), 45.4 (NCH_2), 46.7 ($^1J_{CP}=120.7$ Hz, C(1)), 66.5 (NCH_2), 118.0 ($^2J_{CP}=11.7$ Hz, CN), 119.2 ($^1J_{CP}=85.8$ Hz, PPh_2), 130.4 ($^2J_{CP}=13$ Hz, PPh_2), 132.7 ($^3J_{CP}=10.1$ Hz, PPh_2), 134.4 ($^4J_{CP}=2.5$ Hz, PPh_2), 168.2 ($^2J_{CP}=13.6$ Hz, C(2)). IR, ν_{max} (cm^{-1}): 3047, 3021, 2966, 2929, 2867, 2179, 1560, 1402, 1106, 1008, 759, 727, 522. MS FAB, *m/z* (%): 349 (M^+, 100). Anal. Calcd for $C_{22}H_{26}N_2PI$: C 55.47; H 5.50; N 5.88; P 6.50; I 26.64. Found: C 55.50; H 5.51; N 5.94; P 6.38; I 26.91.

4.2.6. Benzyl(1-cyano-2-pyrrolidin-1-ylprop-1-enyl) diphenylphosphonium bromide (5c). Procedure B was applied. Beige solid (1.90 g, 53%). Mp 168–172 °C (benzene). ^{31}P NMR δ 22.4. ^1H NMR ($CDCl_3$) δ 1.97 (3H, s, CH_3), 2.02–2.10 (2H, m, CH_2), 2.17–2.24 (2H, m, CH_2), 3.86 (2H, t, $^3J_{HH}=6.9$ Hz, NCH_2), 4.14 (2H, t, $^3J_{HH}=6.9$ Hz, NCH_2), 4.34 (2H, d, $^2J_{PH}=14.1$ Hz, PCH_2), 6.85 (2H, d, $^3J_{HH}=7.2$ Hz, Ph), 7.17 (2H, t, $^3J_{HH}=7.2$ Hz, Ph), 7.29 (1H, t, $^3J_{HH}=7.2$ Hz, Ph), 7.61–7.81 (10H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 24.4 (CH_2), 24.6 ($^3J_{CP}=3.5$ Hz, C(3)), 25.6 (CH_2), 34.3 ($^1J_{CP}=53.8$ Hz, PCH_2), 46.8 ($^1J_{CP}=121.8$ Hz, C(1)), 53.3 (NCH_2), 53.8 (NCH_2), 118.4 ($^2J_{CP}=12.3$ Hz, CN), 118.5 ($^1J_{CP}=87.7$ Hz, PPh_2), 127.1 ($^2J_{CP}=8.1$ Hz, Ph), 128.4 ($^5J_{CP}=3.8$ Hz, Ph), 128.6 ($^3J_{CP}=3.9$ Hz, Ph), 130.0 ($^2J_{CP}=12.7$ Hz, PPh_2), 130.7 ($^4J_{CP}=5.1$ Hz, PPh_2), 133.4 ($^3J_{CP}=10.0$ Hz, PPh_2), 134.5 (Ph), 168.8 ($^2J_{CP}=14.0$ Hz, C(2)). IR, ν_{max} (cm^{-1}): 3047, 2958, 2886, 2867, 2790, 2165, 1550, 1436, 1402, 1338, 1106, 1008, 748, 701, 545. MS FAB, *m/z* (%): 411 (M^+, 100). Anal. Calcd for $C_{27}H_{28}N_2PBr$: C 65.99; H 5.74; N 5.70; P 6.30; Br 16.26. Found: C 65.90; H 5.77; N 5.62; P 6.18; Br 16.64.

4.2.7. [1-Cyano-4-(dimethylamino)-2-pyrrolidin-1-ylbuta-1,3-dienyl](methyl)diphenylphosphonium iodide (11a). Procedure C was applied. Pink solid (0.88 g, 77%). Mp 219–221 °C (benzene). ^{31}P NMR δ 20.4 (q, $^2J_{PH}=12.6$ Hz). ^1H NMR ($CDCl_3$) δ 2.14 (4H, br m, CH_2), 2.45 (3H, s, NCH_3), 2.64 (3H, d, $^2J_{PH}=12.6$ Hz, PCH_3), 2.9 (3H, s, NCH_3), 3.78 (4H, br m, NCH_2), 4.99 (1H, d, $^3J_{HH}=12$ Hz, C(3)H), 6.62 (1H, d, $^3J_{HH}=12$ Hz, C(4)H), 7.61–7.95 (10H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 13.2 ($^1J_{CP}=64.4$ Hz, PCH_3), 25.7 (CH_2), 38.4 (NCH_3), 44.9 (NCH_3), 50.2 ($^1J_{CP}=135$ Hz, C(1)), 52.7 (NCH_2), 92.8 (C(3)), 121.4 ($^2J_{CP}=12.4$ Hz, CN), 126.1 ($^1J_{CP}=90.6$ Hz, PPh_2), 130.1 ($^2J_{CP}=12.7$ Hz, PPh_2), 132.3 ($^3J_{CP}=9.9$ Hz, PPh_2), 133.9 ($^4J_{CP}=2.2$ Hz, PPh_2), 154.2 (C(4)), 166.3 ($^2J_{CP}=13.4$ Hz, C(2)). IR, ν_{max} (cm^{-1}): 3010, 2969, 2942, 2877, 2154, 1625, 1521, 1436, 1386, 1282, 1109, 973, 899, 748, 690, 541. MS FAB, *m/z* (%): 390 (M^+, 100). Anal. Calcd for $C_{24}H_{29}N_3PI$: C 55.71; H 5.65; N 8.12; P 5.99; I 24.53. Found: C 55.61; H 5.69; N 8.03; P 6.08; I 24.67.

4.2.8. [1-Cyano-4-(dimethylamino)-2-pyrrolidin-1-ylbuta-1,3-dienyl](ethyl)diphenylphosphonium iodide (11b). Procedure C was applied. Yellow solid (0.88 g, 75%). Mp 233–235 °C (benzene). ^{31}P NMR δ 27.4 (m). ^1H NMR ($CDCl_3$) δ 1.10 (3H, dt, $^3J_{PH}=19.8$ Hz, $^3J_{HH}=7.2$ Hz, PCH_2CH_3), 2.14 (4H, br m, CH_2), 2.51 (3H, s, NCH_3), 2.89–3.01 (5H, m, PCH_2, NCH_3), 3.80 (4H, br m, NCH_2), 4.95 (1H, d, $^3J_{HH}=12$ Hz, C(3)H), 6.60 (1H, d, $^3J_{HH}=12$ Hz, C(4)H), 7.65–7.87 (10H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 6.9 ($^2J_{CP}=5.3$ Hz, PCH_2CH_3), 18.7 ($^1J_{CP}=58.4$ Hz, PCH_2), 25.5 (CH_2), 33.8 ($^1J_{CP}=131$ Hz, C(1)), 38.5 (NCH_3), 45.3 (NCH_3), 52.3 (NCH_2), 91.7 (C(3)), 121.4 ($^2J_{CP}=12.5$ Hz, CN), 124.1 ($^1J_{CP}=88.1$ Hz, PPh_2), 130.0 ($^2J_{CP}=12.4$ Hz, PPh_2), 132.5 ($^3J_{CP}=9.6$ Hz, PPh_2), 133.9 ($^4J_{CP}=2.7$ Hz, PPh_2), 155.2 (C(4)), 166.2 ($^2J_{CP}=13.1$ Hz, C(2)). IR, ν_{max} (cm^{-1}): 3052, 3020, 2960, 2935, 2883, 2159, 1621, 1515, 1427, 1392, 1328, 1270, 1106, 981, 777, 738, 694, 561. MS FAB, *m/z* (%): 404 (M^+, 100). Anal. Calcd for $C_{25}H_{31}N_3PI$: C 56.50; H 5.88; N 7.91; P 5.83; I 23.88. Found: C 56.47; H 5.90; N 7.90; P 5.87; I 23.75.

4.2.9. Benzyl[1-cyano-4-(dimethylamino)-2-pyrrolidin-1-ylbuta-1,3-dienyl]diphenylphosphonium bromide (11c). Procedure C was applied. Yellow solid (0.70 g, 58%). Mp 215–217 °C (benzene). ^{31}P NMR δ 23.4. ^1H NMR ($CDCl_3$) δ 2.01 (4H, br m, CH_2), 2.49 (3H, br s, NCH_3), 2.99 (3H, br s, NCH_3), 3.56 (4H, br m, NCH_2), 4.40 (2H, d, $^2J_{PH}=13.5$ Hz, PCH_2), 5.08 (1H, d, $^3J_{HH}=13.8$ Hz, C(3)H), 6.75 (1H, d, $^3J_{HH}=13.8$ Hz, C(4)H), 6.78 (2H, d, $^3J_{HH}=7.2$ Hz, Ph), 7.14–7.25 (3H, m, Ph), 7.61–7.77 (10H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 25.3 (CH_2), 30.5 ($^1J_{CP}=134$ Hz, C(1)), 31.0 ($^1J_{CP}=53$ Hz, PCH_2), 38.5 (NCH_3), 45.2 (NCH_3), 52.0 (NCH_2), 92.3 (C(3)), 121.7 ($^2J_{CP}=11.5$ Hz, CN), 123.8 ($^1J_{CP}=87.3$ Hz, PPh_2), 127.8 ($^2J_{CP}=8.5$ Hz, Ph), 128.0 ($^5J_{CP}=4.5$ Hz, Ph), 128.2 ($^3J_{CP}=3.7$ Hz, Ph), 129.7 ($^2J_{CP}=12.3$ Hz, PPh_2), 130.8 ($^4J_{CP}=5.4$ Hz, PPh_2), 133.0 ($^3J_{CP}=8.6$ Hz, PPh_2), 133.9 ($^4J_{CP}=2.6$ Hz, Ph), 156.0 (C(4)), 165.9 ($^2J_{CP}=13.3$ Hz, C(2)). IR, ν_{max} (cm^{-1}): 3060, 2975, 2935, 2875, 2157, 1621, 1577, 1519, 1423, 1390, 1332, 1274, 1106, 968, 815, 746, 541. MS FAB, *m/z* (%): 466 (M^+, 466). Anal. Calcd for $C_{30}H_{33}N_3PBr$: C 65.94; H 6.09; N 7.69; P 5.67; Br 14.62. Found: C 65.90; H 6.05; N 7.73; P 5.53; Br 14.75.

4.2.10. [1-Cyano-4-(dimethylamino)-2-pyrrolidin-1-ylbuta-1,3-dienyl](methyl)(methylthio)(morpholin-4-yl) phosphonium iodide (14). Compound **13** (0.45 g, 1.3 mmol) was refluxed in methyl iodide (5 mL) for 1 h. Then solution was evaporated in vacuo. The residue was thoroughly washed with methanol. Yellow solid (0.61 g, 95%). Mp 161–164 °C. ^{31}P NMR δ 71.3. ^1H NMR ($CDCl_3$) δ 2.13 (4H, br m, CH_2), 2.54 (3H, d, $^3J_{PH}=14.7$ Hz, SCH_3), 2.54 (3H, d, $^2J_{PH}=12.6$ Hz, PCH_3), 3.07 (3H, s, NCH_3), 3.30 (3H, s, NCH_3), 3.37 (4H, br m, $PNCH_2$), 3.66 (4H, br m, NCH_2), 3.79 (4H, br m, OCH_2), 5.01 (1H, dd, $^3J_{HH}=6$ Hz, $^4J_{PH}=0.9$ Hz, C(3)H), 7.19 (1H, d, $^3J_{HH}=6$ Hz, C(4)H). ^{13}C NMR ($CDCl_3$) δ 13.5 ($^2J_{CP}=5$ Hz, SCH_3), 16.4

($^1J_{CP}$=75.5 Hz, PCH_3), 25.5 (CH_2), 38.6 (NCH_3), 40.4 ($^1J_{CP}$=148 Hz, C(1)), 45.8 ($PNCH_2$), 46.2 (NCH_3), 52.5 (NCH_2), 66.8 ($^3J_{CP}$=7.5 Hz, OCH_2), 92.8 (C(3)), 120.2 ($^2J_{CP}$=12.6 Hz, CN), 155.5 (C(4)), 164.8 ($^2J_{CP}$=16.3 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2954, 2913, 2879, 2840, 2144, 1623, 1508, 1438, 1386, 1292, 1249, 1110, 1074, 960, 919, 881, 781, 611, 551. MS FAB, *m/z* (%): 369 (M^+, 100). Anal. Calcd for $C_{17}H_{30}N_4OPSI$: C 41.13; H 6.09; N 11.29; P 6.24; S 6.46; I 25.57. Found: C 41.10; H 6.11; N 11.26; P 6.19; S 6.49; I 25.50.

4.2.11. (1-Cyano-2-pyrrolidin-1-ylprop-1-enyl)(methyl)(methylthio)(morpholin-4-yl)phosphonium iodide (15). Enamine **12** (0.4 g, 1.3 mmol) was refluxed in methyl iodide (5 mL) 1 h. Then solution was evaporated in vacuo. The residue was thoroughly washed with acetone. Yellow solid (0.48 g, 83%). Mp 115–118 °C. ^{31}P NMR δ 70.2. ^1H NMR ($CDCl_3$) δ 2.05–2.22 (4H, m, CH_2), 2.55 (3H, s, CH_3), 2.60 (3H, d, $^3J_{PH}$=14.7 Hz, SCH_3), 2.76 (3H, d, $^2J_{PH}$=12.9 Hz, PCH_3), 3.39 (4H, br m, $PNCH_2$), 3.73–3.88 (6H, br m, OCH_2(4H), NCH_2), 4.00 (2H, br m, NCH_2). ^{13}C NMR ($CDCl_3$) δ 13.4 ($^2J_{CP}$=4 Hz, SCH_3), 17.2 ($^1J_{CP}$=74.4 Hz, PCH_3), 24.0 ($^3J_{CP}$=3 Hz, C(3)), 24.7 (b, CH_2), 25.5 (b, CH_2), 45.5 ($PNCH_2$), 52.0 ($^1J_{CP}$=142 Hz, C(1)), 53.7 (b, NCH_2), 54.2 (b, NCH_2), 66.6 ($^3J_{CP}$=6.0 Hz, OCH_2), 117.8 ($^2J_{CP}$=13 Hz, CN), 168.6 ($^2J_{CP}$=17.1 Hz, C(2)). IR, ν_{max} (cm^{-1}): 2967, 2910, 2896, 2858, 2171, 1618, 1517, 1423, 1380, 1284, 1110, 954, 798, 549. MS FAB, *m/z* (%): 314 (M^+, 100). Anal. Calcd for $C_{14}H_{25}N_3OPSI$: C 38.10; H 5.71; N 9.52; P 7.02; S 7.27; I 28.76. Found: C 38.13; H 5.73; N 9.51; P 6.95; S 7.25; I 28.75.

4.3. General procedure for λ^5-phosphinines

Procedure A. A stirring suspension of phosphonium salts **4** or **5** (1 mmol) in DMADMF (15 mL) was boiled at 110 °C for 8 h. After cooling, the reaction mixture was poured into water (40 mL). The precipitated solid was collected and recrystallized from an appropriate solvent.

Procedure B. To a stirring solution of salt **11** (0.4 mmol) in dry DMF (20 mL) DBU (120 mg, 0.8 mmol) was added. The solution was heated at 130 °C for appropriate time and after cooling, the reaction mixture was poured into water (40 mL). The precipitated solid was collected and recrystallized from an appropriate solvent.

Procedure C. A stirring suspension of phosphonium salts **11** (1 mmol) in DMADMF (15 mL) was boiled at 110 °C for appropriate time. After cooling, the reaction mixture was poured into water (40 mL). The precipitated solid was collected and recrystallized from an appropriate solvent.

4.3.1. 1,1-Dimorpholin-4-yl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (6a). Procedure A was applied. Beige solid (0.23 g, 64%). Mp 177–178 °C (MeOH). ^{31}P NMR δ 53.1 (d, $^3J_{PH}$=44.4 Hz). IR, ν_{max} (cm^{-1}): 3048, 2964, 2913, 2842, 2159, 1540, 1511, 1419, 1369, 1315, 1257, 1112, 1078, 964, 943, 821, 680, 489. MS, *m/z* (%): 362 (M^+, 53), 305 (28), 277 (17), 276 (18), 192 (71), 191 (100), 190 (26), 162 (19), 118 (23), 56 (25). Anal. Calcd for $C_{18}H_{27}N_4O_2P$: C 59.66; H 7.51; N 15.46; P 8.55. Found: C 59.65; H 7.54; N 15.39; P 8.39.

4.3.2. 6-Methyl-1,1-dimorpholin-4-yl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (6b). Procedure A was applied. Light brown solid (0.10 g, 27%). Mp 141–144 °C (MeOH). ^{31}P NMR δ 53.3 (d, $^3J_{PH}$=40.5 Hz). IR, ν_{max} (cm^{-1}): 2956, 2925, 2871, 2183, 1561, 1456, 1259, 1133, 1110, 1085, 1043, 968. MS, *m/z* (%): 376 (M^+, 100), 319 (36), 290 (38), 206 (72), 205 (95), 204 (33), 203 (61), 173 (54), 118 (46), 56 (30). Anal. Calcd for $C_{19}H_{29}N_4O_2P$: C 60.62; H 7.77; N 14.88; P 8.23. Found: C 60.65; H 7.75; N 14.81; P 8.31.

4.3.3. 1,1-Dimorpholin-4-yl-6-phenyl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (6c). Procedure A was applied. Light brown solid (0.17 g, 40%). Mp 165–167 °C (*i*-PrOH). ^{31}P NMR δ 51.7 (d, $^3J_{PH}$=39 Hz). IR, ν_{max} (cm^{-1}): 2958, 2919, 2852, 2157, 1544, 1508, 1479, 1367, 1294, 1253, 1112, 1085, 970, 740, 703. MS, *m/z* (%): 438 (M^+, 99), 381 (24), 352 (19), 267 (44), 266 (33), 235 (100), 118 (51), 56 (29). Anal. Calcd for $C_{24}H_{31}N_4O_2P$: C 65.74; H 7.13; N 12.78; P 7.06. Found: C 65.77; H 7.14; N 12.77; P 6.99.

4.3.4. 1,1-Diphenyl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (7a). Procedure A was applied. Orange solid (0.15 g, 43%). Procedure B was applied, 4 h (0.17 g, 50%). Procedure C was applied, 8 h (0.12 g, 34%). Mp 154–156 °C (MeOH). ^{31}P NMR δ 16.3 (m). IR, ν_{max} (cm^{-1}): 3052, 2960, 2923, 2858, 2159, 1538, 1506, 1479, 1363, 1321, 1105, 813, 744, 692, 555. MS, *m/z* (%): 344 (M^+, 36), 159 (100). Anal. Calcd for $C_{22}H_{21}N_2P$: C 76.73; H 6.15; N 8.13; P 8.99. Found: C 76.73; H 6.11; N 8.10; P 9.05.

4.3.5. 6-Methyl-1,1-diphenyl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (7b). Procedure A was applied. Light brown solid (0.09 g, 26%). Procedure B was applied, 10 h. The phosphinine was registered by ^{31}P NMR spectroscopy, but we failed to separate it. Procedure C was applied, 5 days, The phosphinine was registered by ^{31}P NMR spectroscopy, but we failed to separate it. Mp 145–150 °C (hexane). ^{31}P NMR δ 20.4 (m). IR, ν_{max} (cm^{-1}): 3054, 2971, 2954, 2925, 2875, 2179, 1565, 1523, 1436, 1346, 1178, 1116, 750, 723, 694, 559. MS, *m/z* (%): 358 (M^+, 35), 173 (100). Anal. Calcd for $C_{23}H_{23}N_2P$: C 77.07; H 6.47; N 7.82; P 8.64. Found: C 77.01; H 6.46; N 7.88; P 8.59.

4.3.6. 1,1,6-Triphenyl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (7c). Procedure A was applied. Yellow solid (0.18 g, 44%). Procedure B was applied, 0.5 h (0.29 g, 70%). Procedure C was applied, 4 h (0.23 g, 55%). Mp 165–170 °C (*i*-PrOH). ^{31}P NMR δ 15.8 (m). IR, ν_{max} (cm^{-1}): 3074, 3054, 2966, 2913, 2867, 2157, 1533, 1508, 1479, 1367, 1290, 1245, 1095, 935, 875, 746, 694, 539, 495. MS, *m/z* (%): 420 (M^+, 33), 235 (100). Anal. Calcd for $C_{28}H_{25}N_2P$: C 79.98; H 5.99; N 6.66; P 7.37. Found: C 79.95; H 5.97; N 6.56; P 7.46.

4.3.7. 4-Formyl-1,1-diphenyl-3-pyrrolidin-1-yl-1λ^5-phosphinine-2-carbonitrile (19). Procedure C was applied, 8 h. The phosphinine **7a** was collected as described in the general procedure C. The aqueous solution was left for 10 h and precipitated beige solid was collected by filtration, washed with acetone yielding 10% of the aldehyde. Mp 185–190 °C (acetone). ^{31}P NMR δ 13.3 (m). IR, ν_{max} (cm^{-1}):

3050, 2967, 2920, 2861, 2161, 1672, 1538, 1510, 1462, 1341, 1319, 1109, 820, 745, 701, 578. MS, *m/z* (%): 372 (M^+, 15), 355 (37), 183 (27), 159 (29), 85 (51), 83 (60). Anal. Calcd for $C_{23}H_{21}N_2OP$: C 74.18; H 5.68; N 7.52; P 8.32. Found: C 74.20; H 5.67; N 7.48; P 8.22.

4.4. Synthesis of phosphorylated enamines 8c and 12

4.4.1. 2-(Diphenylphosphoroselenoyl)-3-pyrrolidin-1-ylbut-2-enenitrile (8c). To a stirred solution of Ph_2PCl (3.24 g, 14.7 mmol) in dichloromethane (30 mL) under dry argon, a solution of enamine **1** (2 g, 14.7 mmol) and Et_3N (1.93 g, 19 mmol) in dichloromethane (20 mL) was added dropwise. After 7 h finely powdered selenium (1.16 g, 15 mmol) was added and the reaction mixture was stirred till almost complete dissolution of the selenium, which took 24 h. The reaction mixture was filtered off, washed with water. The organic layer was separated, dried (Na_2SO_4), and evaporated in vacuo. The residue was crystallized from *i*-PrOH. Yellow solid (2.81 g, 48%). Mp 170–172 °C. ^{31}P NMR δ 33.1. ^1H NMR ($CDCl_3$) δ 1.97 (4H, br m, CH_2), 2.25 (3H, s, CH_3), 3.52 (2H, br m, NCH_2), 3.91 (2H, br m, NCH_2), 7.42–7.58 (6H, m, PPh_2), 7.92 (4H, dd, $^3J_{HH}$= 8.1 Hz, $^3J_{PH}$=14.1 Hz, PPh_2). ^{13}C NMR ($CDCl_3$) δ 22.9 ($^3J_{CP}$=7.0 Hz, C(4)), 24.8 (b, CH_2), 25.6 (b, CH_2), 51.5 (b, NCH_2), 52.4 (b, NCH_2), 64.7 ($^1J_{CP}$=98.5 Hz, C(2)), 120.3 ($^2J_{CP}$=10.1 Hz, CN), 128.4 ($^2J_{CP}$=13.1 Hz, PPh_2), 131.5 ($^4J_{CP}$=3 Hz, PPh_2), 132.5 ($^3J_{CP}$=11.1 Hz, PPh_2), 132.8 ($^1J_{CP}$=80.1 Hz, PPh_2), 167.8 ($^2J_{CP}$=16.1 Hz, C(3)). IR, ν_{max} (cm^{-1}): 3047, 2966, 2923, 2873, 2173, 1537, 1434, 1403, 1346, 1091, 696, 568, 528. MS, *m/z* (%): 399 (M^+, 34), 398 (18), 320 (61), 319 (100), 243 (21), 212 (42), 185 (33), 183 (59), 108 (65), 83 (44), 70 (27), 68 (50), 42 (31), 41 (32). Anal. Calcd for $C_{20}H_{21}N_2PSe$: C 60.16; H 5.30; N 7.01; P 7.76. Found: C 60.11; H 5.25; N 6.99; P 7.79.

4.4.2. 2-[Methyl(morpholin-4-yl)phosphorothioyl]-3-pyrrolidin-1-ylbut-2-enenitrile (12). To a stirred solution of $MePCl_2$ (1.71 g, 14.7 mmol) in dichloromethane (20 mL) under dry argon, a solution of enamine **1** (2 g, 14.7 mmol) and Et_3N (1.93 g, 19 mmol) in dichloromethane (30 mL) was added dropwise. Then, a solution of morpholine (1.28 g, 14.7 mmol) and Et_3N (1.48 g, 14.7 mmol) in dichloromethane (20 mL). After 1 h, finely powdered sulfur (0.47 g, 14.7 mmol) was added and the reaction mixture was stirred till almost complete dissolution of the sulfur, which took 12 h. The reaction mixture was washed with water. The organic phase was separated, dried (Na_2SO_4) and evaporated in vacuo. The residue was crystallized from *i*-PrOH. Yellow solid (1.80 g, 41%). Mp 130–135 °C. ^{31}P NMR δ 63.8. ^1H NMR ($CDCl_3$) δ 1.95 (3H, d, $^2J_{PH}$=13.2 Hz, PCH_3), 2.03 (4H, br m, CH_2), 2.46 (3H, s, CH_3), 3.09–3.31 (4H, m, $PNCH_2$), 3.54 (2H, br m, NCH_2), 3.66 (4H, t, $^3J_{HH}$=4.2 Hz, OCH_2), 3.90 (2H, br m, NCH_2). ^{13}C NMR ($CDCl_3$) δ 20.8 (C(4)), 21.5 ($^1J_{CP}$=78.1 Hz, PCH_3), 24.4 (b, CH_2), 25.4 (b, CH_2), 44.5 ($PNCH_2$), 51.0 (b, NCH_2), 51.9 (b, NCH_2), 65.0 ($^1J_{CP}$=124 Hz, C(2)), 67.0 ($^3J_{CP}$=8.1 Hz, OCH_2), 121.4 ($^2J_{CP}$=13.8 Hz, CN), 167.3 ($^2J_{CP}$=12.8 Hz, C(3)). IR, ν_{max} (cm^{-1}): 2964, 2956, 2902, 2844, 2161, 1538, 1454, 1411, 1346, 1249, 1110, 962, 916. MS, *m/z* (%): 299 (M^+, 50), 214 (99), 213 (48), 199 (100), 181 (81), 136 (61), 135 (64), 87 (53), 69 (73), 42 (45). Anal. Calcd for $C_{13}H_{22}N_3OPS$: C 52.16; H 7.41; N 14.04; P 10.35; S 10.71. Found: C 52.15; H 7.45; N 14.00; P 10.31; S 10.71.

4.5. Synthesis of dienamines 9, 10, and 13

Procedure A. Enamine **8** or **13** (3 mmol) was boiled in DMADMF (20 mL) at 110 °C with stirring collecting methanol for an appropriate time. The precipitate formed was filtered and washed with *i*-PrOH.

4.5.1. 5-(Dimethylamino)-2-(diphenylphosphoryl)-3-pyrrolidin-1-ylpenta-2,4-dienenitrile (9a). Procedure A was applied, 10 h. Yellow solid (0.74 g, 63%). Mp 238–240 °C. ^{31}P NMR δ 27.1. ^1H NMR ($CDCl_3$) δ 1.99 (4H, br m, CH_2), 2.71 (6H, br s, NCH_3), 3.59 (4H, br m, NCH_2), 4.16 (1H, d, $^3J_{HH}$=12.3 Hz, C(4)H), 7.33–7.47 (6H, m, PPh_2), 7.72 (1H, d, $^3J_{HH}$=12.3 Hz, C(5)H), 7.79–7.93 (4H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 25.5 (CH_2), 37.1 (b, NCH_3), 44.5 (b, NCH_3), 51.1 (NCH_2), 56.1 ($^1J_{CP}$=134 Hz, C(2)), 90.9 ($^3J_{CP}$=1.7 Hz, C(4)), 123.5 ($^2J_{CP}$=14.5 Hz, CN), 127.8 ($^2J_{CP}$=11.5 Hz, PPh_2), 130.3 ($^4J_{CP}$=1.9 Hz, PPh_2), 131.4 ($^3J_{CP}$=8.4 Hz, PPh_2), 135.6 ($^1J_{CP}$=110.9 Hz, PPh_2), 155.1 (C(5)), 168.5 ($^2J_{CP}$=10.6 Hz, C(3)). IR, ν_{max} (cm^{-1}): 3074, 3050, 2981, 2944, 2871, 2146, 1625, 1506, 1436, 1390, 1301, 1168, 1110, 719, 703, 568, 526. MS, *m/z* (%): 391 (M^+, 63), 390 (64), 376 (91), 347 (52), 201 (39), 190 (47), 121 (100), 70 (43), 42 (22). Anal. Calcd for $C_{23}H_{26}N_3OP$: C 70.57; H 6.69; N 10.73; P 7.91. Found: C 70.54; H 6.68; N 10.75; P 7.90.

4.5.2. 5-(Dimethylamino)-2-(diphenylphosphorothioyl)-3-pyrrolidin-1-ylpenta-2,4-dienenitrile (9b). Procedure A was applied, 16 h. Yellow solid (0.71 g, 58%). Mp 211–214 °C. ^{31}P NMR δ 44.1. ^1H NMR ($CDCl_3$) δ 1.98 (4H, br m, CH_2), 2.65 (6H, br s, NCH_3), 3.6 (4H, br m, NCH_2), 4.38 (1H, d, $^3J_{HH}$=11.7 Hz, C(4)H), 7.26 (1H, d, $^3J_{HH}$= 11.7 Hz, C(5)H), 7.37–7.49 (6H, m, PPh_2), 7.91–8.05 (4H, m PPh_2). ^{13}C NMR ($CDCl_3$) δ 25.7 (CH_2), 37.2 (b, NCH_3), 44.1 (b, NCH_3), 51.5 (NCH_2), 53.8 ($^1J_{CP}$=118.2 Hz, C(2)), 91.3 (C(4)), 124.2 ($^2J_{CP}$=12.6 Hz, CN), 128.1 ($^2J_{CP}$= 12.6 Hz, PPh_2), 130.6 ($^4J_{CP}$=2.5 Hz, PPh_2), 131.8 ($^3J_{CP}$= 10.1 Hz, PPh_2), 136.4 ($^1J_{CP}$=88.0 Hz, PPh_2), 155.0 (C(5)), 168.0 ($^2J_{CP}$=12.6 Hz, C(3)). IR, ν_{max} (cm^{-1}): 3054, 2969, 2950, 2935, 2869, 2156, 1621, 1429, 1386, 1284, 1093, 971, 767, 705, 628, 549. MS, *m/z* (%): 407 (M^+, 98), 374 (17), 298 (16), 217 (18), 190 (67), 185 (28), 121 (100), 70 (47), 42 (22). Anal. Calcd for $C_{23}H_{26}N_3PS$: C 67.79; H 6.43; N 10.31; P 7.60; S 7.87. Found: C 67.77; H 6.44; N 10.27; P 7.65; S 7.90.

4.5.3. 5-(Dimethylamino)-2-(diphenylphosphoroselenoyl)-3-pyrrolidin-1-ylpenta-2,4-dienenitrile (9c). Procedure A was applied, 3 days. Yellow solid (0.84 g, 62%). Mp 160–165 °C. ^{31}P NMR δ 34.0. ^1H NMR ($CDCl_3$) δ 1.98 (4H, br m, CH_2), 2.65 (6H, s, NCH_3), 3.61 (4H, br m, NCH_2), 4.46 (1H, d, $^3J_{HH}$=11.7 Hz, C(4)H), 7.16 (1H, d, $^3J_{HH}$=11.7 Hz, C(5)H), 7.34–7.49 (6H, m, PPh_2), 7.92–8.03 (4H, m, PPh_2). ^{13}C NMR ($CDCl_3$) δ 25.6 (CH_2), 37.1 (b, NCH_3), 44.3 (b, NCH_3), 51.5 (NCH_2), 52.2 ($^1J_{CP}$= 109.4 Hz, C(2)), 91.9 (C(4)), 123.8 ($^2J_{CP}$=11.3 Hz, CN), 128.0 ($^2J_{CP}$=12.6 Hz, PPh_2), 130.6 ($^4J_{CP}$=2.5 Hz, PPh_2), 132.3 ($^3J_{CP}$=10.1 Hz, PPh_2), 135.5 ($^1J_{CP}$=79.3 Hz, PPh_2), 154.8 (C(5)), 168.2 ($^2J_{CP}$=12.6 Hz, C(3)). IR, ν_{max} (cm^{-1}):

3057, 2942, 2919, 2869, 2146, 1652, 1508, 1434, 1386, 1280, 1091, 971, 566, 547. MS, *m*/*z* (%): 454 (M^+, 100), 375 (26), 374 (55), 331 (18), 305 (26), 265 (45), 263 (23), 188 (18), 185 (23), 154 (25), 136 (20), 121 (24). Anal. Calcd for $C_{23}H_{26}N_3PSe$: C 60.79; H 5.77; N 9.25; P 6.82. Found: C 60.77; H 5.77; N 9.13; P 6.74.

4.5.4. 5-(Dimethylamino)-2-(diphenylphosphino)-3-pyrrolidin-1-ylpenta-2,4-dienenitrile (10). To a suspension of dienamine **9c** (1 g, 2.2 mmol) in benzene $P(NMe_2)_3$ (0.39 g, 2.4 mmol) was added, and the reaction mixture was boiled at 80 °C till complete dissolution. The solution was evaporated in vacuo. $SeP(NMe_2)_3$ was distilled off from the reaction mixture in high vacuo 0.03 mm at 150 °C. The targeted product **10** left in the residue. Pale yellow amorphous solid (0.74 g, 90%). ^{31}P NMR δ −5.7. ^1H NMR (C_6D_6) δ 1.25 (4H, br m, CH_2), 2.05 (6H, s, NCH_3), 3.34 (4H, br m, NCH_2), 4.35 (1H, dd, $^3J_{HH}=12.3$ Hz, $^4J_{PH}=1.8$ Hz, C(4)H), 6.70 (1H, d, $^3J_{HH}=12.3$ Hz, C(5)H), 7.08–7.27 (6H, m, PPh_2), 7.92 (4H, dd, $^3J_{HH}=7.5$ Hz, $^3J_{PH}=7.5$ Hz, PPh_2). ^{13}C NMR (C_6D_6) δ 25.7 (CH_2), 39.8 (b, NCH_3), 51.3 (NCH_2), 91.0 ($^3J_{CP}=6.8$ Hz, C(4)), 123.5 ($^2J_{CP}=4.7$ Hz, CN), 128.2 (PPh_2), 128.6 ($^3J_{CP}=6$ Hz, PPh_2), 133.5 ($^2J_{CP}=20.1$ Hz, PPh_2), 142.3 ($^1J_{CP}=13$ Hz, PPh_2), 155.5 ($^4J_{CP}=10.4$ Hz, C(5)), 169.0 ($^2J_{CP}=38.6$ Hz, C(3)). MS, *m*/*z* (%): 375 (M^+, 84), 331 (100), 262 (48), 201 (79), 191 (28), 185 (43), 183 (58), 147 (35), 121 (80), 108 (56), 70 (30), 42 (49). Anal. Calcd for $C_{23}H_{26}N_3P$: C 73.58; H 6.98; N 11.19; P 8.25. Found: C 73.55; H 7.03; N 11.15; P 8.19.

4.5.5. 5-(Dimethylamino)-2-[methyl(morpholin-4-yl) phosphorothioyl]-3-pyrrolidin-1-ylpenta-2,4-dienenitrile (13). Procedure A was applied, 24 h. Yellow solid (0.64 g, 60%). Mp 160–161 °C. ^{31}P NMR δ 65.8. ^1H NMR ($CDCl_3$) δ 1.92 (3H, d, $^2J_{PH}=12.6$ Hz, PCH_3), 1.97 (4H, br m, CH_2), 3.02 (6H, br s, NCH_3), 3.14–3.22 (4H, m, NCH_2), 3.52 (4H, br m, NCH_2), 3.63–3.70 (4H, m, OCH_2), 4.61 (1H, d, $^3J_{HH}=12$ Hz, C(4)H), 7.69 (1H, d, $^3J_{HH}=12$ Hz, C(5)H). ^{13}C NMR ($CDCl_3$) δ 21.9 ($^1J_{CP}=77.3$ Hz, PCH_3), 25.6 (CH_2), 45.2 ($PNCH_2$), 51.4 (NCH_2), 54.1 ($^1J_{CP}=131$ Hz, C(2)), 67.4 ($^3J_{CP}=7.6$ Hz, OCH_2), 89.9 (C(4)), 124.5 ($^2J_{CP}=14.8$ Hz, CN), 155.7 (C(5)), 167.7 ($^2J_{CP}=12.2$ Hz, C(3)). MS, *m*/*z* (%): 354 (M^+, 92), 269 (33), 268 (30), 254 (39), 191 (35), 190 (42), 148 (100), 121 (63), 70 (49), 42 (19). Anal. Calcd for $C_{16}H_{27}N_4OPS$: C 54.22; H 7.68; N 15.81; P 8.74; S 9.05. Found: 54.21; H 7.65; N 15.81; P 8.78; S 9.10.

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An unusual stereochemical outcome of radical cyclization: synthesis of (+)-biotin

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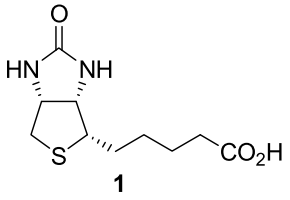
Abstract—An enantioselective synthesis of (+)-biotin **1** starting from naturally available cysteine is described. The key steps are the unusual stereochemical outcome of radical cyclization of compound **10** to prepare 5,5-fused system **11**, and the introduction of C4-sidechain at C_6 in **13** via a Grignard reaction.

1. Introduction

(+)-Biotin **1** is one of the water-soluble B-complex vitamins. In bound from, it is widely distributed as a cell constituent of animal and human tissues.



1

Biochemically, (+)-biotin functions as a cofactor in carboxylation reactions and is also involved in important processes such as gluconeogenesis and fatty acid synthesis.[1] The importance of (+)-biotin in human nutrition and animal health has stimulated the development of new synthetic routes towards this vitamin. To date, a number of new synthetic routes involving different strategies for control of the three adjacent chiral centers have been reported.[2] The formation of five membered rings using radical cyclization has been used extensively in the last few years for the synthesis of complex molecules.[3] From these reports it is evident that the hex-5-enyl radicals predominantly undergo exo cyclization resulting in the formation of 1,5-cis derivatives. Only very few examples are reported where formation of 1,5-trans product is reported.[3b,c,i,j] However, these are restricted to the formation of monocyclic adducts. Although the formation of bicyclic compounds employing radical cyclizations leading to 1,5-trans adducts are known,[3d] they are restricted to the formation of 6,5-fused systems. We are not aware of any instance of acyliminium radical cyclization leading to the formation of 5,5-fused system with 1,5-trans stereochemistry. In our earlier route we have reported an efficient conversion of **10** to a bicyclic 5,5-fused system, utilizing acyliminium ion chemistry[2d] for the synthesis of biotin. Based on literature precedents,[3] it was our premise that radical cyclization of **10** would lead to all cis bicyclic ether **11a**, which is the intermediate having the requisite stereochemistry for the synthesis of biotin. Our continued interest in the synthesis of biotin[2d–f] led us to explore radical cyclization of enol ether **10**. Herein, we describe an interesting approach to the synthesis of (+)-biotin using intramolecular radical cyclization of α-amido radical to the silyl enol ether in **10**. This manuscript delineates our findings towards this end. To the best of our knowledge there is only one report of (+)-biotin synthesis using intramolecular cyclization onto an alkyne.[4]

2. Results and discussion

Our synthetic route to **1** is outlined in the Schemes 1–3. According to the planned synthesis, hydantoin **4** was prepared from L-cysteine hydrochloride hydrate by a literature procedure.[5,6] Reduction of hydantoin **4** with sodium borohydride gave hydroxy imidazothiazolone **5** in

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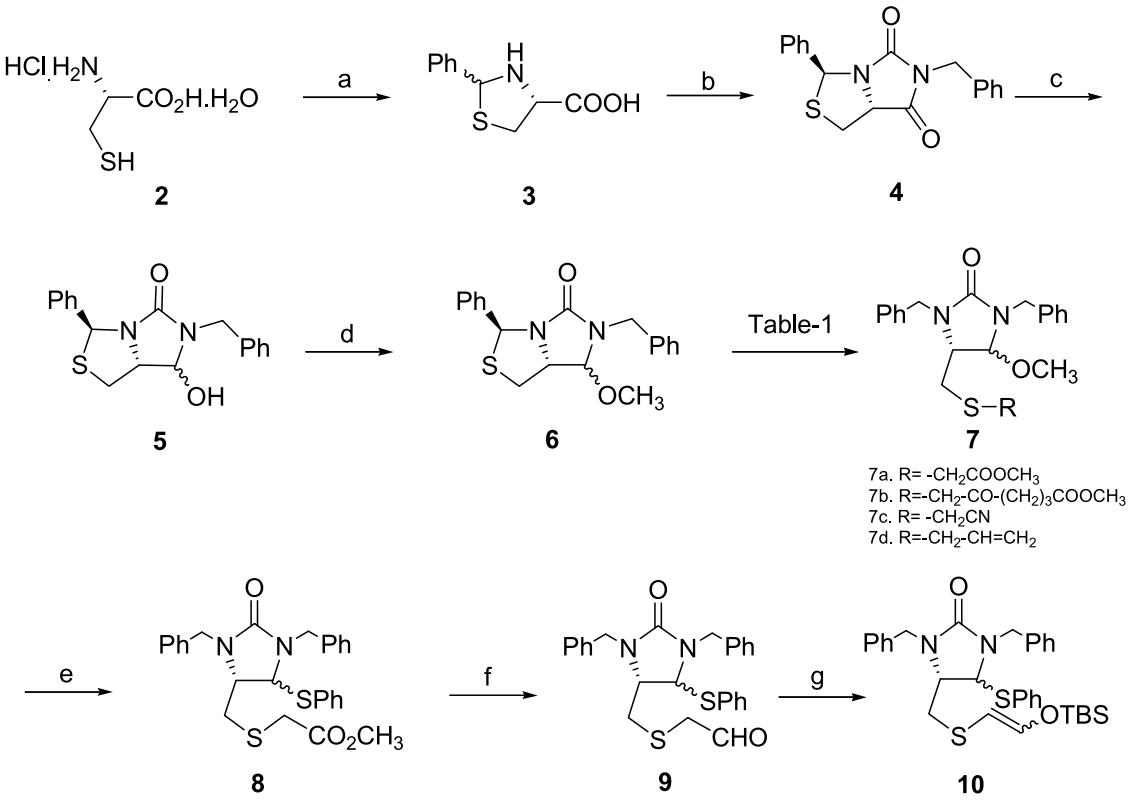
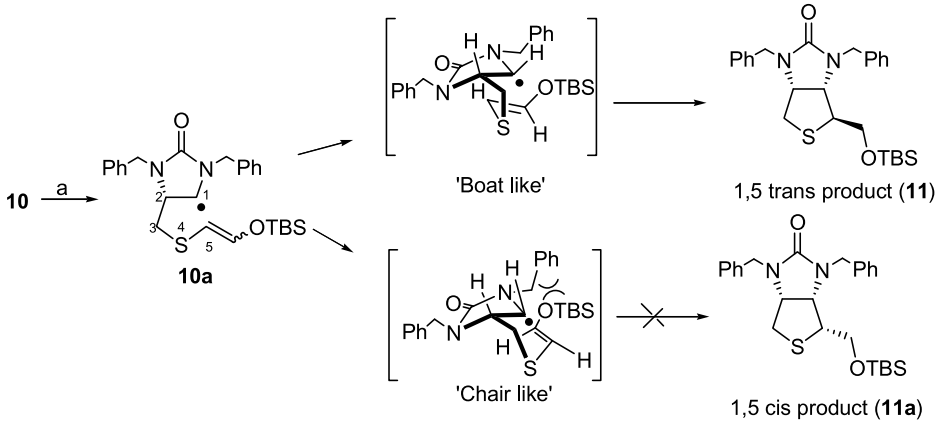


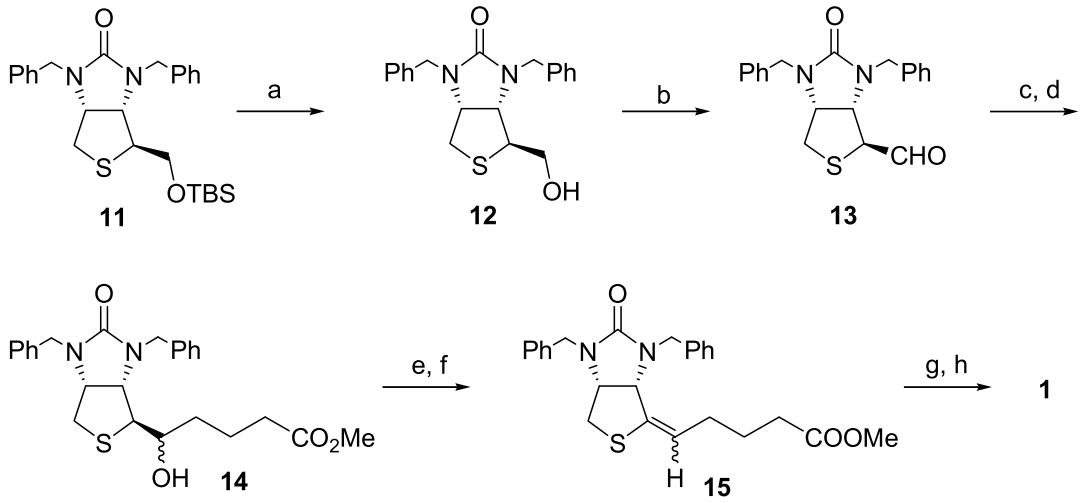
Scheme 1. (a) PhCHO, KOAc, MeOH:H_2O (1:1), rt, 6 h, 98%; (b) BnNCO, DCM, 60 min, concd HCl, 60 min, reflux, 90 min, 90%; (c) $NaBH_4$, MeOH, 0 °C to rt, 1 h, 99%; (d) MeOH, *p*-TSA (cat.), 15 min, 98%; (e) PhSH, *p*-TSA (cat.), DCM 10 min, 93%; (f) DIBAL-H, toluene, −78 °C, 2 h, 78%; (g) TBSCl, DCM, DBU, reflux, 30 min, 80%.



Scheme 2. (a) Bu_3SnH, AIBN, benzene, reflux, 4 h, 53%.

98% yield, which on methoxylation in the presence of cat. *p*-TSA furnished methoxy imidazothiazolone **6**. Initial attempts to effect reductive cleavage of carbon–sulfur bond under conventional reaction conditions (Zn/AcOH) resulted in exclusive formation of eliminated product by loss of methanol.

It was therefore, necessary to cleave the carbon–sulphur bond of **6** under nonacidic conditions, was achieved by three different methods. Amongst them, compound **6** on reductive cleavage of carbon–sulphur bond with Bu_3SnH in the presence of cat. amounts of AIBN in benzene at elevated temperatures furnished the corresponding tin thiolate, which without isolation was alkylated with ethyl chloroacetate under anhydrous conditions in acetone using K_2CO_3, furnished **7a**. Potassium carbonate was proved necessary for the success of the reaction. Additionally carbon–sulphur bond cleavage was also achieved by using two other methods. viz. (a) Li-naphthalide at −78 °C, (b) Zn/NH_4Cl according to conditions of Houlton.[7] The resulting thiol in both cases without isolation was alkylated under basic conditions with alkyl halides (see Table 1) to furnish the *S*-alkylated compounds (**7a**–**7c**). In order to establish the generality of this protocol, the reductive cleavage of carbon–sulphur bond was studied with a variety of allyl halides. The results of the reductive cleavage followed by



Scheme 3. (a) $BF_3 \cdot Et_2O$, $CHCl_3$, rt, 2 h, 75%; (b) $(COCl)_2$, DMSO, DCM, Et_3N, −78 °C to rt, 2.5 h, 61%; (c) Mg, $BrCH_2CH_2CH_2Br$, THF, 12 h, then cooled to −15 °C, CO_2, 2 h, rt; (d) CH_2N_2, 15 min, 76% (two steps); (e) MsCl, Et_3N, DCM, 0 °C to rt, 3 h; (f) DBU, 60 °C, 12 h, 80% (two steps); (g) 10% Pd–C, H_2, 200 psi, 65 °C, 6 h, 99%; (h) HBr (47%), reflux, 5 h, 75%.

Table 1

	7 (% Yield)			
Alkylating agent	$ClCH_2COOMe$	$ClCH_2C(O)(CH_2)_3COOMe$	$ClCH_2CN$	$ClCH_2CH{=}CH_2$
Method A[a]	**7a** 80%	**7b** 70%	**7c** 78%	**7d** 85%
Method B[b]	**7a** 74%	**7b** 64%	**7c** 76%	**7d** 80%
Method C[c]	**7a** 63%	**7b** 58%	**7c** 70%	**7d** 73%

[a] Reduction of C–S bond with tri-*n*-butyltin hydride.
[b] Reduction of C–S bond with lithium-naphthalide.
[c] Reduction of C–S bond with zinc and saturated aqueous NH_4Cl.

alkylation are tabulated in Table 1. These results clearly establish the superiority of tri-*n*-butyltin hydride as an efficient reagent for reductive cleavage of carbon–sulphur bond as compared to Li-naphthalide or Zn/NH_4Cl.

Compound **7a** was then taken up for the synthesis of biotin. Thus, **7a** was converted to its thiophenyl derivative **8** with excess of thiophenol in dichloromethane and cat. amount of *p*-TSA. The ester moiety in the compound **8** was then reduced to aldehyde **9** with DIBAL-H in toluene at −78 °C, the crude aldehyde **9** was then converted to its TBS enol ether **10** (trans:cis=3:1) by using TBDMSCl, and DBU in dichloromethane at reflux for 30 min. The crucial step of synthesis, the radical cyclisation of silyl enolether **10** according to literature precedents[3] was expected to undergo exo cyclisation leading to 1,5-cis substituted bicyclic skeleton **11a**, which would serve as an ideal precursor for the synthesis of biotin. However, when the silyl enol ether **10** was refluxed with Bu_3SnH and catalytic amount of AIBN under argon atmosphere, a single cyclized product **11** was obtained in 53% yield, which was eventually shown to be the undesired 5,5-fused system **11** with incorrect stereo-center at C-5 position.

The exclusive formation of 1,5-trans product **11** (carbon having radical assigned 1 in hex-5-enyl system **10a**) is unexpected since other structurally related radicals and their carbocyclic analogues[3d] give a mixture with mostly 1,5-cis products. This may be attributed to the manifestation of steric and electronic effects of the acylimido radical. Additionally the presence of electronegative nitrogen may also destabilize the transition state leading to the formation of *syn* product.[3h] We believe that the bulky *N*-benzyl groups of imidazolidinone tend to occupy quasi equatorial positions. The formation of 1,5-trans product **11** can be rationalized by a boat like transition state of **10a** (Scheme 2) in which the pseudo-axial radical attacks the C=C of the enol ether in pseudo-equatorial side chain. By this way the steric compression between *N*-benzyl adjacent to radical carbon and the bulky OTBS group of enol ether could be relieved as compared to the chair like transition state leading to the formation of 1,5-cis product **11a**. This unusual behavior may also be ascribed to the presence of sulfur atom in the chain, which mimics the six membered ring formation.

This reaction shows that 1,5-trans cyclized products could be synthesized by appropriately controlling the steric requirements. More studies are required to arrive at a proper conclusion.

Although the stereochemistry at the C-5 was not the desired one, we decided to proceed further and rectify it at the later stages of the synthesis. In the next step TBS group was deprotected[8] and oxidized to the corresponding aldehyde under Swern oxidative conditions to furnish bicyclic aldehyde **13** with undesired configuration at C-5 position (with respect to (+)-biotin) as the sole product. Since the isomer **13** is thermodynamically more stable, it cannot be epimerized at the C-5 position. The side chain of biotin was

introduced by the addition of excess of 1,3-propane dimagnesium dibromide in THF at −15 °C followed by quenching with CO_2[9] at −20 °C to furnish the carboxylic acid. The carboxylic acid thus formed was characterized as its methyl ester **14** by treating with diazomethane. The hydroxy methyl ester **14** was then converted to (+)-biotin by straight forward functional group manipulations. The hydroxyl function of **14** was protected as its mesylate and subsequent treatment of this with DBU afforded known exocyclic olefin.[10] Hydrogenation of this double bond followed by debenzylation furnished (+)-biotin in 60% yields over four steps.

3. Conclusion

The synthesis of (+)-biotin starting from the commercially available L-cysteine hydrochloride hydrate has been achieved. The noteworthy feature of this synthesis is the unusual stereochemistry observed during the radical cyclization to furnish the cis fused bicyclic system, which highlights the ability of radical cyclizations to form 1,5-trans products of hexenyl radicals by appropriate control of steric requirements.

4. Experimental

4.1. General methods

All solvents were freshly distilled before use and dry solvents were distilled under argon from Na/benzophenone. Melting points are uncorrected. Chemical shifts in ^{1}H and ^{13}C NMR are reported relative to residual solvents. Abbreviations for ^{1}H NMR: s, singlet; d, doublet; m, multiplet. Progress of the reactions were monitored by TLC using Merck silica gel. $60F_{254}$ precoated plates and visualized by fluorescence quenching or by charring after treatment with the mixture of *p*-anisaldehyde–H_2SO_4 in ethanol. The products were purified by column chromatography (SiO_2).

Analytical data of all known compounds were compared with the literature, and new compounds were fully characterized.

4.1.1. (2*RS*,4*R*)-2-Phenylthiazolidine-4-carboxylic acid (3).[5] To a solution of L-cysteine hydrochloride hydrate **2** (60 g, 0.34 mol), in water (525 mL) was added potassium acetate (36 g, 0.37 mol) was added and allowed to stir till a solution was obtained. To this solution 95% of methanol (525 mL) was added followed by immediate addition of benzaldehyde (44.2 g, 0.42 mol) in one portion. The reaction mixture was kept at 25 °C for 3 h and an additional 3 h at 0 °C. The product was formed as a solid was filtered, washed with methanol, and dried to afford **3** as a white solid. Yield: 72.0 g (98%). Mp 155 °C (lit.[5] 159–160 °C), $[\alpha]_D$ −133 (*c* 1, DMSO) IR (KBr, cm^{-1}): 3040, 2960, 2700–2400 (NH_3^+), 1600–1550 (CO_2^-) 1360. ^{1}H NMR (DMSO-d_6, 200 MHz): 3.50–3.30 (m, 2H, CH_2); 4.40–4.0 (dd, 1H, CHCOOH); 5.80 (s, 1H, CH); 6.80 (bm, 1H, NH); 7.40 (m, 5H). Mass (*m*/*z*): 209 (M^+, 34), 170 (39), 164 (65), 137 (100), 77 (10), 65 (8), 55 (7).

4.1.2. 6-Benzyl-3-phenyl(3*S*,7a*R*)perhydroimidazo[1,5-*c*][1,3]thiazol-5,7-dione (4). In a 500 mL two-necked round bottom flask filled with nitrogen, (20.0 g, 95.6 mmol) thiazolidine carboxylic acid **3** was placed in 150 mL of anhydrous THF. To this suspension, a solution of (15.2 g, 1.143 mol) benzyl isocyanate in 50 mL of THF was added dropwise over a period of 20 min. The reaction mixture was stirred for 1 h at 60 °C. The reaction mixture was then cooled to 0 °C and concd HCl (20.0 mL) was added and the reaction mixture was allowed to stir for 90 min at 60 °C. Then the reaction mixture was allowed to cool to room temperature, water was added and extracted with ethyl acetate (3×200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. After triturating with methanol the hydantoin **4** was obtained as a white crystalline solid 27.8 g, (90%). Mp 78 °C, $[\alpha]_{365}^{20}$ +1010 (*c* 1, $CHCl_3$); $[\alpha]_D$ −250 (*c* 1.08, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050. ^{1}H NMR ($CDCl_3$, 200 MHz): 3.17 (dd, 1H, *J*=7.82, 11.2 Hz); 3.30 (dd, 1H, *J*=6.81, 11.2 Hz); 4.52 (t, 1H, *J*=7.32 Hz); 4.68 (s, 2H); 6.43 (s, 1H); 7.39 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 33.2 (t), 42.81 (t), 65.19 (d), 65.82 (d), 126.36 (d), 127.41 (d), 127.91 (d), 128.05 (d), 125.15 (d), 128.28 (d), 128.42 (d), 128.48 (d), 128.72 (d), 128.80 (d), 135.44 (s), 139.04 (s), 158.54 (s, C=O), 171.0 (s, C=O). Mass (*m*/*z*): 325 (M+1, 30), 324 (M^+, 100), 323 (M−1, 40), 291 (9), 278 (4), 233 (28), 162 (22), 145 (5), 132 (8), 122 (14), 117 (39), 104 (9), 91 (38), 77 (10), 65 (8), 55 (7). Anal. Calcd for $C_{18}H_{16}N_2O_2S$: C, 66.64; H, 4.97; N, 8.64; S, 9.88. Found: C, 66.38; H, 5.17; N, 8.43; S, 9.65.

4.1.3. (3*S*,7a*R*)-6-Benzyl-7-hydroxy-3-phenyltetrahydro-5*H*-imidazo[1,5-*c*][1,3]thiazol-5-one (5). The imidazolidinone **4** (32.4 g, 0.1 mmol) was taken in aqueous THF or methanol (300 mL) and cooled to 0 °C. Sodium borohydride (5.6 g, 0.15 mol) was added gradually in small portions over a period of time (30 min). After addition of sodium borohydride was complete, the reaction mixture was brought to room temperature and stirring continued for additional half an hour. The reaction mixture was then quenched with water and the contents were extracted with ethyl acetate. The combined layers were washed with water (100 mL), brine (100 mL) and dried over anhydrous Na_2SO_4 and filtered. After concentration under reduced pressure a white crystalline solid of hydroxy imidazothiazolone **5**, which was sufficiently pure. Yield: 32.5 g (99%). Mp 113 °C, $[\alpha]_D$ +52.58 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3400, 3010, 2960, 1700, 1510, 1438, 1310, 1239, 1160, 959. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.92 (dd, 1H, *J*=6.83, 11.72 Hz); 3.23 (d, 1H, *J*=10.26 Hz, –O*H*, D_2O exchangeable); 3.33 (dd, 1H, *J*=5.37, 11.72 Hz); 4.18 (d, 1H, *J*=15.14 Hz); 4.19 (m, 1H, *J*=5.37, 6.83 Hz, –C*H*–CH–OH); 4.78 (d, 1H, *J*=15.14 Hz); 5.04 (dd, 1H, *J*=6.84, 10.26 Hz, N–C*H*–OH); 6.38 (s, 1H); 7.30 (m, 8H); 7.40 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz): 31.60 (t), 43.83 (t), 64.37 (d), 66.03 (d), 77.74 (d), 126.08 (d), 127.93 (d), 128.03 (2C, d), 128.34 (2C, d), 128.41 (2C, d), 128.55 (2C, d), 136.40 (s), 140.98 (s), 159.55 (s, C=O). Mass (*m*/*z*): 326 (M^+, 25), 308 (19), 280 (13), 192 (9), 187 (19), 160 (6), 147 (5), 132 (27), 121 (36), 104 (23), 91 (100), 77 (14), 65 (6).

4.1.4. (3*S*,7a*R*)-6-Benzyl-7-methoxy-3-phenyltetrahydro-5*H*-imidazo[1,5-*c*][1,3]thiazol-5-one (6). To hydroxy imidazothiazolone **5** (32.6 g, 0.1 mol) dissolved in anhydrous methanol (300 mL) was added cat. amount of *p*-TSA and the reaction mixture was stirred at room temperature for 10 min. After completion of the reaction (by TLC) the reaction mixture was quenched with solid sodium carbonate and filtered. Removal of solvent and extraction with EtOAc furnished the methoxy imidazothiazolone **6**. Yield: 33.8 g (99%). Mp 83 °C, $[\alpha]_D$ −210 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 2930, 1705, 1510, 1420, 1360, 1236, 1160, 1005. ^1H NMR ($CDCl_3$, 200 MHz): 2.55 (t, 1H, *J*=9.75 Hz); 3.13 (dd, 1H, *J*=4.87, 12.19 Hz); 4.0 (dd, 1H, *J*=4.87, 9.75 Hz); 3.30 (s, 3H); 4.21 (d, 1H, *J*=15.14 Hz); 4.65 (s, 1H); 4.90 (d, 1H, *J*=15.14 Hz); 6.45 (s, 1H); 7.38 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 36.39 (t), 44.60 (t), 52.96 (q), 64.79 (d), 65.37 (d), 86.87 (d), 126.0 (d), 127.65 (d), 127.73 (d), 127.82 (d), 128.13 (d), 128.29 (2C, d), 128.42 (d), 128.55 (d), 128.70 (d), 136.12 (s), 141.36 (s), 160.01 (s, C=O). Mass (*m*/*z*): 340 (M^+, 24), 309 (6), 294 (54), 240 (6), 203 (19), 187 (5), 174 (13), 144 (6), 132 (42), 121 (8), 106 (33), 91 (100), 77 (13), 65 (6). Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Found: C, 67.10; H, 5.87; N, 8.56; S, 8.90.

4.2. General procedure for the reductive cleavage of C–S bond of methoxy imidazothiazolone 6

(*A*) *By using tri-n-butyltin hydride*. A solution of methoxy imidazothiazolone **6** (0.34 g, 1.0 mmol), tributyltin hydride (0.349 g, 1.2 mmol) and AIBN (50 mg) in dry benzene (4 mL) was refluxed for 30 min with addition of few crystals (10 mg) of AIBN at the end of every 10 min. The progress of the reaction was monitored by TLC. After completion of reaction, the organic solvent was evaporated and the crude reaction mixture was stirred with chloro compound (1.0 mmol) and anhydrous potassium carbonate (0.414 g, 0.3 mmol) in anhydrous acetone (10 mL) for 10–12 h at room temperature. Filtration and evaporation of organic solvent furnished a residue, which was column chromatographed on silica gel using 35% ethyl acetate:pet. ether as eluent to furnish *S*-alkylated compounds.

(*B*) *By using Li/Arene*. To a cooled (−78 °C) suspension of lithium (0.0347 g, 0.011 mmol) and naphthalene (0.0034 g; 0.026 mmol) in tetrahydrofuran (20 mL) was added methoxy imidazothiazolone **6** (0.340 g, 1.0 mmol) in tetrahydrofuran (10 mL) and stirred for 3 h. The reaction mixture was quenched with water as an electrophile and allowed to warm to room temperature over a period of 1 h. The reaction mixture was filtered through a pad of Celite® and washed with ethyl acetate. The organic layer was separated from filtrate and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and the solvent was removed under reduced pressure to furnish the crude residue, which was subjected to alkylation with halo compounds as mentioned in method A.

(*C*) *By using Zn/saturated NH_4Cl*. To a solution of methoxy imidazothiazolinone **6** (0.34 g, 1.0 mmol) in THF (7 mL) was added activated zinc (2 g, 30.5 mmol) and saturated aqueous ammonium chloride solution (7 mL). The mixture was stirred vigorously at 25 °C under nitrogen atmosphere. Progress of the reaction was monitored by TLC. After 12 h the reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2×30 mL). The organic layer was washed with two 20 mL portions of saturated aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure. The crude mass was subjected to S-alkylation with alkyl halides as mentioned in method A.

4.2.1. Methyl ({[(4*R*)-1,3-dibenzyl-5-methoxy-2-oxoimidazolidin-4-yl]methyl}thio)acetate (7a). Yield: 0.386 g (80%). $[\alpha]_D$ −18.4 (*c* 1.04, $CHCl_3$) IR (neat, cm^{-1}): 3006, 2930, 1725, 1701, 1450, 1358, 1234, 1077. ^1H NMR ($CDCl_3$, 200 MHz): 2.50 (dd, 1H, *J*=8.3, 12.50 Hz); 2.71 (dd, 1H, *J*=4.16, 12.50 Hz); 2.87 (s, 2H); 3.01 (s, 3H); 3.58 (dd, 1H, *J*=4.16, 8.3 Hz); 3.64 (s, 3H); 4.0 (d, 1H, *J*=15.46 Hz); 4.31 (d, 1H, *J*=15.46 Hz); 4.52 (d, 1H, *J*=15.34 Hz); 4.57 (s, 1H); 5.11 (d, 1H, *J*=15.46 Hz); 7.36 (m, 10H). Mass (*m*/*z*): 414 (M^+, 1), 399 (1), 382 (3), 309 (5), 295 (15), 277 (10), 203 (2), 181 (5), 161 (4), 132 (5), 117 (2), 105 (6), 91 (100), 77 (4), 65 (14).

4.2.2. ({[(4*R*)-1,3-Dibenzyl-5-methoxy-2-oxoimidazolidin-4-yl]-methyl}thio)acetonitrile (7c). Yield: 0.297 g (78%). $[\alpha]_D$ +49.73 (*c* 1.0, $CHCl_3$) IR (neat, cm^{-1}): 2925, 2230, 1703, 1463, 1359, 1237, 1077. ^1H NMR ($CDCl_3$, 200 MHz): 2.62 (dd, 1H, *J*=7.54, 11.32 Hz); 2.80 (dd, 1H, *J*=3.89, 11.32 Hz); 3.03 (s, 3H); 3.05 (s, 2H); 3.45 (m, 1H); 4.15 (dd, 2H, *J*=15.10 Hz); 4.50 (d, 1H, *J*=1.3 Hz); 4.90 (dd, 2H, *J*=15.10 Hz); 7.35 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz): 17.12 (t), 33.3 (t), 44.6 (t), 45.5 (t), 52.3 (q), 56.3 (d), 88.1 (d), 116.0 (s), 127.5 (d), 127.8 (2C, d), 128.2 (3C, d), 128.5 (2C, d), 128.8 (2C, d), 136.4 (s), 136.8 (s), 158.2 (s, C=O). Mass (*m*/*z*): 381 (M^{+1}, 1), 361 (1), 349 (1), 295 (18), 277 (4), 269 (4), 257 (1), 233 (4), 204 (3), 187 (3), 177 (15), 162 (3), 149 (4), 134 (6), 121 (9), 106 (10), 91 (100), 77 (4), 65 (13). Anal. Calcd for $C_{21}H_{23}N_3O_2S$: C, 66.12; H, 6.08; N, 11.01; S, 8.41. Found: C, 66.30; H, 5.85; N, 10.82; S, 8.65.

4.2.3. (4*R*)-4-[(Allylthio)methyl]-1,3-dibenzyl-5-methoxyimidazolidin-2-one (7d). Yield: 0.325 g (85%). $[\alpha]_D$ +41.3 (*c* 1, $CHCl_3$) IR (neat, cm^{-1}): 3062, 3026, 2922, 1709, 1620, 1494, 1424, 1356, 1224, 1094, 1029. ^1H NMR ($CDCl_3$, 200 MHz): 2.21 (dd, 1H, *J*=9.28, 13.68 Hz); 2.58 (dd, 1H, *J*=3.90, 13.68 Hz); 2.93 (d, 2H, *J*=7.33 Hz); 3.07 (s, 3H); 3.33 (m, 1H, *J*=3.90, 9.28 Hz); 4.08 (d, 1H, *J*=15.62 Hz); 4.10 (d, 1H, *J*=15.62 Hz); 4.47 (d, 1H, *J*=0.97 Hz); 4.91 (m, 4H); 5.58 (m, 1H); 7.29 (m, 10H). ^{13}C NMR ($CDCl_3$, 50 MHz): 30.92 (d), 35.01 (d), 44.53 (q), 52.34 (2C, t), 56.77 (t), 88.24 (t), 117.53 (t), 127.36 (d), 127.48 (d), 127.61 (d), 127.94 (d), 128.21 (2C, d), 128.46 (2C, d), 128.67 (d), 133.78 (d), 137.02 (s), 137.16 (s), 159.73 (s, C=O). Mass (*m*/*z*): 382 (M^{+1}, 1), 362 (1), 351 (1), 295 (18), 277 (4), 269 (4), 257 (1), 233 (4), 162 (3), 149 (4), 134 (6), 121 (9), 106 (10), 91 (100), 77 (4), 65 (13). Anal. Calcd for $C_{22}H_{26}N_2O_2S$: C, 69.08; H, 6.85; N, 7.32; S, 8.38. Found: C, 69.30; H, 6.55; N, 7.65; S, 8.59.

4.2.4. Methyl ({[(4*S*)-1,3-dibenzyl-2-oxo-5-(phenylthio)-imidazolidin-4-yl]methyl}thio)acetate (8). Methoxy imidazolidine **7** (4.14 g, 10 mmol) was dissolved in thiophenol (20 mL) and the solution was cooled to 0 °C.

To this was then added cat. amount of *p*-TSA (20 mg, 0.1 mmol) and the mixture was stirred at 0 °C for 5 min. Mixture of DCM (20 mL) and water (5 mL) was added to reaction mixture, organic layer was separated, washed with brine (5 mL), dried over anhydrous Na_2SO_4 and filtered. Rotary evaporation of solvent under reduced pressure and chromatographic purification (20% ethyl acetate:pet. ether) afforded 4-thiophenoxy-imidazolidine **8**. Yield: 4.70 g (93%). $[\alpha]_D$ −19.36 (*c* 0.98; $CHCl_3$) IR (neat, cm^{-1}): 3030, 2920, 2875, 1725, 1695, 1583, 1495, 1420, 1386, 1365, 1064. ^1H NMR ($CDCl_3$, 200 MHz): 2.53 (dd, 1H, *J*= 14.0, 7.5 Hz); 2.70 (dd, 1H, *J*=14.0, 3.7 Hz); 2.9 (s, 2H); 3.60 (ddd, 1H, *J*=3.7, 3.7, 7.5 Hz); 4.0 (d, 1H, *J*=15.5 Hz); 3.65 (s, 3H); 4.3 (d, 1H, *J*=15.5 Hz); 4.53 (d, 1H, *J*= 15.0 Hz); 4.57 (d, 1H, *J*=3.7 Hz); 5.1 (d, 1H, *J*=15.0 Hz); 7.09 (m, 3H); 7.28 (m, 12H). Mass (*m/z*): 383 (M^+ −109, 18), 277 (100), 264 (7), 187 (7), 110 (7), 91 (54). Anal. Calcd for $C_{27}H_{28}N_2O_3S_2$: C, 65.83; H, 5.73; N, 5.69; S, 13.02. Found: C, 65.63; H, 5.53; N, 5.39; S, 12.91.

4.2.5. ({[(4*S*)-1,3-Dibenzyl-2-oxo-5-(phenylthio)imidazolidin-4-yl]methyl}thio)acetaldehyde (9). Thiophenoxy methyl ester **8** (2.21 g, 4.37 mmol) was taken in a 100 mL two-necked round bottom flask along with 30 mL of anhydrous toluene under an atmosphere of argon. The flask was cooled to −78 °C and DIBAL-H (0.68 g, 4.8 mmol) was added slowly at −78 °C and was stirred for 2 h. After 2 h (TLC) it was quenched with 2.0 mL of MeOH and 2.0 mL of water. The solution was then stirred for half an hour and the white solid thus obtained was filtered. The filtrate was evaporated under reduced pressure and the residue taken in EtOAc and washed with water. The organic layer was then dried over anhydrous Na_2SO_4, filtered and the product obtained was chromatographed on silica gel with 25% ethyl acetate:pet. ether to yield the product aldehyde **9** (1.57 g) in 78% as a colorless viscous liquid. $[\alpha]_D$ −26.7 (*c* 0.9, $CHCl_3$) IR (neat, cm^{-1}): 3010, 2900, 1710, 1700, 1600, 1580, 1495, 1450, 1390, 1140, 1070. ^1H NMR ($CDCl_3$, 200 MHz): 2.32 (m, 2H); 2.80 (d, 2H, *J*=3.6 Hz); 3.45 (m, 1H); 3.94 (d, 1H, *J*=15.2 Hz); 4.27 (d, 1H, *J*=15.2 Hz); 4.40 (d, 1H, *J*=15.2 Hz); 4.48 (d, 1H, *J*=4 Hz); 5.10 (d, 1H, *J*=15.2 Hz); 7.13 (m, 15H); 9.14 (t, 1H). Mass (*m/z*): 353 (M^+ −109, 5), 294 (6), 149 (5), 141 (7), 132 (14), 91 (100), 84 (11), 77 (17), 69 (13), 65 (18).

4.2.6. (5*R*)-1,3-Dibenzyl-4-methoxy-5-[({(*E*/*Z*)-2-[(trimethyl-silyl)oxy]vinyl}thio)methyl]imidazolidin-2-one (10). A solution of *t*-butyldimethylsilyl chloride (0.255 g, 1.69 mmol) in anhydrous DCM (5 mL) was added via syringe to a solution of aldehyde **9** (0.650 g, 1.41 mmol) in DCM (20 mL). After 5 min, DBU (0.28 g, 1.3 mmol) was added dropwise and mixture was heated to reflux. After 30 min (TLC) the reaction mixture was concentrated and purified by column chromatography eluting with 10% ethyl acetate:pet. ether to furnish 0.65 g, (80%) of TBS enol ether as a semi solid. IR (neat, cm^{-1}): 2910, 2840, 1695, 1600, 1595, 1450, 1420, 1375, 1210, 1100, 940. ^1H NMR ($CDCl_3$, 200 MHz): 0.1 (s, 6H); 0.8 (s, 9H); 2.20 (dd, 1H, *J*=7.0, 13.0 Hz); 2.40 (dd, 1H, *J*=4.0, 13.0 Hz); 3.40 (m,1H); 3.90 (d, 1H, *J*=15.0 Hz); 4.20 (d, 1H, *J*=15.0 Hz); 4.30 (d, 1H, *J*=15.0 Hz); 4.55 (d, 1H, *J*=3.5 Hz); 5.0 (d, 1H, *J*= 15.0 Hz); 5.15 (d, 1H, *J*=11.6 Hz); 6.56 (d, 1H, *J*= 11.6 Hz); 7.0 (m, 3H); 7.35 (m, 12H). Mass (*m/z*): 467 (M^+ −109, 5), 277 (40), 203 (7), 110 (29), 91 (100), 73 (28), 65 (13). Anal. Calcd for $C_{32}H_{40}N_2O_2S_2Si$: C, 66.62; H, 6.99; N, 4.86; S, 11.12. Found: C, 66.40; H, 6.78; N, 4.70; S, 11.01.

4.2.7. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-4-({[*tert*-butyl(dimethyl)-silyl]oxy}methyl)tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (11). A solution of phenylthio enol ether **10** (0.30 g, 0.52 mmol), tributyltin hydride (0.18 g, 0.63 mmol) and AIBN (cat.) in dry benzene (20 mL) was refluxed for 4 h with addition of few crystals of AIBN at the end of 2 h. After removal of benzene under reduced pressure, crude product thus obtained was purified by column chromatography (SiO_2) (10% ethyl acetate:pet. ether) to furnish the bicyclic silyl ether **11** (0.13 g, 53%) as a viscous liquid. $[\alpha]_D$ +46.2 (*c* 1.09, $CHCl_3$) IR (neat, cm^{-1}): 2910, 2840, 1690, 1600, 1580, 1495, 1460, 1360, 1250, 1100. ^1H NMR ($CDCl_3$, 200 MHz): 0.01 (s, 6H); 0.78 (s, 9H); 2.90 (d, 2H, *J*=2.0 Hz); 3.28 (dd, 1H, *J*=4.8, 8.1 Hz); 3.40 (dd, 1H, *J*=8.1, 10.1 Hz, CH_2–OTBS); 3.50 (dd, 1H, *J*=4.8, 10.1 Hz, C*H*$_2$–OTBS); 4.09 (m, 2H); 4.17 (d, 1H, *J*=15.0 Hz); 4.24 (d, 1H, *J*=15.0 Hz); 4.75 (d, 1H, *J*= 15.4 Hz); 4.80 (d, 1H, *J*=15.4 Hz); 7.25 (m, 10H). Mass (*m/z*): 468 (M^+, 8), 453 (21), 435 (4), 411 (90), 91 (100). Anal. Calcd for $C_{26}H_{36}N_2O_2SSi$: C, 66.62; H, 7.74; N, 5.98; S, 6.87. Found: C, 66.40; H, 7.68; N, 5.68; S, 6.76.

4.2.8. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-4-(hydroxymethyl) tetrahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (12). To TBDMS ether **11** (0.312 g, 0.66 mmol) dissolved in anhydrous dichloromethane (10 mL) under nitrogen atmosphere was added borontrifluoride etherate (0.473 g, 3.3 mmol). After stirring at room temperature (2 h), the reaction mixture was neutralized with 1 M $NaHCO_3$ solution and extracted with DCM (2×10 mL). Combined organic layers were washed with water (2×10 mL), brine, dried over anhydrous Na_2SO_4, filtered and chromatographed (SiO_2) to furnish the alcohol **12** (0.177 g, 75%) as a viscous liquid. $[\alpha]_D$ +60.38 (*c* 2, $CHCl_3$) IR (neat, cm^{-1}): 3400, 2910, 1690, 1600, 1505, 1480, 1380, 1260, 1100. ^1H NMR ($CDCl_3$, 200 MHz): 2.20 (br s, 1H, D_2O exchangeable); 2.69 (dd, 1H, *J*=4.6, 10.6 Hz); 2.71 (dd, 1H, *J*=5.1, 10.6 Hz); 3.30 (s, 2H); 3.83 (d, 1H, *J*=8.1 Hz); 4.01 (m, 2H); 4.07 (d, 1H, *J*=15.0 Hz); 4.08 (d, 1H, *J*=15.4 Hz); 4.71 (app. t, 2H, *J*=15.4 Hz); 7.30 (m, 10H). Mass (*m/z*): 354 (M^+, 22), 307 (7), 277 (23), 263 (20), 187 (9), 149 (7), 91 (100), 65 (13), 57 (10). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 67.77; H, 6.26; N, 7.90; S, 9.05. Found: C, 67.40; H, 6.28; N, 7.70; S, 8.95.

4.2.9. (3a*S*,4*S*,6a*R*)-1,3-Dibenzyl-2-oxohexahydro-1*H*-thieno-[3,4-*d*]imidazole-4-carbaldehyde (13). To a flame dried 50 mL round bottom flask equipped with a magnetic stirrer under nitrogen atmosphere was added dichloromethane (5 mL, freshly distilled over P_2O_5). The flask was cooled to −78 °C and oxalyl chloride (0.050 g, 0.395 mmol) was added, followed by DMSO (0.061 g, 0.790 mmol). After the mixture was stirred at −78 °C, a solution of alcohol **12** (0.070 g, 0.197 mmol) in DCM (2 mL) was added by syringe. The resulting cloudy solution was stirred at −78 °C for 1 h. Et_3N (0.12 g, 1.185 mmol) was added and the milky white solution was stirred for

30 min at −78 °C. Reaction mixture was allowed to warm gradually to ambient temperature. After 2 h, water (10 mL) was added and the organic layer was separated, washed with saturated aqueous NH_4Cl (2 mL), aqueous $NaHCO_3$ (2 mL), and brine (5 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered, evaporated under reduced pressure and chromatographic purification (SiO_2) of the residue (25% ethyl acetate:pet. ether) furnished aldehyde **13** as a solid (0.043 g, 61%). Mp 140–141 °C, $[\alpha]_D$ −62.4 (*c* 0.75, $CHCl_3$) IR (neat): 3120, 2940, 1720, 1695, 1605, 1595, 1500, 1450, 1250. ^{1}H NMR ($CDCl_3$, 200 MHz): 2.29 (dd, 1H, *J*=4.7, 13.2 Hz); 2.68 (dd, 1H, *J*=4.7, 13.2 Hz); 3.59 (s, 1H); 4.11 (dd, 1H, *J*=4.7, 7.8 Hz); 4.16 (d, 1H, *J*=15.4 Hz); 4.34 (d, 1H, *J*=7.9 Hz); 4.36 (d, 1H, *J*=15.4 Hz); 4.47 (d, 1H, *J*=15.4 Hz); 4.68 (d, 1H, *J*=15.4 Hz); 7.25 (m, 10H); 9.13 (s, 1H). Mass (*m*/*z*): 352 (M^+, 5), 323 (5), 277 (93), 264 (6), 91 (100), 65 (6). Anal. Calcd for $C_{20}H_{22}N_2O_2S$: C, 68.16; H, 5.72; N, 7.95; S, 9.1. Found: C, 67.73; H, 6.06; N, 7.81; S, 9.35.

4.2.10. Methyl 5-[(3a*S*,4*S*,6a*R*)-1,3-dibenzyl-2-oxohexahydro-1*H*-thieno[3,4-*d*]imidazol-4-yl]-5-hydroxypentanoate (14). Under nitrogen atmosphere, magnesium (0.061 g, 2.54 mmol) turnings were initially introduced into THF (10 mL) and the mixture was heated to boiling. A solution of dibromopropane (0.516 g, 2.54 mmol) in THF (10 mL) was added to this suspension during 30 min. The reaction mixture was heated to reflux for 45 min and subsequently stirred at room temperature for 12 h. It was then cooled to −15 °C and a solution of cyclic aldehyde **13** (0.18 g, 0.51 mmol) in THF (10 mL) was added dropwise in the course of 30 min at a temperature between −14 and −16 °C. After stirring for 10 min the reaction vessel was evacuated and charged with CO_2 atmosphere. To this reaction mixture solid carbon dioxide (~1 g) was added. After 1 h, dil HCl (1 N, 5 mL) was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water (20 mL), brine (20 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the crude product was subjected to esterification with diazomethane. Chromatographic purification of the residue (50% ethyl acetate:pet. ether) furnished hydroxy methyl ester **14** (0.176 g, 76%); as a viscous liquid. IR (neat, cm^{-1}): 3310, 3032, 2928, 1743, 1700, 1440, 1342, 1231, 1079, 789. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.25 (m, 2H); 1.59 (m, 2H); 2.22 (t, 2H, *J*=7.3 Hz); 2.70 (dd, 1H, *J*=2.4, 12.2 Hz); 2.91 (dd, 1H, *J*=1.5, 12.2 Hz); 3.20 (m, 1H, *J*=1.5 Hz); 3.28 (br s, 1H); 3.64 (s, 3H); 3.94 (dd, 1H, *J*=7.8, 8.3 Hz); 4.06 (m, 2H); 4.12 (d, 1H, *J*=15.6 Hz); 4.21 (d, 1H, *J*=15.6 Hz); 4.73 (d, 1H, *J*=15.1 Hz); 4.75 (d, 1H, *J*=15.1 Hz); 7.28 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 20.97 (t), 33.48 (t), 35.07 (t), 36.23 (t), 46.27 (t), 46.82 (t), 51.52 (q), 59.49 (d), 62.39 (d), 65.65 (d), 71.63 (d), 127.51 (d), 127.60 (d), 127.97 (2C, d), 128.03 (2C, d), 128.61 (2C, d), 128.67 (2C, d), 136.97 (2C, s), 159.31 (s, C=O), 173.66 (s, C=O). Mass (*m*/*z*): 454 (M^+, 5), 407 (4), 363 (11), 324 (33), 277 (55), 233 (11), 187 (21), 149 (14), 91 (100), 65 (11). Anal. Calcd for $C_{25}H_{30}N_2O_4S$: C, 66.05; H, 6.65; N, 6.16; S, 7.05. Found: C, 66.12; H, 6.36; N, 5.98; S, 6.87.

4.2.11. Methyl (5*E*/*Z*)-5-[(3a*S*,6a*R*)-1,3-dibenzyl-2-oxohexahydro-4*H*-thieno[3,4-*d*]imidazol-4-ylidene] pentanoate (15). The hydroxy ester **14** (0.15 g, 0.330 mmol) was dissolved in anhydrous DCM (20 mL), cooled to 0 °C and triethyl amine (0.067 g, 0.33 mmol), added. To this reaction mixture MsCl (0.045 g, 0.393 mmol) was added and mixture was stirred at room temperature for 3 h, then diluted with water, and extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were washed with dil HCl, aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4. Removal of the solvent in vacuum yielded 0.172 g (98%) of mesylate as a dark yellow viscous liquid.

The crude mesylate (0.170 g, 0.32 mmol) was dissolved in anhydrous DBU (0.486 g, 3.2 mmol) and heated to 60 °C for 12 h. After completion of reaction, the reaction mixture was acidified with dil HCl (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography of the residue over silica gel using ethyl acetate/pet. ether (35:65) mixture as eluent furnished the olefin **15** as pale yellow viscous liquid. Yield: (0.110 g, 80%); viscous liquid. $[\alpha]_D$ + 194 (*c* 1, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3032, 2928, 1743, 1701, 1634, 1440, 1415, 1342, 1219, 1143, 1079, 789. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.72 (m, 2H); 2.12 (m, 2H); 2.31 (t, *J*=7.3 Hz, 2H); 3.05 (dd, *J*=9.2, 10.2 Hz, 1H); 3.12 (dd, *J*=4.4, 10.2 Hz, 1H); 3.70 (s, 3H); 4.05 (d, *J*=15.4 Hz, 1H); 4.10 (ddd, *J*=4.4, 7.3, 9.5 Hz, 1H); 4.25 (d, *J*=15.1 Hz, 1H); 4.30 (d, *J*=7.32 Hz, 1H); 4.85 (d, *J*=15.4 Hz, 1H); 5.01 (d, *J*=16.0 Hz, 1H); 5.54 (t, *J*=7.3 Hz, 1H); 7.35 (m, 10H). Mass (*m*/*z*): 436 (M^{+1}, 1), 422 (1), 405 (1), 345 (1), 309 (45), 263 (37), 187 (6), 173 (4), 158 (4), 143 (5), 132 (17), 117 (8), 105 (25), 91 (100), 77 (10), 65 (6).

4.2.12. Dibenzylbiotin methyl ester. A mixture of olefin **15** (0.100 g, 0.23 mmol) and 10% palladium on charcoal (10 mg) in methanol (20 mL) was hydrogenated (200 psi) at 65 °C for 8 h. After cooling to room temperature, the catalyst was removed by filtration and the filtrate was evaporated under reduced pressure to give the crude *N*,*N*′-dibenzyl biotin methyl ester, which was subjected to debenzylation without further purification. Mp 78–80 °C, $[\alpha]_D$ −42.13 (*c* 1.05, $CHCl_3$) IR ($CHCl_3$, cm^{-1}): 3028, 2932, 2840, 1741, 1698, 1448, 1440, 1425, 1347, 1198, 1134, 1081, 792. ^{1}H NMR ($CDCl_3$, 200 MHz): 1.67 (m, 6H); 2.33 (t, 2H); 3.10 (m, 1H); 3.69 (s, 3H); 3.90 (m, 3H); 4.15 (d, *J*=15.4 Hz, 1H); 4.75 (d, *J*=15.6 Hz, 1H); 5.10 (d, *J*=15.4 Hz, 1H); 7.32 (m, 10H). ^{13}C NMR ($CDCl_3$, 125 MHz): 24.42 (t), 28.14 (t), 28.29 (t), 33.65 (t), 34.53 (t), 46.40 (t), 47.76 (t), 51.25 (d), 54.05 (d), 60.99 (d), 62.46 (q), 127.42 (d, 2C), 128.04 (d, 4C), 128.45 (d, 4C), 136.79 (s, 2C); 160.83 (s, C=O), 173.66 (s, C=O). Mass (*m*/*z*): 438 (M^+, 8), 347 (13), 277 (31), 265 (13), 240 (9), 187 (18), 149 (4), 91 (100), 77 (3), 65 (9).

4.2.13. D-(+)-Biotin. *N*,*N*′-Dibenzyl biotin methyl ester (0.1 g, 0.23 mmol) was added to a solution of 47% hydrobromic acid (5 mL). The reaction mixture was stirred under reflux for 5 h. After cooling to room temperature, the reaction mixture was extracted with toluene (2×10 mL). The aqueous phase was concentrated under reduced pressure to dryness. The residue was dissolved in anhydrous methanol (5 mL) and refluxed for 2 h in the presence of concd H_2SO_4 (one drop). The reaction mixture was

neutralized with solid $NaHCO_3$, filtered and concentrated under reduced pressure. Crude solid thus obtained was dissolved in methanol (10 mL) and charcoal added, heated and filtered. The filtrate was concentrated under reduced pressure to furnish a residue, which was chromatographed to furnish a white solid. The solid was heated on a water bath with 1 N NaOH (10 mL) and the progress of the reaction monitored by TLC. The solvent was reduced to 5 mL and neutralized with concd HCl to pH 2. The white solid thus obtained was filtered and dried at 80 °C under vacuum to give pure **1** (0.041 g, 78%). Mp 230–231 °C (lit.[11] 229.5–230 °C), $[\alpha]_D+89.7$ (*c* 1.01, 0.1 N NaOH) lit.[11] $[\alpha]_D+91.3$ (*c*, 1.0, 0.1 N NaOH) IR (KBr, cm^{-1}): 3308, 2929, 1701, 1672. ^1H NMR ($CDCl_3$): δ 1.30–1.67 (m, 6H, 3×CH2); 2.14 (t, 2H, $J=7.3$ Hz); 2.62 (dd, 1H, $J=1.7$, 12.5 Hz); 2.78 (dd, 1H, $J=4.7$, 12.5 Hz); 3.16 (m, 1H); 4.19 (m, 1H); 4.28 (m, 1H); 6.41 (s, 1H, NH); 6.52 (s, 1H).

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Addition reactions to chiral aziridine-2-carboxaldimine toward various enantiopure nitrogen-containing heterocycles

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Abstract—Chiral (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldimine was utilized as a nitrogen-containing starting substrate for the preparation of various enantiopure nitrogen-containing heterocycles. The additions of nucleophiles including organomagnesium reagents, cyanotrimethylsilane and ketene acetal to the chiral (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldimine proceeded in highly stereoselective manner via chelation controlled transition states. Subsequent treatment of adducts with triphosgene and NaH yielded 5-substituted-4-chloromethylimidazolidin-2-ones. This imine was also served as either aza-diene or aza-dienophile with olefin or diene to provide hetero-Diels–Alder adducts 2-aziridinylpiperidines or 1,2,3,4-tetrahydroquinolines.

1. Introduction

Commercial success to produce both enantiomers of aziridine-2-carboxylates in optically pure forms enables us to provide enantiomerically pure α- or β-amino ester and their derivatives.[1,2] We would like to extend their synthetic utilities for the construction of enantiopure diamine compounds based on the reaction of the substrate aziridin-2-carboxaldimine that is readily available from aziridine-2-carboxylate. The additions to the chiral (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**) would afford amino alkyl aziridines (**2** and **3**), 2-aziridinylpiperidines (**4**) and 1,2,3,4-tetrahydroquinolines (**5**) via many different reaction pathways including nucleophilic additions and Diels–Alder reactions shown in Scheme 1. The subsequent chemical transformations of aziridine ring of the adduct by the known methods[1] can afford various enantiopure nitrogen-containing cyclic and acyclic molecules.

Throughout the study we had an insight into the transition state conformation with better understanding the factors governing the stereochemical pathways of the addition reactions.

2. Results and discussion

(2′*R*,1″*R*)-(4-Methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**) was prepared from the condensation of (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldehyde and *p*-anisidine. *p*-Methoxyphenyl moiety is readily removed to give free amine after the reaction with cerium(IV) ammonium nitrate.[3] Nucleophilic addition to imines[4] is a useful synthetic route toward the amines with expectation of certain degree of stereoselectivity. Addition of organometallic compounds including MeMgBr and MeLi without any additive did not provide the addition product even at room temperature for 15 h and all the starting imine was recovered unreacted. This suggests that the starting imine is not reactive enough toward alkyl metal compounds whose reactivity can be increased by the addition of a suitable Lewis acid. Among all tested Lewis acids $BF_3 \cdot OEt_2$ was the best to promote the reactivity without breaking the aziridine ring. The best result was obtained with the addition of four equivalents of MeMgBr at −10 °C with $BF_3 \cdot OEt_2$ to give the methylated product **2a** in 86% yield[5] (entry 5). Lower temperatures or smaller amounts of MeMgBr resulted in either no reaction or lower yield

Keywords: Aziridine-2-carboxaldimine; Addition; Nucleophiles; Hetero-Diels–Alder reaction.
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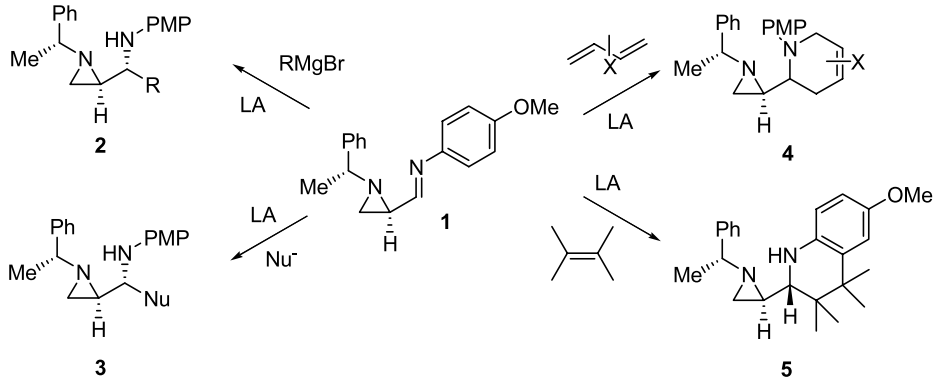


Scheme 1.

(entries 1–4). Addition of MeLi provided a slightly lower yield (76%, entry 6). The addition of a methyl group proceeded in a completely stereoselective manner to give a single isomer judging from ^{1}H NMR and HPLC regardless of the source of the organometallic reagents.

Under the same reaction conditions were added various alkyl and arylmagnesium reagents (Table 1). Ethyl magnesium bromide gave **2b** in a similar yield (82%) in a completely stereoselective manner (entry 7). This was further tested by addition of vinyl magnesium bromide resulting **2c** in 71% yield with diastereoselectivity of 97:3 based on ^{1}H NMR integration (entry 8). Much lower stereoselectivity was observed in the addition of allyl- and *n*-butylmagnesium bromide with diastereoselectivities of 62:38 (**2d** and **2d′**) and 91:9 (**2e** and **2e′**), even though the reaction yields were 82 and 72%, respectively (entries 9 and 10). Changing the alkylating agent to *n*-butyllithium form *n*-butylmagnesium bromide showed lower selectivity of 84:16 in 63% yield (entry 11). Addition of aryl magnesium reagents such as PhMgBr, *p*-tolyl-MgBr, *p*-FPhMgBr was completely stereoselective to give products **2f**, **2g**, and **2h** in 75, 68, and 71% yields, respectively (entries 12–14).

The utility of imines can be expanded by the addition of nucleophile other than organometallic reagents as shown in Table 2.[6] The addition of nitrile to imine as in Strecker reaction was studied using cyanotrimethylsilane (**6**).[7] The substrate we used, (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldimine, was inert without any additives. However, reaction with cyanotrimethylsilane in CH_2Cl_2 with 50 mol% of $BF_3\cdot OEt_2$ at room temperature for 3 h yielded the products **3a** and **3a′** as a diastereomeric mixture with the ratio of 69:31 in 91% yield with *threo* isomer **3a** as the major product (entry 1). Trials to improve the diastereoselectivity by changing Lewis acids such as $ZnCl_2$, $Sc(OTf)_3$, $Ti(O\textit{i}\text{-}Pr)_4$, TMSTf, $CeCl_3$ were not successful to show similar stereoselectivity in a little lower yield. When we used CsF that is known to be a good catalyst[7c] in the addition of imine, the reaction showed a little better ratio of 78:22 in 85% yield (entry 2). It is also noteworthy that the reaction with TMSCl as an additive gave products **3a** and **3a′** with the ratio of 45:55 in 62% yield (entry 3).

Another nucleophile ketene silyl acetal (**7**)[8] was added to (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldimine (**1**) in the presence of 50 mol% of $BF_3\cdot OEt_2$ to afford β-amino-carboxylated **3b** as a single isomer with aziridine ring conserved in 87% yield (entry 4).

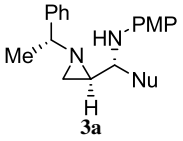
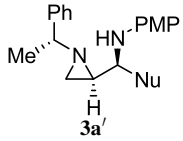
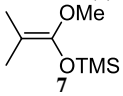
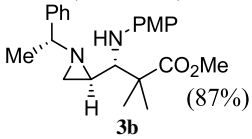
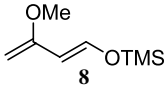
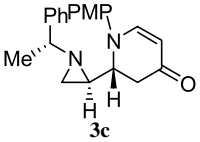
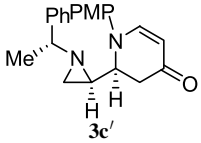
All of adducts aminomethylaziridines **2** and **3** were converted to other cyclic or acyclic dinitrogen containing compounds by the known methods.[1] We wished to convert them to the valuable enantiopure 4,5-disubstituted imidazolin-2-ones, some of which have important biological activities.[9] This was achieved with triphosgene and NaH to give 5-alkyl or 5-aryl-4-chloromethylimidazolidin-2-one (**9**) in good yield (Scheme 2 and Table 3).[10] The reaction

Table 1. The addition of organometallic reagents to chiral (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**)

Entries	Reagents	Equiv	Temperature (°C)	Time (h)	Yield	Product	Ratio
1	MeMgBr	2	−78	10	No rxn		
2	MeMgBr	2	−10	10	40 (60)		
3	MeMgBr	4	−78	4	45 (55)	**2a**	>99:<1
4	MeMgBr	2	−10	3	65 (10)	**2a**	>99:<1
5	MeMgBr	4	−10	3	86	**2a**	>99:<1
6	MeLi	4	−78	5	76	**2a**	>99:<1
7	EtMgBr	4	−10	4	82	**2b**	>99:<1
8	VinylMgBr	4	−10	3	71	**2c**, **2c′**	97:3
9	AllylMgBr	4	−10	3	82	**2d**, **2d′**	62:38
10	*n*-BuMgBr	4	−10	3	72	**2e**, **2e′**	91:9
11	*n*-BuLi	4	−10	3	63	**2e**, **2e′**	84:16
12	PhMgBr	3	−10	3	75	**2f**	>99:<1
13	*p*-TolylMgBr	3	−10	3	68	**2g**	>99:<1
14	*p*-FPhMgBr	3	−10	3	71	**2h**	>99:<1

All reactions were carried out in the presence of 1 mol equiv of $BF_3\cdot OEt_2$. Isolated yield. Determined by ^{1}H NMR.

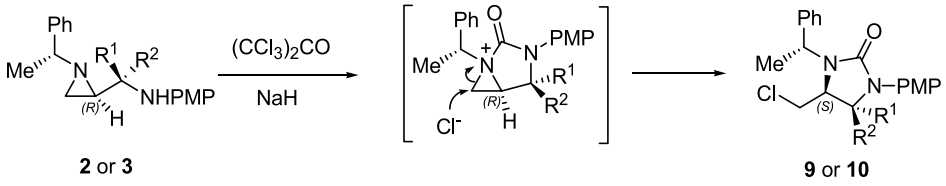
Table 2. The addition of nucleophiles to chiral (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine

Entry	Nucleophile	Lewis acid[a]	Products (% yield, ratio)[b,c]	
1	TMSCN (**6**)	$BF_3 \cdot OEt_2$	 **3a**	 **3a′** (91%, 69:31)
2	TMSCN (**6**)	CsF		(85%, 78:22)
3	TMSCN (**6**)	TMSCI		(62%, 45:55)
4	 **7**	$BF_3 \cdot OEt_2$	 **3b** (87%)	
5	 **8**	$BF_3 \cdot OEt_2$	 **3c**	 **3c′** (81%, 71:29)

[a] Lewis acid (0.5 mol equiv) was added.
[b] Yields were not optimized.
[c] The ratio was determined by ^{1}H NMR spectrum.

proceeded smoothly with the formation of the aziridium ion intermediate shown in the bracket of Scheme 2 that was known from our early observations. All of the alkyl or aryl addition products (**2a**–**2h**) yielded the corresponding chloromethylimidazolidin-2-ones (**9a**–**9h**) in high yields between 97 and 71% yields regardless of the stereochemistry as either *threo* or *erythro*. This reaction also worked with other addition products **3a**, **3a′**, and **3b** to afford chloromethylimidazolidin-2-ones **10a**, **10a′**, and **10b** in 75, 82, and 67% yields, respectively. These transformations from aminomethylaziridine (**2** or **3**) to 4-chloromethylimidazolidin-2-one (**9**) provide a useful tool to determine the initial stereochemical outcomes of the original adducts **2** or **3** with nucleophlies whether they are *threo* or *erythro*.

The stereochemistry of the addition product **2a** (R^1=Me, R^2=H) was identified after its conversion to 5-methyl-4-chloromethylimidazolidin-2-one (**9a**) by treatment with triphosgene and NaH in THF. The coupling constant of the two adjacent imidazolidinone ring protons at C-4 and C-5 was measured to be 3.2 Hz (entry 1), which corresponds to trans-relationship. This implies that methyl addition occurred from *re*-face via a chelation controlled transition state. The stereochemistry of the initial addition products **2b**



2 or **3** **9** or **10**

Scheme 2.

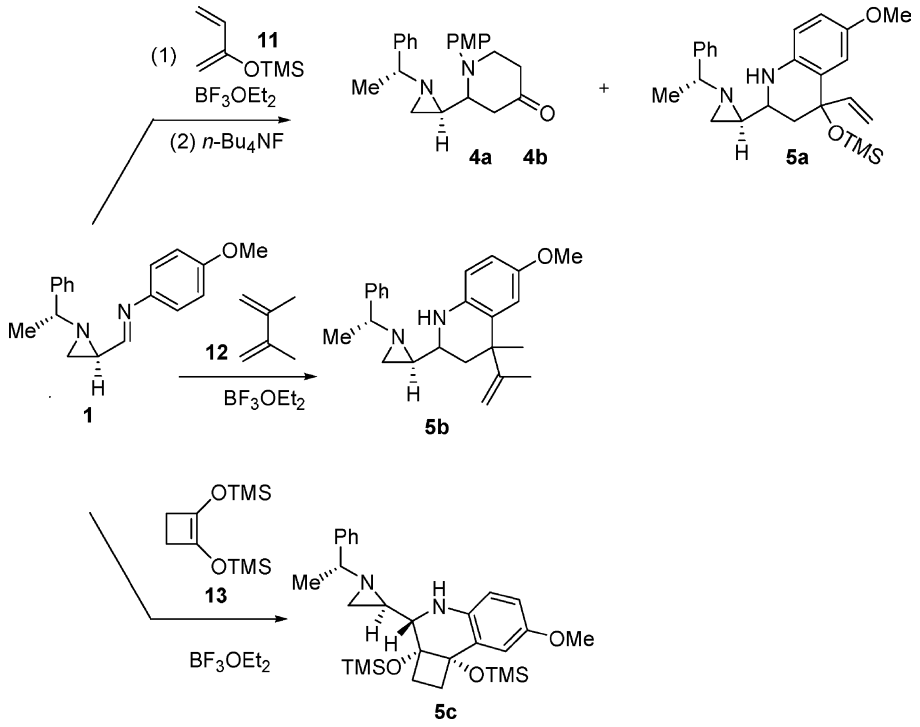
Table 3. Preparation of 5-alkyl or 5-aryl-4-chloromethylimidazolidin-2-one (**9**) from the reactions of the corresponding 2-aminomethylaziridine (**2** and **3**) with triphosgene and NaH

Entry	Substrate	R^1	R^2	Product	Yield (%)[a]	*J* (Hz)[b]
1	**2a**	Me	H	**9a**	94	3.2
2	**2b**	Et	H	**9b**	91	3.0
3	**2c**	Vinyl	H	**9c**	87	3.4
4	**2d**	Allyl	H	**9d**	79	2.6
5	**2d′**	H	Allyl	**9d′**	71	6.4
6	**2e**	*n*-Bu	H	**9e**	96	3.2
7	**2e′**	H	*n*-Bu	**9e′**	83	6.6
8	**2f**	Ph	H	**9f**	97	3.0
9	**2g**	Tolyl	H	**9g**	92	3.2
10	**2h**	*p*-FPh	H	**9h**	89	2.6
11	**3a**	CN	H	**10a**	75	3.0
12	**3a′**	H	CN	**10a′**	82	7.1
13	**3b**	CMe_2CO_2Me	H	**10b**	67	3.4

[a] All reactions were carried out at −78 °C for 2 h.
[b] Coupling constants of the imidazoline ring protons at C-4 and C-5.

and **2c** were identified as *threo* by judging the coupling constants of the two imidazolidinone ring protons at C-4 and C-5 of **9b** and **9c** as 3.0 and 3.4 Hz, respectively (entries 2 and 3). The stereochemistry of all major products **2d**, **2e**, **2f**, **2g** and **2h** were confirmed to be *threo* from the observed coupling constants of 2.6–3.2 Hz corresponding to *trans* relationship of two neighboring imidazolidinone ring protons of compounds **9d**, **9e**, **9f**, **9g**, **9h** (entries 4, 6, 8, 9, and 10). The minor *erythro* isomers **2d′** and **2e′** isolated from the addition of allyl- and *n*-butylMgBr were converted by the same method to *cis*-5-chloromethylimidazolidin-2-ones **9d′** and **9e′** whose coupling constants between two ring protons at C-4 and C-5 were 6.4 and 6.6 Hz, respectively (entries 5 and 7). The initial adduct of nitrile to imine was obtained as inseparable diastreomeric mixture of **3a** and **3a′**, which were also converted to 5-chloromethylimidazolidin-2-ones **10a** and **10a′** at which stage two diastereomers were separated by column chromatography. The similar stereochemical relationship was observed from the coupling constants between two protons at C-4 and C-5 as 3.0 Hz for the major isomer and 7.1 Hz for the minor isomer, respectively (entries 11 and 12). The single isomer **10b** showed 3.4 Hz of coupling constant to indicate that the original adduct of ketene acetal **3b** was *threo* as expected.

The success of the addition of ketene silyl acetal **7** in entry 4 of the Table 2 prompted us to expand the reaction with another electron rich nucleophile 3-methoxytrimethylsilyloxybutadiene (**8**) known as the Danishefsky diene. The reaction with the additive, 50 mol% $BF_3 \cdot OEt_2$, was successful to give 4-oxopiperidines (**3c** and **3c′**) as a diastereomeric mixture with the ratio of 71:29 in 81% yields (entry 5 of Table 2). Formation of cyclic adducts 4-oxopiperidines would be explained by the addition of 3-methoxytrimethylsilyloxybutadiene (**8**) as a nucleophile to the imine like Mannich-type reaction followed by intramolecular cyclization.[11] The same reaction product can be formed from aza-Diels–Alder reaction between the imine (**1**) and 3-methoxytrimethylsilyloxybutadiene (**8**) as an aza-dienophile and a diene, respectively.[12] This prompted us to expand the utility of the imine substrate (1″*R*,2′*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**) for aza-Diels–Alder reactions with a different diene to provide 2-aziridinylpiperidines **4** (Schemes 1 and 3). Addition of 2-trimethylsilyloxybutadiene (**11**) to the imine in the presence of 50 mol% $BF_3 \cdot OEt_2$ yielded cycloadducts as an inseparable mixture. Those adducts were subsequently treated with *n*-Bu_4F to remove TMS to afford separable adducts **4a**, **4b**, and **5a**. The ratio of two diasteromers **4a** and **4b** was 83:17 in 48% yield while unexpected product **5a** also obtained in 32% yield as a single stereoisomer. Formation of 4-oxopiperidines (**4a** and **4b**) can be explained by aza-Diels–Alder reactions between the imine (**1**) and 2-trimethylsilyloxybutadiene (**11**) in the same manner as observed in the formation of the ring compound in entry 5 of the Table 2, followed by desilylation. However, formation of 1,2,3,4-tetrahydroquinolines (**5**) bearing aziridine ring at C-2 indicates that the imine substrate can perform as an azadiene with an electron rich olefin in a reverse electron demand aza-Diels–Alder reaction.[12,13] Reactions with electron rich olefins such as 2,3-dimethyl-1,3-butadiene (**12**) and bis-1,2-trimethylsilyloxycyclobutene (**13**) afforded 1,2,3,4-tetrahydroquinolines **5b** and **5c** in 62 and 68% yields, respectively (Scheme 3). Even though 1,2,3,4-tetrahydroquinoline **5b** was obtained as a single stereoisomer, the absolute stereochemistry of newly formed C–C bonds could not be identified. Fortunately adduct **5c** coming from the reaction with bis-1,2-trimethylsilyloxycyclobutene was obtained as a single crystal whose structure was fully identified by X-ray crystallography as shown in Figure 1.[14] The configuration of C-2 of 1,2,3,4-tetrahydroquinoline in **5c** showed *R*, which



Scheme 3.

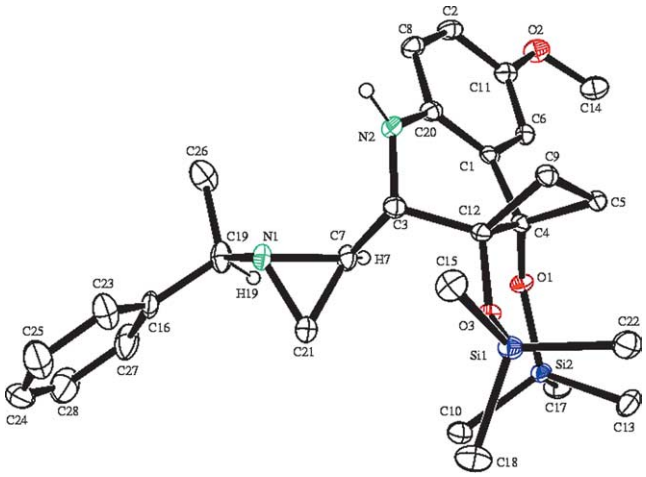


Figure 1.

came from the same facial selectivity as in the nucleophilic addition reactions for the preparation of **2** and **3** in the Scheme 1. This draws a conclusion that initial bond formation on the imine carbon and the coming counterpart approaches from *re*-face via a chelation controlled transition state. All of these successful reactions informed us that (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**) may have dual role as an azadiene and also an azadienophile in the reactions with proper dienophiles and dienes to yield either 2-aziridinylpiperidines (**4**) or 1,2,3,4-tetrahydroquinolines (**5**).

All of the addition reactions to (2*R*,1′*R*)-(1′-phenylethyl) aziridine-2-carboxaldimine with various nucleophiles, dienes and dienophiles yielded *threo* products with chelation controlled transition state that is quite general for the addition reaction of alkyl metal reagents to α,β-epoxyimine without any additives.[15] However, in the presence of $BF_3 \cdot OEt_2$ as a Lewis acid non-chelation controled product was dominant on the addition reaction of alkyl Grignard to α,β-epoxyimine.[15a,16] We have learned that the same addition reaction of α,β-aziridinylimine (**1**) led chelation controlled product. Because the Lewis acid $BF_3 \cdot OEt_2$ we used in the reactions has dual roles, that is, activating the imine and chelating the two nitrogens of the substrate as shown in **14** of Figure 2. Therefore, the transition state becomes quite rigid and the coming nucleophile attacks the substrate from *re*-face more favorably than from *si*-face. The rigidity of the transition state is supported by the observation of the strong binding between boron and aziridine ring nitrogen in a single crystal

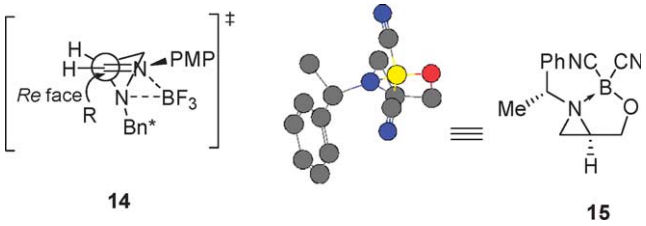


Figure 2. The possible transition state (**14**) to lead the major isomer of the nucleophilic addition from *re*-face to (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldimine and the X-ray structure (**15**) of dicyano[[(1*R*)-(1-phenylethyl)-aziridin-2-yl]methanolato-*O,N*]boron.

structure of dicyano[[(1*R*)-(1-phenylethyl)-aziridin-2-yl]methanolato-*O,N*]boron (**15**) shown in Figure 2.[17] This crystalline structure features that there is a quite strong chelation between boron and nitrogen without altering the aziridine ring conformation. Therefore, we assume that the transition state conformation of the addition reaction is quite similar to the structure **15** and is rigid enough for the coming nucleophile or olefin to approach from the *re*-face more favorably.

The same stereochemical pathway was observed during the reduction of 2-acylaziridine with $NaBH_4$ and $ZnCl_2$ in methanol. High stereoselectivity was observed from the tight binding between the nitrogen of aziridine ring and the carbonyl oxygen by Zn^{+2} metal.[18]

In conclusion, the enantiomerically pure (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine plays a multi-role substrate for the reactions with nucleophiles, dienes and olefins to yield aminomethylaziridines, 2-aziridinylpiperidines and 1,2,3,4-tetrahydroquinolines, respectively. High stereoselectivity was observed throughout these addition reactions via a chelation controlled transition state with *re*-face preference.

3. Experimental

3.1. General methods

^1H and ^{13}C NMR spectra were recorded on a Varian 200 or 500 (300 or 500 MHz for ^1H and 50.3 or 125.7 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as an internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analysis was taken on a Perkin-Elmer 240 DS elemental analyzer. Melting point was measured by Mel-II capillary melting point apparatus. Optical rotation was measured with Rudolph Research Autopole 3 polarimeter. The silica gel used for column chromatography was Merck 230–400 mesh. Thin-layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness.

3.1.1. (2′*R*,1″*R*)-(4-Methoxyphenyl){[1-(1″-phenylethyl) aziridin-2′-yl]methylene}amine (1). (2*R*,1′*R*)-(1′-phenylethyl)aziridine-2-carboxaldehyde (175 mg, 1 mmol) in 5 mL CH_2Cl_2 was added dropwise into *p*-anisidine solution (123 mg, 1 mmol) in 20 mL CH_2Cl_2 with anhydrous $MgSO_4$ (1.20 g, 10 mmol). This solution was stirred for 5 h at room temperature until all the starting material was consumed. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The product was purified by recrystallization from EtOH to give 272 mg of product in 97% yield. This product should be kept under dry condition not for longer than a week.

Yellowish solid. Mp 68–69 °C. ^1H NMR (200 MHz, $CDCl_3$) δ 1.46 (d, $J=6.2$ Hz, 3H), 1.73 (d, $J=6.6$ Hz, 1H), 1.92 (d, $J=1.8$ Hz, 1H), 2.48–2.52 (m, 1H), 2.56 (q, $J=6.2$ Hz, 1H), 3.79 (s, 3H), 6.84–7.13 (m, 4H), 7.24–7.43 (m, 6H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.0, 33.4, 42.8, 55.4, 69.7,

114.2, 122.0, 126.7, 127.2, 128.4, 143.8, 143.9, 159.2, 162.9. HRMS (EI) calcd for $C_{18}H_{20}N_2O$: 280.1576, found 280.1572.

3.2. General procedure for addition reactions of alkyl or aryl magnesium bromide

Into the solution of (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**, 280 mg, 1 mmol) in 10 mL of ethyl ether was added ethereal solution of alkyl or aryl magnesium bromide (3 mmol) and $BF_3 \cdot OEt_2$ (0.15 mL, 1.0 mmol). The resultant solution was stirred under −10 °C for the completion before the reaction was quenched by adding ice-water. The reaction product was isolated with ethyl ether (15 mL×4). The ethereal solution was washed with brine twice. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel flash column chromatography provided the analytically pure addition product.

3.2.1. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]ethyl}amine (2a). Liquid. $[\alpha]_D$ 33.5 (*c* 2.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.14 (d, J=4.2 Hz, 3H), 1.28 (d, J=6.2 Hz, 3H), 1.24–1.62 (m, 2H), 2.36 (q, J=6.6 Hz, 1H), 3.32–3.41 (m, 1H), 3.40 (q, J=6.8 Hz, 1H), 3.63 (s, 3H), 6.52–6.71 (m, 4H), 7.14–7.31 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 19.5, 23.49, 30.37, 44.2, 48.9, 55.6, 69.3, 114.6, 114.6, 126.6, 126.7, 128.1, 141.8, 144.8, 151.6. HRMS (EI) calcd for $C_{19}H_{24}N_2O$: 296.1889, found 296.1883. Anal. Calcd for $C_{19}H_{24}N_2O$: C, 77.0; H, 8.16; N, 9.45. Found: C, 76.8; H, 8.09; N, 9.42.

3.2.2. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]propyl}amine (2b). Liquid. $[\alpha]_D$ 70.0 (*c* 0.2 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.06 (t, J=7.2 Hz, 3H), 1.19 (d, J=5.8 Hz 1H), 1.38 (d, J=6.6 Hz, 3H), 1.51–1.68 (m, 4H), 2.45 (q, J=6.6 Hz, 1H), 3.17 (td, J=6.6 Hz, 3.4 Hz, 1H), 3.72 (s, 3H), 6.61–6.78 (m, 4H), 7.24–7.41 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 10.8, 23.4, 27.4, 30.4, 42.7, 55.3, 55.6, 69.3, 114.3, 114.6, 126.6, 126.7, 128.1, 142.6, 144.6, 151.4. HRMS (EI) calcd for $C_{20}H_{26}N_2O$: 310.2045, found 310.2042.

3.2.3. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]prop-2-enyl}amine (2c). Liquid. $[\alpha]_D$ 34.5 (*c* 0.5 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.21–1.25 (m, 1H), 1.38 (d, J=6.6 Hz, 3H), 1.58–1.71 (m, 2H), 2.42 (q, J=6.6 Hz, 1H), 3.70 (s, 3H), 3.2–3.76 (m, 1H), 5.20 (d, J=9 Hz, 1H), 5.26 (d, J=16 Hz, 1H), 5.81 (ddd, J=16.0, 9.0, 6.0 Hz, 1H), 6.56–6.79 (m, 4H), 7.16–7.41 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.6, 30.3, 37.3, 42.8, 56.5, 69.0, 114.5, 114.7, 115.6, 126.6, 126.8, 128.1, 134.8, 141.5, 144.4, 151.7. HRMS (EI) calcd for $C_{20}H_{24}N_2O$: 308.1889, found 308.1892.

3.2.4. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]but-3-enyl}amine (2d). Liquid. $[\alpha]_D$ 2.98 (*c* 3.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.29–1.33 (m, 1H), 1.41 (d, J=6.6 Hz, 3H), 1.61–1.77 (m, 2H), 2.38–2.54 (m, 3H), 3.14 (q, J=6.6 Hz, 1H), 3.72 (s, 3H), 5.16 (d, J=10 Hz, 1H), 5.18 (d, J=16 Hz, 1H), 5.80–6.10 (m, 1H), 6.57–6.76 (m, 4H), 7.24–7.33 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1, 23.4, 32.7, 42.1, 55.5, 56.7, 68.0, 114.5, 114.7, 115.7, 126.7, 126.9, 128.2, 138.7, 141.7, 144.4, 151.8. HRMS (EI) calcd for $C_{21}H_{26}N_2O$: 322.2045, found 322.2038.

3.2.5. (1*S*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]but-3-enyl}amine (2d′). Liquid. $[\alpha]_D$ 40.1 (*c* 3.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.30–1.41 (m, 1H), 1.65 (d, J=6.6 Hz, 3H), 1.68–1.72 (m, 2H), 2.35–2.40 (m, 3H), 3.30 (q, J=6.6 Hz, 1H), 3.72 (s, 3H), 5.15 (d, J=10 Hz, 1H), 5.18 (d, J=16 Hz, 1H), 5.80–6.01 (m, 1H), 6.61–6.79 (m, 4H), 7.21–7.40 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1, 23.5, 30.5, 34.3, 42.5, 53.6, 55.7, 69.4, 114.6, 114.7, 117.3, 126.7, 126.8, 128.2, 135.4, 142.2, 144.6, 151.7. HRMS (EI) calcd for $C_{21}H_{26}N_2O$: 322.2045, found 322.2044.

3.2.6. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]pentyl}amine (2e). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.79 (t, J=7.0 Hz, 3H), 1.09–1.42 (m, 7H), 1.27 (d, J=6.6 Hz, 3H), 1.43–1.68 (m, 2H), 2.33 (q, J=6.6 Hz, 1H), 3.12 (q, J=6.4 Hz, 1H), 3.64 (s, 3H), 6.50–6.80 (m, 4H), 7.15–7.30 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1, 22.8, 23.5, 28.6, 32.2, 33.8, 44.1, 53.7, 55.9, 69.4, 114.3, 114.7, 126.7, 126.8, 128.2, 142.7, 144.7, 151.4. HRMS (EI) calcd for $C_{22}H_{30}N_2O$: 338.2358, found 338.2364.

3.2.7. (1*S*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]pentyl}amine (2e′). Viscous oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.78 (t, J=7.0 Hz, 3H), 1.08–1.45 (m, 7H), 1.26 (d, J=6.6 Hz, 3H), 1.50–1.72 (m, 2H), 2.36 (q, J=6.6 Hz, 1H), 3.12–3.21 (m, 1H), 3.64 (s, 3H), 6.48–6.68 (m, 4H), 7.16–7.25 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 14.1, 22.8, 23.3, 28.0, 32.6, 33.0, 44.0, 53.7, 55.8, 69.7, 114.7, 114.9, 126.7, 126.9, 128.2, 142.1, 144.4, 151.8. HRMS (EI) calcd for $C_{22}H_{30}N_2O$: 338.2358, found 338.2360.

3.2.8. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]-1-[phenyl]methyl}amine (2f). Liquid. $[\alpha]_D$ 18.9 (*c* 3.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08 (d, J=6.8 Hz, 3H), 1.19 (d, J=6.2 Hz, 1H), 1.66–1.78 (m, 2H), 2.25 (q, J=6.6 Hz, 1H), 3.55 (s, 3H), 4.04–4.08 (m, 1H), 6.35–6.57 (m, 4H), 7.10–7.33 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.6, 31.5, 45.4, 55.6, 58.9, 69.1, 114.6, 114.8, 126.5, 126.7, 127.0, 127.1, 128.3, 128.5, 141.5, 142.8, 144.3, 151.7. HRMS (EI) calcd for $C_{24}H_{26}N_2O$: 358.2045, found 358.2049.

3.2.9. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]-1-[*p*-tolyl]methyl}amine (2g). Liquid. $[\alpha]_D$ 5.3 (*c* 5.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23–1.29 (m, 4H), 1.82–1.94 (m, 2H), 2.26 (s, 3H), 2.28–2.41 (m, H), 3.59 (s, 3H), 4.08 (bs, 1H), 6.45–6.66 (m, 4H), 7.05–7.33 (m, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 20.9, 23.5, 31.4, 45.5, 55.4, 58.8, 69.0, 114.4, 114.8, 126.6, 126.8, 128.1, 129.1, 136.5, 138.5, 139.5, 140.5, 141.5, 144.1, 151.6. HRMS (EI) calcd for $C_{25}H_{28}N_2O$: 372.2202, found 372.2204.

3.2.10. (1*R*,2′*R*,1″*R*)-(4-Methoxyphenyl){1-[1′-(1″-phenylethyl)aziridin-2′-yl]-1-[*p*-fluorophenyl]methyl}-amine (2h). Liquid. $[\alpha]_D$ 30.8 (*c* 2.0 in EtOAc); ^{1}H NMR

(200 MHz, $CDCl_3$) δ 1.12 (d, J=6.6 Hz, 3H), 1.23 (d, J=6.4 Hz, 1H), 1.71–1.80 (m, 2H), 2.33 (q, J=6.6 Hz, 1H), 3.59 (s, 3H), 4.11 (d, J=4.4 Hz, 1H), 6.36–6.62 (m, 4H), 6.90–7.34 (m, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.6, 31.3, 45.2, 55.6, 58.0, 69.0, 114.6, 114.8, 115.2, 115.6, 126.7, 127.0, 127.9, 128.0, 128.2, 128.3, 138.4, 138.5, 141.2, 144.2, 151.8, 159.5, 164.3. HRMS (EI) calcd for $C_{24}H_{25}FN_2O$: 376.1951, found 376.1948.

3.3. General Procedure for the preparation of 3

To a solution of (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**, 414 mg, 1.48 mmol) in 20 mL of CH_2Cl_2 under nitrogen atmosphere was added the nucleophile (1.48 mmol) at −10 °C. The mixture was stirred at room temperature for 2–3 h until the reaction was completed. Then the reaction was quenched by adding water at 0 °C and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (15 mL×5). The combined extracts was dried over anhydrous $MgSO_4$ and the solvent was evaporated to give the crude product, which was purified by silica gel flash chromatography to obtain analytically pure product.

3.3.1. (2*R*,2′*R*,1″*R*)-2-(*p*-Methoxyphenylamino)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]acetonitrile (3a). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.39–1.49 (m, 1H), 1.47 (d, J=6.6 Hz, 3H), 1.90 (d, J=4.0 Hz, 1H), 2.09 (dd, J=5.8, 2.2 Hz, 1H), 2.55 (d, J=6.6 Hz, 1H), 3.70 (s, 3H), 4.29 (q, J=6.6 Hz, 1H), 6.60–6.87 (m, 4H), 7.18–7.32 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.6, 29.7, 39.2, 46.6, 55.6, 68.8, 114.9, 115.9, 119.0, 126.7, 127.3, 128.4, 138.3, 143.6, 153.6. HRMS (EI) calcd for $C_{19}H_{21}N_3O$: 307.1685, found 307.1691.

3.3.2. (3*R*,2′*R*,1″*R*)-2,2-Dimethyl-3-(4-methoxyphenylamino)-3-[1′-(1″-phenylethyl)aziridin-2′-yl]propionic acid methyl ester (3b). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.07 (d, J=6.2 Hz, 1H), 1.31 (s, 9H), 1.43 (d, J=2.4 Hz, 1H), 1.58–1.62 (m, 1H), 2.47 (q, J=6.6 Hz, 1H), 3.38 (s, 1H), 3.59 (s, 3H), 3.64 (s, 3H), 3.98 (s, 1H), 6.63–6.73 (m, 4H), 7.14–7.26 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 21.6, 22.9, 30.2, 40.2, 47.4, 51.4, 55.2, 61.6, 69.0, 114.3, 114.4, 126.6, 128.0, 143.2, 144.2, 151.5, 177.0. HRMS (EI) calcd for $C_{23}H_{30}N_2O_3$: 382.2256, found 382.2251.

3.3.3. (2*R*,2′*R*,1″*R*)-1-(4-Methoxyphenyl)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]-2,3-dihydro-1*H*-pyridin-4-one (3c). Liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.28 (d, J=6.5 Hz, 1H), 1.36 (d, J=3.5 Hz, 1H), 1.44 (d, J=6.5 Hz, 3H), 2.00–2.04 (m, 1H), 2.41 (q, J=6.5 Hz, 1H), 2.84 (dd, J=16.5, 2.5 Hz, 1H), 3.05 (dd, J=16.5, 7.0 Hz, 1H), 3.62 (td, J=7.0, 2.5 Hz, 1H), 3.80 (s, 3H), 5.21 (d, J=8.0 Hz, 1H), 6.87 (d, J=7.0 Hz, 2H), 7.11 (d, J=9.0 Hz, 2H), 7.21–7.23 (m, 1H), 7.26–7.30 (m, 5H). ^{13}C NMR (125.7 MHz, $CDCl_3$) δ 23.5, 34.1, 38.5, 39.7, 55.7, 62.6, 69.5, 100.8, 114.8, 124.0, 126.8, 127.2, 128.5, 138.5, 144.2, 149.8, 157.8, 191.1. HRMS (EI) calcd for $C_{22}H_{24}N_2O_2$: 348.1838, found 348.1834.

3.3.4. (2*S*,2′*R*,1″*R*)-1-(4-Methoxyphenyl)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]-2,3-dihydro-1*H*-pyridin-4-one (3c′). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, J=6.5 Hz, 3H), 1.47 (d, J=6.5 Hz, 1H), 1.62 (d, J=3.0 Hz, 1H), 2.37–2.46 (m, 2H), 3.02 (dd, J=16.5, 6.0 Hz, 1H), 3.59 (t, J=7.5 Hz, 1H), 3.83 (s, 3H), 4.12 (q, J=6.5 Hz, 1H), 5.28 (dd, J=6.5, 1.0 Hz, 1H), 6.94 (d, J=9.0 Hz, 2H), 7.26–7.30 (m, 1H), 7.33–7.38 (m, 4H), 7.45 (dd, J=7.0, 1.5 Hz, 1H), 7.59 (d, J=8.5 Hz, 2H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.7, 32.3, 39.1, 39.3, 55.8, 63.2, 70.1, 102.0, 114.6, 121.6, 126.9, 127.4, 128.6, 138.4, 144.3, 147.5, 156.9, 191.3. HRMS (EI) calcd for $C_{22}H_{24}N_2O_2$: 348.1838, found 348.1840.

3.4. General procedure for 5-alkyl or 5-aryl-4-chloromethylimidazolidin-2-one (9 and 10)

To a solution of (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]alkyl}amine (**2** or **3**, 310 mg, 1.05 mmol) in 15 mL of THF under nitrogen atmosphere was added NaH (144 mg, 6 mmol) at −10 °C. The mixture was stirred for 1 h at −10 °C. To the mixture was slowly added triphosgene solution (0.356 g, 1.2 mmol) in THF (5 mL) at −10 °C. The mixture was stirred for 2 h at −10 °C. The reaction was quenched with water at −10 °C and warmed to room temperature. The aqueous layer was extracted with CH_2Cl_2 (10 mL×5). The combined organic extracts was dried over $MgSO_4$ and the solvent was evaporated in vacuo to give the crude product as a white solid, which was purified by silica gel flash chromatography to give analytically pure product.

3.4.1. (4*S*,5*R*,1′*R*)-4-Chloromethyl-1-(4-methoxyphenyl)-5-methyl-3-(1′-phenylethyl)imidazolidin-2-one (9a). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, J=6.2 Hz, 3H), 1.50 (d, J=7.4 Hz, 3H), 2.92 (dt, J=7.0, 3.2 Hz, 1H), 3.32 (dd, J=11.4, 7.6 Hz, 1H), 3.42 (dd, J=11.4, 3.2 Hz, 1H), 3.65 (s, 3H), 3.90 (qd, J=6.2, 3.2 Hz, 1H), 5.25 (q, J=7.4 Hz, 1H), 6.72–6.78 (m, 2H), 7.11–7.27 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.7, 19.4, 45.5, 51.2, 54.6, 55.4, 58.8, 114.1, 123.1, 127.3, 127.7, 128.6, 131.4, 139.8, 156.2, 156.8. HRMS (EI) calcd for $C_{20}H_{23}ClN_2O_2$: 358.1448, found 358.1453.

3.4.2. (4*S*,5*R*,1′*R*)-4-Chloromethyl-5-ethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9b). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.45 (t, v=6.6 Hz, 3H), 1.01–1.53 (m, 2H), 1.50 (d, J=6.2 Hz, 3H), 3.05 (q, J=2.8 Hz, 1H), 3.29–3.55 (m, 2H), 3.63 (s, 3H), 3.78 (dt, J=7.8, 3.0 Hz, 1H), 5.23 (q, J=6.6 Hz, 1H), 6.61–6.76 (m, 2H), 7.11–7.27 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 7.61, 18.7, 24.6, 46.1, 51.4, 55.3, 55.6, 59.4, 114.0, 123.2, 127.3, 127.7, 128.5, 131.4, 139.6, 156.1, 156.8. HRMS (EI) calcd for $C_{21}H_{25}ClN_2O_2$: 372.1605, found 372.1594.

3.4.3. (4*S*,5*R*,1′*R*)-4-Chloromethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)-5-vinylimidazolidin-2-one (9c). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.59 (d, J=7.4 Hz, 3H), 3.11 (td, J=4.4, 3.4 Hz, 1H), 3.45 (d, J=4.4 Hz, 3H), 3.70 (s, 3H), 4.31 (dd, J=6.0, 3.4 Hz, 1H), 5.01 (d, J=8.2 Hz, 1H), 5.15 (d, J=18.0 Hz, 1H), 5.21–5.45 (m, 1H), 6.76–6.81 (m, 2H), 7.18–7.35 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.5, 45.1, 51.3, 55.3, 58.0, 61.0, 113.9, 118.3, 122.3, 127.3, 127.7, 128.6, 132.1, 135.8,

139.4, 155.9, 157.1. HRMS (EI) calcd for $C_{21}H_{23}ClN_2O_2$: 370.1448, found 370.1441.

3.4.4. (4*S*,5*R*,1′*R*)-5-Allyl-4-chloromethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9d). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.51 (d, J=7.0 Hz, 3H), 2.47 (d, J=7.2 Hz, 2H), 3.47–3.71 (m, 3H), 3.76 (s, 3H), 4.12 (dt, J=7.2, 2.6 Hz, 1H), 4.93–5.02 (m, 2H), 5.38 (q, J=7.0 Hz, 1H), 5.50–5.57 (m, 1H), 6.85 (d, J=8.8 Hz, 2H), 7.20–7.31 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.4, 31.1, 41.8, 50.7, 55.4, 55.6, 56.7, 114.1, 118.0, 125.1, 127.3, 127.6, 128.7, 130.9, 133.4, 139.1, 156.8, 158.7. HRMS (EI) calcd for $C_{22}H_{25}ClN_2O_2$: 384.1605, found 384.1603.

3.4.5. (4*S*,5*S*,1′*R*)-5-Allyl-4-chloromethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9d′). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.52 (d, J=7.4 Hz, 3H), 1.60–1.75 (m, 1H), 2.02–2.09 (m, 1H), 3.10–3.13 (m, 1H), 3.35–3.41 (m, 2H), 3.37 (s, 3H), 3.85 (dt, J=6.4, 3.4 Hz, 1H), 4.52 (d, J=17.0 Hz, 1H), 4.78 (d, J=8.4 Hz, 1H), 5.16–5.33 (m, 2H), 6.77 (d, J=8.8 Hz, 2H), 7.11–7.27 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.7, 36.5, 45.9, 51.4, 55.1, 55.4, 58.0, 114.2, 119.5, 123.5, 127.5, 127.8, 128.6, 131.2, 131.5, 139.7, 156.3, 156.8. HRMS (EI) calcd for $C_{22}H_{25}ClN_2O_2$: 384.1605, found 384.1611.

3.4.6. (4*S*,5*R*,1′*R*)-5-*n*-Butyl-4-chloromethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9e). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.47 (t, J=7.0 Hz, 3H), 0.65–1.13 (m, 4H), 1.35–1.45 (m, 2H), 1.38 (d, J=6.4 Hz, 3H), 3.09 (dt, J=7.4, 3.2 Hz, 1H), 3.28–3.47 (m, 2H), 3.61 (s, 3H), 3.69–3.77 (m, 1H), 5.15 (q, J=6.4 Hz, 1H), 6.69–6.73 (m, 2H), 7.05–7.19 (m, 7H). HRMS (EI) calcd for $C_{23}H_{29}ClN_2O_2$: 400.1918, found 400.1916.

3.4.7. (4*S*,5*S*,1′*R*)-5-*n*-Butyl-4-chloromethyl-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9e′). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.44 (t, J=7.0 Hz, 3H), 0.78–1.20 (m, 4H), 1.46–1.49 (m, 2H), 1.49 (d, J=6.4 Hz, 3H), 3.06 (td, J=7.0, 6.6 Hz, 1H), 3.25–3.52 (m, 2H), 3.65 (s, 3H), 3.71–3.82 (m, 1H), 5.16 (q, J=6.4 Hz, 1H), 6.71–6.78 (m, 2H), 7.11–7.27 (m, 7H). HRMS (EI) calcd for $C_{23}H_{29}ClN_2O_2$: 400.1918, found 400.1921.

3.4.8. (4*S*,5*R*,1′*R*)-4-Chloromethyl-1-(4-methoxyphenyl)-5-phenyl-3-(1′-phenylethyl)imidazolidin-2-one (9f). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.58 (d, J=7.0 Hz, 3H), 3.21–3.27 (m, 1H), 3.50–3.64 (m, 1H), 3.64 (s, 3H), 4.85 (d, J=3.0 Hz, 2H), 5.33 (q, J=7.0 Hz, 1H), 6.66–7.00 (m, 4H), 7.12–7.27 (m, 10H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.6, 45.5, 51.5, 55.3, 60.8, 62.2, 113.9, 121.7, 125.8, 127.1, 128.0, 128.2, 128.8, 129.4, 132.1, 139.4, 139.9, 155.6, 157.3. HRMS (EI) calcd for $C_{25}H_{25}ClN_2O_2$: 420.1605, found 420.1602.

3.4.9. (4*S*,5*R*,1′*R*)-4-Chloromethyl-1-(4-methoxyphenyl)-5-(4-methylphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9g). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=6.6 Hz, 3H), 2.18 (s, 3H), 3.21–3.26 (m, 1H), 3.48 (d, J=4.4 Hz, 2H), 3.61 (s, 3H), 4.80 (d, J=3.2 Hz, 1H), 5.32 (q, J=7.4 Hz, 1H), 6.67 (d, J=8.6 Hz, 2H), 6.86–6.95 (m, 4H), 7.13–7.25 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.6, 20.9, 45.4, 51.5, 55.2, 60.9, 62.0, 113.8, 121.8, 125.8, 127.1, 127.6, 128.5, 129.4, 132.1, 136.9, 137.7, 139.4, 155.6, 157.3. HRMS (EI) calcd for $C_{26}H_{27}ClN_2O_2$: 434.1761, found 434.1762.

3.4.10. (4*S*,5*R*,1′*R*)-4-Chloromethyl-5-(4-fluorophenyl)-1-(4-methoxyphenyl)-3-(1′-phenylethyl)imidazolidin-2-one (9h). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.57 (d, J=7.8 Hz, 3H), 3.19–3.34 (m, 1H), 3.59 (s, 3H), 3.64 (d, J=3.4 Hz, 2H), 4.83 (d, J=2.6 Hz, 1H), 5.32 (q, J=7.4 Hz, 1H), 6.58–6.88 (m, 4H), 6.89–7.21 (m, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.6, 45.5, 51.6, 56.9, 60.7, 61.7, 114.0, 115.5, 121.7, 126.9, 127.1, 127.4, 127.6, 128.1, 128.6, 128.8, 135.7, 138.2, 139.5, 155.8, 157.9. HRMS (EI) calcd for $C_{25}H_{24}ClFN_2O_2$: 438.1510, found 438.1513.

3.4.11. (4*S*,5*S*,1′*R*)-4-Chloromethyl-5-cyano-3-(4-methoxyphenyl)-1-(1′-phenylethyl)imidazolidin-2-one (10a). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.50 (d, J=7.0 Hz, 3H), 3.28–3.40 (m, 1H), 3.51–3.63 (m, 2H), 3.61 (s, 3H), 4.50 (d, J=3.0 Hz, 1H), 5.17 (q, J=7.0 Hz, 1H), 6.78 (d, J=8.8 Hz, 4H), 7.10–7.30 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.4, 44.4, 49.9, 51.7, 55.2, 56.3, 114.3, 116.4, 124.0, 127.1, 128.1, 128.7, 129.5, 138.2, 155.6, 157.5. Anal. Calcd HRMS (EI) calcd for $C_{20}H_{20}ClN_3O_2$: 369.1244, found 369.1241.

3.4.12. (4′*S*,5′*R*,1″*R*)-2-[4′-Chloromethyl-1′-(4-methoxyphenyl)-2-oxo-3- (1″-phenylethyl)imidazolidin-5′-yl]-2,2-dimethylpropionate acid methyl ester (10b). Liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.74 (s, 3H), 0.82 (s, 3H), 1.58 (d, J=7.2 Hz, 3H), 3.10–3.19 (m, 1H), 3.12 (s, 3H), 3.45 (dd, J=11.0, 1.8 Hz, 1H), 3.55 (dd, J=11.0, 4.2 Hz, 1H), 3.65 (s, 3H), 4.27 (d, J=2.2 Hz, 1H), 5.13 (q, J=7.2 Hz, 1H), 6.75 (d, J=8.8 Hz, 2H), 7.20–7.34 (m, 7H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 18.6, 19.9, 20.1, 46.2, 47.9, 51.3, 52.1, 54.2, 55.0, 63.6, 113.5, 126.7, 127.4, 127.7, 128.4, 131.4, 139.0, 157.1, 157.2, 175.3. HRMS (EI) calcd for $C_{24}H_{29}ClN_2O_4$: 444.1816, found 444.1823.

3.5. Cycloaddition reaction with 2-trimethylsilyloxy-1,3-butadiene (4a, 4b and 5a)

Into the solution of (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}amine (**1**, 280 mg, 1.0 mmol) in 10 mL of CH_2Cl_2 were added 2-trimethylsilyloxy-1,3-butadiene (**11**, 142 mg, 1.0 mmol) and $BF_3\cdot OEt_2$ (56 mg, 0.4 mmol) at room temperature. The resultant solution was stirred for 0.5 h until all the starting material was consumed. Then the reaction was quenched by adding water. The reaction product was isolated with CH_2Cl_2 (20 mL×4). The solution was washed with brine twice. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in 10 mL THF. Into this solution was added ethereal solution n-Bu_4NF (4 mmol). The reaction mixture was stirred for 30 min and quenched by adding water. The organic layer was treated in the standard protocol. The crude reaction mixture was obtained after removal of solvent under reduced pressure. Careful chromatographic separation and purification yielded the analytically pure products **4a** (137 mg), **4b** (21 mg) and **5a** (13 mg).

3.5.1. 1-4-Methoxyphenyl)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]piperidin-4-one, major isomer (4a). Viscous liquid. $[\alpha]_D$ 3.85 (*c* 1.5 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.23 (d, J=6.2 Hz, 3H), 1.37–1.84 (m, 3H), 2.45–2.87 (m, 5H), 3.34–3.97 (m, 3H), 3.76 (s, 3H), 6.81–7.02 (m, 4H), 7.21–7.30 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.4, 33.9, 40.8, 41.2, 44.9, 47.4, 55.6, 63.8, 69.8, 114.4, 121.1, 126.8, 127.2, 128.4, 143.7, 144.3, 154.9, 208.9. HRMS (EI) calcd for $C_{22}H_{26}N_2O_2$: 350.1994, found 350.1991.

3.5.2. 1-4-Methoxyphenyl)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]piperidin-4-one, minor isomer (4b). Viscous liquid. $[\alpha]_D$ 9.40 (*c* 5 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.43 (d, J=6.2 Hz, 3H), 1.27–1.84 (m, 3H), 2.39–2.98 (m, 5H), 3.21–3.77 (m, 3H), 3.87 (s, 3H), 6.76–7.48 (m, 9H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 23.3, 31.4, 40.5, 41.6, 42.8, 44.9, 55.8, 59.1, 69.9, 114.7, 117.7, 126.9, 127.1, 128.4, 143.9, 144.5, 153.4, 209.4. HRMS (EI) calcd for $C_{22}H_{26}N_2O_2$: 350.1994, found 350.1208.

3.5.3. 6-Methoxy-2-[1′-(1″-phenylethyl)aziridin-2′-yl]-4-trimethylsilanyloxy-4-vinyl-1,2,3,4-tetrahydroquinoline (5a). Gummy liquid. $[\alpha]_D$ 2.55 (*c* 1.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 9H), 1.27 (d, J=6.8 Hz, 3H), 1.31–1.87 (m, 4H), 1.57 (dd, 2H), 2.51 (q, J=6.6 Hz, 1H), 3.57–3.83 (m, 2H), 3.75 (s, 3H), 5.30 (dd, J=7.8, 1.8 Hz, 1H), 5.56 (dd, J=15.2, 1.8 Hz, 1H), 6.06 (dd, J=15.2, 7.8 Hz, 1H), 6.97–6.83 (m, 3H), 7.28–7.46 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 1.93, 2.01, 23.6, 29.8, 41.6, 43.0, 47.8, 56.0, 56.1, 69.6, 74.0, 113.4, 114.9, 115.2, 116.5, 122.7, 126.9, 127.2, 128.5, 128.6, 139.1, 144.1, 144.8, 150.7. HRMS (EI) calcd for $C_{25}H_{34}N_2O_2Si$: 422.2390, found 422.2383.

3.5.4. 6-Methoxy-4-methyl-4-(1-methylethenyl)-2-[1′-(1″-phenylethyl)aziridin-2′-yl]-1,2,3,4-tetrahydroquinoline (5b). The starting imine (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)aziridin-2′-yl]methylene}-amine (**1**, 403 mg, 1.35 mmol) was dissolved in 10 mL of CH_2Cl_2 and then were added excess amount of 2,3-dimethyl-1,3-butadiene (**12**, 123 mg, 1.50 mmol) and $BF_3\cdot OEt_2$ (85 mg, 0.6 mmol) at 0 °C. T he resultant solution was stirred for 2 h at room temperature. After the reaction was completed according to TLC the reaction was quenched by adding saturated $NaHCO_3$ solution. The reaction product was isolated with CH_2Cl_2 (15 mL×4), which was washed with brine twice. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Product was further purified by flash column chromatography to afford the titled products 224 mg as a diastereomeric mixture in 49% yield.

Gummy liquid. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.15–1.83 (m, 5H), 1.28 (s, 3H), 1.89–2.12 (m, 2H), 2.52 (q, J=6.7 Hz, 1H), 2.95 (tq, J=6.7, 3.4 Hz, 1H), 3.74 (s, 3H), 4.12–4.25 (m, 1H), 4.75–5.12 (m, 1H), 6.54–6.78 (m, 2H), 7.28–7.64 (m, 2H). 13C NMR (50.3 MHz, $CDCl_3$) δ 14.35, 20.25, 21.23, 23.67, 30.30, 31.50, 38.06, 42.73, 45.39, 52.72, 55.72, 60.55, 69.51, 111.93, 112.95, 113.44, 116.12, 126.90, 127.26, 128.44, 128.56, 129.25, 138.18, 144.37, 151.46, 152.45. HRMS (EI) calcd for $C_{24}H_{30}N_2O$: 362.2358, found 362.2351.

3.5.5. (2a*R*,3*S*,8b*S*,2′*R*,1″*R*)-7-Methoxy-3-[1′-(1″-phenylethyl)aziridin-2′-yl]-2a,8b-bistrimethylsilyloxy-1,2,2a,3,4,8b-hexahydrocyclobuta[*c*]quinoline (5c). The starting imine (2′*R*,1″*R*)-(4-methoxyphenyl){[1-(1″-phenylethyl)-aziridin-2′-yl]methylene}amine (**1**, 350 mg, 1.25 mmol) was dissolved in 15 mL of CH_2Cl_2 and then were added bis-1,2-trimethylsilyloxycyclobutene (**13**, 290 mg, 1.25 mmol) and $BF_3\cdot OEt_2$ (71 mg, 0.5 mmol) at −78 °C. The resultant solution was stirred for 2 h at −78 °C. After the reaction was completed according to TLC the reaction was quenched by adding saturated $NaHCO_3$ solution. The reaction product was isolated with CH_2Cl_2 (15 mL×4), which was washed with brine twice. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. Analytically pure product 433 mg was obtained after flash column chromatography in 68% yield.

White soild. Mp 140–141 °C. $[\alpha]_D$ −2.30 (*c* 3.0 in EtOAc); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.12–0.31 (s, 18H), 1.29 (d, J=4.2 Hz, 3H), 1.50 (d, J=6.2 Hz, 2H), 1.72 (d, J=3.6 Hz, 1H), 1.88–2.16 (m, 4H), 2.33 (q, J=6.6 Hz, 1H), 3.81 (s, 3H), 6.57 (d, J=8.8 Hz, 1H), 6.72 (dd, J=8.8 Hz, 2.1 Hz, 1H), 6.95 (d, J=3.0 Hz, 1H), 7.24–7.37 (m, 5H). ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 2.39, 2.94, 23.6, 24.2, 34.7, 36.9, 40.9, 55.7, 59.7, 69.5, 74.7, 83.9, 112.9, 115.1, 116.8, 126.1, 127.1, 128.5, 131.0, 135.6, 144.5, 152.8. HRMS (EI) calcd for $C_{28}H_{41}N_2O_3Si_2$: 509.2656, found 509.2651. Anal. Calcd for $C_{28}H_{41}N_2O_3Si_2$: C, 66.0; H, 8.11; N, 5.49. Found: C, 66.2; H, 8.03; N, 5.52.

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14. Crystallographic data (excluding structure factors) for the structures in Figure 1, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 263352. 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].
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A convenient synthesis of dihydrocoumarins from phenols and cinnamic acid derivatives

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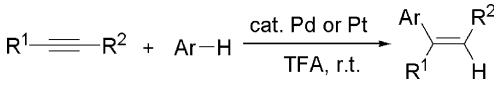
Abstract—A facile procedure for synthesis of dihydrocoumarin derivatives was described. Although the yield of the products in the reaction of phenols with acrylates in trifluoroacetic acid in the presence of $Pd(OAc)_2$ giving coumarins was found to be very low, dihydrocoumarin derivatives were obtained in good to high yields in the absence of $Pd(OAc)_2$ when ethyl cinnamates bearing electron-donating groups were employed in this reaction.

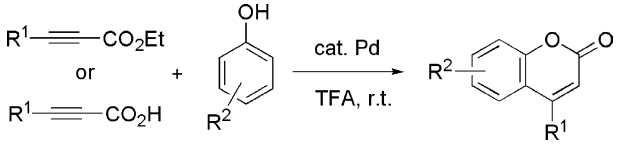
1. Introduction

4-Aryl-3,4-dihydrocoumarins are of synthetic interest because they are present in a number of natural molecules, such as 4-aryl-3,4-dihydrocoumarins (neoflavonoids),[1] complex flavonoids,[2] and 1-arylbenzo[*f*]chroman-3-ones.[3] Although many synthetic methods for 4-aryl-3,4-dihydrocoumarins have been reported up to the present, most of the procedures based on the condensation of phenols with cinnamic acids have been conducted in strong acidic media and at high temperature.[4] Consequently, a mild and simple procedure is strongly desired.

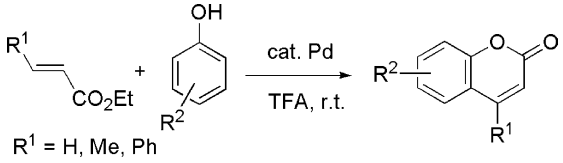
Recently, it has been found that hydroarylation of alkynes takes place in the presence of a palladium or platinum catalyst under mild conditions in trifluoroacetic acid (TFA) (Eq. 1).[5] This hydroarylation reaction efficiently proceeds intramolecularly to afford heterocycles, such as coumarins, quinolines, and thiocoumarins.[5,6] Interestingly, this hydroarylation reaction has been applied to direct synthesis of coumarins from phenols and propiolic acids or esters (Eq. 2).[7] However, the palladium-catalyzed reaction of phenols with ethyl acrylates does not afford dihydrocoumarins via hydroarylation but coumarins derived from the Heck-type coupling reaction followed by intramolecular cyclization (Eq. 3).[8] During the course of our study on hydroarylation reactions, we found that dihydrocoumarins were formed without palladium catalysts when electron-rich cinnamic acids and esters were employed in the hydroarylation reaction.[9] This procedure provides a very mild and convenient method for synthesis of 4-aryl-3,4-dihydrocoumarins. Here we wish to report our findings concerning the synthesis of 4-aryl-3,4-dihydrocoumarins from phenols and electron-rich cinnamic acids and esters.[10]



(1)



(2)



(3)

2. Results and discussion

2.1. Reaction of ethyl 4-methoxycinnamate (1a) with phenols 2

First, the reaction of ethyl 4-methoxycinnamate (**1a**) as an electron-rich substrate with 2-naphthol (**2a**) was examined (Table 1). After dissolving **1a** and **2a** in TFA, the mixture was stirred for 24 h at rt. Workup (neutralization and extraction)

Keywords: Dihydrocoumarins; Phenols; Cinnamic acid derivatives; Trifluoroacetic acid.
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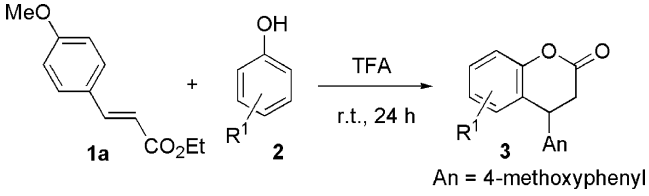
followed by purification (column chromatography on silica gel) gave 1,2-dihydro-1-(4-methoxyphenyl)-3*H*-naphtho-[2,1-*b*]pyran-3-one (**3aa**) quantitatively. This reaction is a very simple and useful method that provides a sophisticated dihydrocoumarin derivative in high yield.

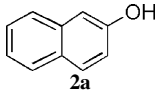
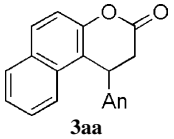
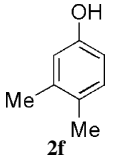
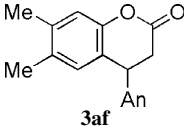
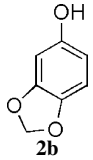
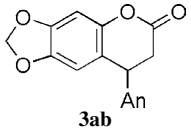
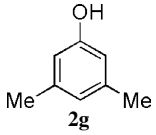
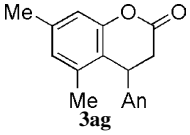
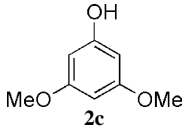
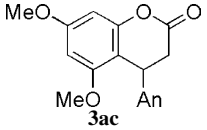
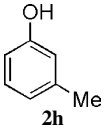
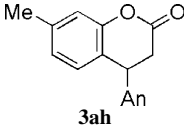
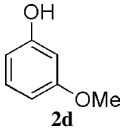
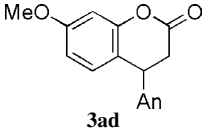
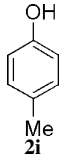
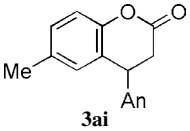
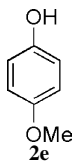
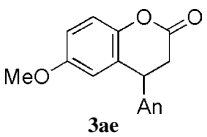
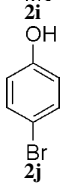
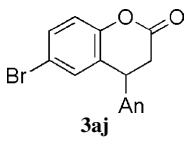
Similar reactions with 3,4-methylenedioxyphenol (**2b**), 3,5-dimethoxyphenol (**2c**), and 3-methoxyphenol (**2d**) gave the corresponding dihydrocoumarins **3ab**, **3ac**, and **3ad** in high yields, respectively. However, the reaction with 4-methoxyphenol (**2e**) afforded 6-methoxy-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (**3ae**) only in 32% yield. The methoxy group of **2e** deactivates the reaction site, the *ortho* position to the hydroxyl group, by an inductive effect. In the reaction of **1a** with 3,4-dimethylphenol (**2f**) and 3,5-di-methylphenol (**2g**), the corresponding dihydrocoumarins **3af** and **3ag** were obtained in high yields, respectively. The reactions with cresols, such as 3-methylphenol (**2h**) and 4-methylphenol (**2i**), gave dihydrocoumarins **3ah** and **3ai** in 60 and 71% yields, respectively. An electron-deficient phenol, 4-bromophenol (**2j**), afforded only 8% yield of dihydrocoumarin (**3aj**), quite differing from the electron-rich phenols. However, it is expected that the reaction at an elevated temperature for a longer time increases the yield of dihydrocoumarins **3**, as observed in the literature.[10]

2.2. Substituent effect on the formation of dihydrocoumarins 3 in the reaction of ethyl cinnamates 1 with phenols 2

To apply the reaction to the synthesis of several substituted dihydrocoumarins **3**, various substituted ethyl cinnamates **1** were employed in the reaction with 2-naphthol (**2a**) (Table 2 and Fig. 1). In the case of **1** bearing electron-rich aryl groups such as 4-methoxyphenyl (**1a**), 3,4-dimethoxyphenyl (**1b**), and 3-hydroxy-4-methoxyphenyl (**1c**), dihydrocoumarins **3aa**, **3ba**, and **3ca** were obtained quantitatively, whereas the reaction of ethyl 4-methylcinnamate (**1d**) afforded only 43% yield of dihydrocoumarin **3da**. In the cases of the substrates bearing a methyl group at the *ortho* position such as ethyl 2,5-dimethycinnamate (**1g**) and 2,4,6-trimethycinnamate (**1h**), no dihydrocoumarins **3** were obtained and the starting

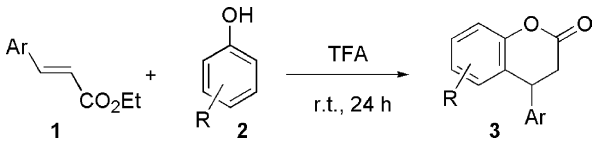
Table 1. Reaction of **1a** with phenols **2**[a]

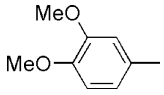
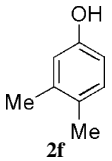
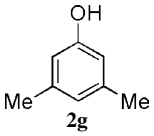
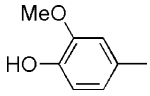
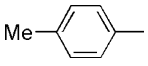
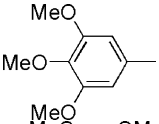
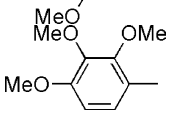


Run	Phenol **2**	Product **3**	Yield (%)	Run	Phenol **2**	Product **3**	Yield (%)
1	 **2a**	 **3aa**	100	6	 **2f**	 **3af**	100
2	 **2b**	 **3ab**	100	7	 **2g**	 **3ag**	98
3	 **2c**	 **3ac**	86	8	 **2h**	 **3ah**	60
4	 **2d**	 **3ad**	71	9	 **2i**	 **3ai**	71
5	 **2e**	 **3ae**	32	10	 **2j**	 **3aj**	8

[a] A solution of **1a** (1 mmol) and **2** (1 mmol) in TFA (1 mL) was stirred at rt for 24 h.

Table 2. Substituent effect of cinnamate **1** on the formation of dihydrocoumarins **3**[a]



Entry	Cinnamate **1**, Ar	Phenol **2**	Dihydrocoumarin **3** (%)
1	**1b**: 	**2a**	**3ba** 100
2	**1b**	 **2f**	**3bf** 100
3	**1b**	 **2g**	**3bg** 100
4	**1c**: 	**2a**	**3ca** 100
5	**1c**	**2f**	**3cf** 100
6	**1c**	**2g**	**3cg** 97
7	**1d**: 	**2a**	**3da** 43
8	**1d**	**2b**	**3db** 9
9	**1e**: 	**2a**	**3ea** 20
10	**1f**: 	**2a**	**3fa** 100

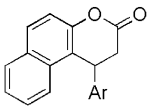
[a] A solution of **1** (1 mmol) and **2** (1 mmol) in TFA (1 mL) was stirred at rt for 24 h.

materials were recovered. The parent ethyl cinnamate (**1i**) also did not undergo any reaction under the same conditions.

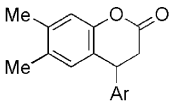
On the other hand, the combination of electron-rich cinnamates **1b**,**c** and electron-rich phenols **2f**,**g** gave almost quantitative yields of dihydrocoumarins **3bf**, **3bg**, **3cf**, and **3cg**, respectively.

2.3. Reaction in a mixed solvent of TFA and 1,2-dichloroethane

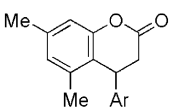
Although the reaction proceeded efficiently in TFA solvent at rt, we examined a decrease of the amount of TFA in a mixed solvent of TFA and 1,2-dichloroethane (Table 3). When the reaction of **1a** with **2g** was conducted in a 1:1



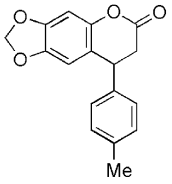
3ba: Ar = 3,4-$(MeO)_2C_6H_3$
3ca: Ar = 4-HO-3-MeC_6H_3
3da: Ar =4-MeC_6H_4
3ea: Ar = 3,4,5-$(MeO)_3C_6H_2$
3fa: Ar = 2,3,4-$(MeO)_3C_6H_2$



3bf: Ar = 3,4-$(Me)_2C_6H_3$
3cf: Ar = 4-HO-3-$MeOC_6H_3$



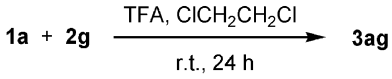
3bg: Ar = 3,4-$(Me)_2C_6H_3$
3cg: Ar = 4-HO-3-$MeOC_6H_3$



3db

Figure 1. Dihydrocoumarins **3** listed in Table 2.

Table 3. Effect of the amount of TFA



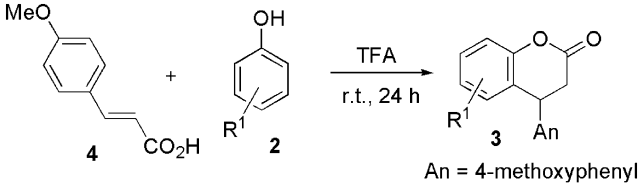
Solvent		Yield (%)
TFA (mL)	$ClCH_2CH_2Cl$ (mL)	
1	0	98
0.5	0.5	93
0.3	0.7	58
0.1	0.9	5

mixture (v/v) of TFA and 1,2-dichloroethane, dihydrocoumarin **3ag** was obtained in 93% yield. Further decrease in the ratio of TFA resulted in a significant decrease in the yield of **3ag**, as seen from Table 3.

2.4. Reaction of 4-methoxycinnamic acid (4) with phenols 3

To extend the above reaction, we examined the reaction of 4-methoxycinnamic acid (**4**) instead of ethyl ester **1a** (Table 4).[10] On the basis of the reaction in a mixture of TFA and 1,2-dichloroethane, we conducted the reaction of **4** in a 2:1 mixture (v/v) of TFA and CH_2Cl_2. When the reaction of **4** with 3,5-dimethylphenol (**2g**) was carried out in a mixed solvent of TFA (1 mL) and CH_2Cl_2 (0.5 mL) at rt for 24 h, dihydrocoumarin **3ag** was obtained quantitatively. Similarly, the reaction with 3,4-dimethyphenol (**2f**) gave dihydrocoumarin **3af** quantitatively, while the reaction with 3-methylphenol (**2h**) decreased the yield of dihydrocoumarin **3ah** (47%). Apparently, the reaction with electron-rich phenols, such as 2-naphthol (**2a**), 3,4-methylenedioxyphenol (**2b**), 3,4-dimethoxyphenol (**2c**), and 3-methoxyphenol (**2d**), afforded the corresponding dihydrocoumarins **3** in high yields. In the case of the reaction with 4-methoxyphenol (**2e**), however, a lower yield (38%) of dihydrocoumarin **3ae** was observed for the reason similar to the reaction of **1a** with **2e**. When the reaction of **4** with phenol (**2k**) was conducted under similar conditions, dihydrocoumarin **3ak** was obtained in 13% yield, together with 85% yield of 3-(4-hydroxyphenyl)-3-(4-methoxyphenyl)propionic acid (**5**).

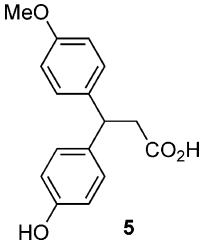
Table 4. Reaction of 4-methoxycinnamic acid **4** with phenols **2**[a]



Entry	Phenol **2**	Dihydrocoumarin **3**	Isolated yield (%)
1	**2a**	**3aa**	85
2	**2b**	**3ab**	99
3	**2c**	**3ac**	90
4	**2d**	**3ad**	72
5	**2e**	**3ae**	38
6	**2f**	**3af**	100
7	**2g**	**3ag**	100
8	**2h**	**3ah**	47
9	**2k**	**3ak**	13[b]

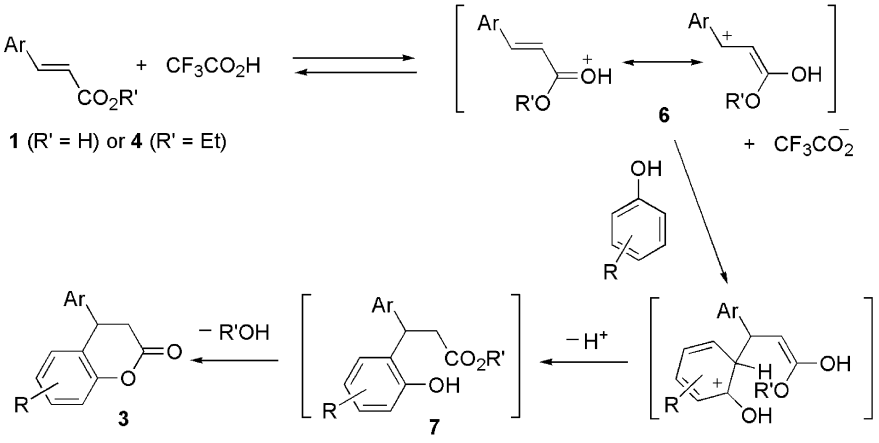
[a] A solution of **4** (1 mmol) and **2** (1 mmol) in TFA (1 mL) and CH_2Cl_2 (0.5 mL) was stirred at rt for 24 h.

[b] 3-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)propionic acid (**5**) was also formed in 85% yield



2.5. Mechanistic consideration

The role of TFA is important in the reaction of cinnamates **1** with phenols **2**, as seen from Table 3. Scheme 1 shows a possible mechanism of the formation of dihydrocoumarins **3**, where the reaction is promoted by protonation of **1** with TFA. Accordingly, electron-donating groups on **1** stabilize the resulting cationic intermediate **6** and facilitate the further reaction. However, an unsubstituted phenyl group is not enough to react with phenols **2**. Since the phenyl groups with the *ortho* methyl substituent cannot participate in the stabilization of the cationic intermediate **6** because of steric hindrance, no products are formed. A similar substituent



Scheme 1.

effect is also observed in the case of phenols **2**. As expected, the reaction with 4-bromophenol (**2j**) results in the low yield of **3**. The electrophilic substitution of phenol **2** by the cationic intermediate **6** gives 3-(2-hydroxyphenyl)propiolate **7**, which immediately undergoes intramolecular transesterification to lead to dihydrocoumarin **3**. The electrophilic substitution of phenol (**2k**) occurs at the *para* position to afford 3-(4-hydroxyphenyl)propionic acid (**5**) predominantly. The behavior of the cationic intermediate **6** toward the phenol is very close to the result of the Friedel–Crafts alkylation of phenol that shows the predominant formation of *para* products.[11]

3. Conclusion

During the course of study on our hydroarylation reactions, we found a convenient and efficient synthesis of 4-aryl-3,4-dihydrocoumarins. This process is conducted under very mild conditions by using electron-rich cinnamic acid derivatives **1** (or **4**) and electron-rich phenols **2**. The convenient procedure involves only a simple mixing of **1** (or **4**) and **2** in TFA at rt, followed by separation by column chromatography. Because of the simplicity and mildness, this procedure is applicable for a variety of 4-aryl-3,4-dihydrocoumarins, along with the previously reported methods (Table 4).

4. Experimental

4.1. General

Melting points were measured with a Yanaco micromelting apparatus and are not corrected. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL AL 300 spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Column chromatography was carried out on silica gel (Silica Gel 60, spherical, Kanto Chemical Co.) with hexane and ethyl acetate as an eluent. Elemental analyses were conducted by the Service Center of the Elemental Analysis of Organic Compounds, Faculty of Science, Kyushu University.

4.2. General procedure for the reaction of cinnamates 1 with phenols 2

In a test tube was placed an ethyl cinnamate **1** (1 mmol), a phenol **2** (1 mmol), and TFA (1 mL). The mixture was stirred at rt for 24 h. The reaction mixture was neutralized with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The product was separated by column chromatography on silica gel and purified by recrystallization from CH_2Cl_2/hexane. A similar procedure was also followed when the reaction of 4-methoxycinnamic acid (**4**) was conducted in a mixed solvent of TFA (1 mL) and CH_2Cl_2 (0.5 mL).

4.2.1. 1,2-Dihydro-1-(4-methoxyphenyl)-3*H*-naphtho-[2,1-*b*]pyran-3-one (3aa).[4e] Mp 130.0–131.0 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.11 (dd, J=15.6, 2.9 Hz, 1H, CH), 3.20 (dd, J=15.6, 6.0 Hz, 1H, CH), 3.72 (s, 3H, OMe), 4.90 (dd, J=6.0, 2.7 Hz, 1H, CH), 6.78 (d, J=8.7 Hz, 2H, ArH), 7.03 (app. d, J=8.4 Hz, 2H, ArH), 7.33 (d, J=8.7 Hz, 1H, ArH), 7.40–7.49 (m, 2H, ArH), 7.79 (d, J=8.4 Hz, 1H, ArH), 7.85 (d, J=8.7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 36.64, 37.45, 55.02, 114.43, 117.37, 117.90, 122.95, 125.09, 127.29, 127.86, 128.58, 129.65, 130.83, 130.93, 132.42, 149.52, 158.75, 167.15.

4.2.2. 4-(4-Methoxyphenyl)-6,7-methylenedioxy-3,4-dihydrocoumarin (3ab). Mp 136.5–137.5 °C (CH_2Cl_2/hexane) (lit.[6] mp 134.6–135.2 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.91 (dd, J=15.8, 8.0 Hz, 1H, CH), 3.00 (dd, J=15.7, 6.0 Hz, 1H, CH), 3.79 (s, 3H, OMe), 4.16 (app. t, J=6.8 Hz, 1H, CH), 5.93 (s, 2H, CH_2), 6.38 (s, 1H, ArH), 6.63 (s, 1H, ArH), 6.86 (app. d, J=8.7 Hz, 2H, ArH), 7.05 (app. d, J=8.7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.14, 39.82, 55.26, 99.06, 101.64, 107.21, 114.48, 118.38, 128.49, 132.35, 144.36, 146.10, 147.41, 158.99, 167.67.

4.2.3. 5,7-Dimethoxy-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (3ac). Mp 133.3–133.8 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.97 (d, J=4.2 Hz, 2H, CH_2), 3.74 (s, 6H, 2OMe), 3.81 (s, 3H, OMe), 4.50 (t, J=4.5 Hz, 1H), 6.27 (d, J=2.1 Hz, 1H, ArH), 6.31 (d, J=2.4 Hz, 1H, ArH), 6.78 (d, J=8.4 Hz, 1H, ArH), 7.02 (d, J=8.7 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 33.67, 37.25, 55.18, 55.53, 55.79, 93.94, 95.08, 106.41, 114.17, 127.74, 133.57, 153.00, 157.36, 158.57, 160.58, 167.74. Anal. Calcd for $C_{18}H_{18}O_5$: C, 68.78; H, 5.77. Found: C, 68.89; H, 5.81.

4.2.4. 7-Methoxy-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (3ad).[4o] Mp 143.6–144.9 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (dd, J=15.8, 8.0 Hz, 1H, CH), 3.03 (dd, J=15.8, 5.9 Hz, 1H, CH), 3.786 (s, 3H, OMe), 3.794 (s, 3H, OMe), 4.23 (app. t, J=6.6 Hz, 1H, CH), 6.63 (dd, J=8.4, 2.4 Hz, 1H, ArH), 6.66 (d, J=2.1 Hz, 1H, ArH), 6.85–6.88 (m, 3H, ArH), 7.06 (app. d, J=8.7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.47, 39.30, 55.26, 55.51, 102.48, 110.68, 114.43, 118.04, 128.51, 128.81, 132.70, 152.39, 158.92, 159.94, 167.72.

4.2.5. 6-Methoxy-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (3ae). Mp 87.8–89.6 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.94 (dd, J=15.9, 7.8 Hz, 1H, CH), 3.03 (dd, J=15.75, 6 Hz, 1H, CH), 3.71 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.24 (t, J=6.9 Hz, 1H, CH), 6.49 (d, J=6 Hz, 1H, ArH), 6.81 (dd, J=8.9, 3.2 Hz, 1H, ArH), 6.87 (app. d, J=8.7 Hz, 2H, ArH), 7.04–7.10 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.11, 40.14, 55.25, 55.57, 113.37, 113.61, 114.46, 117.77, 127.18, 128.57, 132.04, 145.56, 156.27, 158.97, 167.91. Anal. Calcd for $C_{17}H_{16}O_4$: C, 71.82; H, 5.67. Found: C, 71.86; H, 5.65.

4.2.6. 4-(4-Methoxyphenyl)-6,7-dimethyl-3,4-dihydrocoumarin (3af).[4j] Mp 126.5–127.9 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H, Me), 2.24 (s, 3H, Me), 2.92 (dd, J=15.8, 7.4 Hz, 1H, CH), 3.00 (dd, J=15.6, 6.0 Hz, 1H, CH), 3.78 (s, 3H, OMe), 4.21 (t, J=6.8 Hz, 1H, CH), 6.72 (s, 1H, ArH), 6.85 (app. d, J=9.0 Hz, 2H, ArH), 6.89 (s, 1H, ArH), 7.05 (app. d, J=8.4 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 19.00, 19.50, 37.50, 39.62, 55.23, 114.38, 117.79, 122.94, 128.48, 128.91, 132.76, 132.84, 137.27, 149.59, 158.85, 168.10.

4.2.7. 4-(4-Methoxyphenyl)-4,7-dimethyl-3,4-dihydrocoumarin (3ag).[4j] Mp 170.6–171.2 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.14 (s, 3H, Me), 2.32 (s, 3H,

Me), 2.97 (dd, J=15.8, 3.2 Hz, 1H, CH), 3.03 (dd, J=15.3, 5.6 Hz, 1H, CH), 3.74 (s, 3H, OMe), 4.32 (dd, J=5.6, 3.2 Hz, 1H, CH), 6.79 (d, J=8.6 Hz, 2H, ArH), 6.83 (br s, 2H, ArH), 6.95 (d, J=8.6 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.53, 20.99, 37.13, 37.89, 55.15, 114.38, 115.32, 120.43, 127.21, 127.94, 132.28, 136.48, 138.58, 151.97, 158.74, 167.54.

4.2.8. 4-(4-Methoxyphenyl)-7-methyl-3,4-dihydrocoumarin (3ah).[12] Mp 85–87 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 3H, Me), 2.93 (dd, J=15.2, 8.1 Hz, 1H, CH), 3.01 (dd, J=15.6, 6.6 Hz, 1H, CH), 3.77 (s, 3H, OMe), 4.23 (app. t, J=6.9 Hz, 1H, CH), 6.84–6.92 (m, 5H, ArH), 6.95 (app. d, J=9.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.97, 37.30, 39.51, 55.21, 114.38, 117.38, 123.01, 125.33, 127.93, 128.49, 132.47, 138.94, 151.44, 158.86, 168.08.

4.2.9. 4-(4-Methoxyphenyl)-6-methyl-3,4-dihydrocoumarin (3ai).[12] Mp 120.2–120.6 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.24 (s, 3H, Me), 2.93 (dd, J=15.2, 7.5 Hz, 1H, CH), 3.00 (dd, J=15.6, 7.5 Hz, 1H, CH), 3.77 (s, 3H, OMe), 4.22 (t, J=6.8 Hz, 1H, CH), 6.77 (s, 1H, ArH), 6.86 (app. d, J=8.7 Hz, 2H, ArH), 6.99 (d, J=8.4 Hz, 1H, ArH), 7.03–7.07 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.71, 37.28, 39.92, 55.24, 114.34, 116.77, 125.74, 128.54, 128.56, 129.15, 132.43, 134.22, 149.57, 158.92, 167.91.

4.2.10. 7-Bromo-4-(4-methoxyphenyl)-3,4-dihydrocoumarin (3aj). Mp 149.5–150.5 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.96 (dd, J=16.1, 8.3 Hz, 1H, CH), 3.04 (dd, J=15.8, 6.2 Hz, 1H, CH), 3.81 (s, 3H, OMe), 4.26 (app. t, J=7.2 Hz, 1H, CH), 6.89 (app. d, J=8.7 Hz, 2H, ArH), 7.00 (d, J=8.4 Hz, 1H, ArH), 7.05–7.09 (m, 3H, ArH), 7.40 (dd, J=8.7, 2.4 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 36.78, 39.82, 55.32, 114.69, 117.29, 118.84, 128.44, 128.57, 131.02, 131.26, 131.72, 150.72, 159.22, 166.94. Anal. Calcd for $C_{16}H_{13}BrO_3$: C, 57.68; H, 3.93. Found: C, 57.77; H, 3.94.

4.2.11. 4-(4-Methoxyphenyl)-3,4-dihydrocoumarin (2ak).[12] Mp 136.9–138.1 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.98 (dd, J=16.2, 7.8 Hz, 1H, CH), 3.53 (dd, J=17.4, 6.0 Hz, 1H, CH), 3.79 (s, 3H, OMe), 4.30 (t, J=6.8 Hz, 1H), 6.87 (app. d, J=8.7 Hz, 2H, ArH), 6.98 (d, J=7.5 Hz, 1H, ArH), 7.06–7.13 (m, 4H, ArH), 7.29 (td, J=7.8, 1.8 Hz, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.19, 39.90, 55.28, 114.48, 117.08, 124.60, 126.20, 128.26, 128.60, 128.68, 132.20, 151.66, 159.00, 167.73.

4.2.12. 1,2-Dihydro-1-(3,4-dimethoxyphenyl)-3*H*-naphtho[2,1-*b*]pyran-3-one (3ba).[13] Mp 156–159 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.14 (dd, J=3.0, 15.3 Hz, 1H, CH), 3.20 (dd, J=5.7, 15.3 Hz, 1H, CH), 3.78 (s, 3H, OMe), 4.90 (dd, J=3.0, 5.7 Hz, 1H, CH), 6.57–6.60 (m, 1H, ArH), 6.69–6.72 (m, 2H, ArH), 7.33–7.51 (m, 3H, ArH), 7.80–7.88 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.14, 37.49, 55.70, 55.74, 110.05, 11.56, 117.34, 117.76, 118.94, 122.94, 125.13, 127.32, 128.61, 129.75, 130.88, 130.95, 132.97, 148.34, 149.39, 149.55, 167.15.

4.2.13. 1,2-Dihydro-1-(4-hydroxy-3-methoxyphenyl)-3*H*-naphtho[2,1-*b*]pyran-3-one (3ca).[14] Mp 150.4–151.4 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.12 (dd, J=2.7, 10.6 Hz, 1H, CH), 3.19 (dd, J=4.0, 10.6 Hz, 1H, CH), 3.76 (s, 3H, OMe), 4.89 (dd, J=2.7, 4.0 Hz, 1H, CH), 5.52 (s, 1H, OH), 6.60–6.62 (m, 2H, ArH), 6.77–6.80 (m, 1H, ArH), 7.32–7.51 (m, 3H, ArH), 7.79–7.82 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.20, 37.58, 55.69, 109.17, 114.79, 117.31, 117.82, 119.68, 122.96, 125.14, 127.32, 128.59, 129.74, 130.88, 130.96, 132.37, 144.94, 146.96, 149.51, 167.31.

4.2.14. 1,2-Dihydro-1-(4-methylphenyl)-3*H*-naphtho-[2,1-*b*]pyran-3-one (3da). Mp 108.5–109.5 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.26 (s, 3H, Me), 3.13 (dd, J=15.9, 2.7 Hz, 1H, CH), 3.20 (dd, J=15.9, 6.6 Hz, 1H, CH), 4.92 (app. d, J=3.9 Hz, 1H, CH), 6.99–7.08 (m, 4H, ArH), 7.34 (d, J=9.0 Hz, 1H, ArH), 7.40–7.49 (m, 2H, ArH), 7.79 (d, J=7.8 Hz, 1H, ArH), 7.85 (d, J=9.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.87, 37.19, 37.44, 117.45, 117.80, 123.01, 125.12, 126.71, 127.34, 128.64, 129.71, 129.80, 130.95, 131.01, 137.12, 137.49, 149.67, 167.12. Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.41; H, 5.58.

4.2.15. 4-(3,4-Dimethoxyphenyl)-6,7-dimethyl-3,4-dihydrocoumarin (3bf). Mp 141.7–142.8 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H, Me), 2.24 (s, 3H, Me), 2.94 (dd, J=15.8, 7.4 Hz, 1H, CH), 3.01 (dd, J=15.8, 5.9 Hz, 1H, CH), 3.82 (s, 3H, OMe), 3.85 (s, 3H, OMe), 4.21 (t, J=6.6 Hz, 1H, CH), 6.66–6.68 (m, 2H, ArH), 6.74 (s, 1H, ArH), 6.81 (app. d, J=8.7 Hz, 1H, ArH), 6.89 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.87, 19.37, 37.33, 39.91, 55.75 (2OMe), 110.45, 111.43, 117.63, 119.34, 122.70, 128.78, 132.76, 133.17, 137.19, 148.22, 149.20, 149.42, 168.05. Anal. Calcd for $C_{19}H_{20}O_4$: C, 73.06; H, 6.45. Found: C, 73.00; H, 6.46.

4.2.16. 4-(4-Hydroxy-3-methoxyphenyl)-6,7-dimethyl-3,4-dihydrocoumarin (3cf). Mp 141.7–142.8 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 3H, Me), 2.24 (s, 3H, Me), 2.92 (dd, J=16.1, 7.4 Hz, 1H, CH), 3.00 (dd, J=15.9, 6.0 Hz, 1H, CH), 3.82 (s, 3H, OMe), 4.19 (t, J=6.8 Hz, 1H, CH), 6.62–6.63 (m, 2H, ArH), 6.74 (s, 1H, ArH), 6.85 (d, J=8.7 Hz, 1H, ArH), 6.89 (s, 1H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.91, 19.41, 37.45, 40.00, 55.82, 139.77, 114.71, 117.66, 120.26, 122.82, 128.85, 132.55, 132.83, 137.23, 144.88, 146.86, 149.44, 168.24. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.56; H, 6.12.

4.2.17. 4-(3,4-Dimethoxyphenyl)-5,7-dimethyl-3,4-dihydrocoumarin (3bg).[15] Mp 137.9–138.9 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H, Me), 2.34 (d, 3H, Me), 2.94–3.08 (m, 2H, CH_2), 3.80 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.29–4.32 (m, 1H, CH), 6.52 (d, J=8.1 Hz, 1H, ArH), 6.59 (s, 1H, ArH), 6.73 (d, J=8.1 Hz, 1H, ArH), 6.83 (br s, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.54, 20.98, 37.55, 37.87, 55.79 (2OMe), 110.16, 111.51, 115.28, 118.96, 120.25, 127.23, 132.83, 136.51, 138.64, 148.25, 149.30, 151.93, 167.59.

4.2.18. 4-(4-Hydroxy-3-methoxyphenyl)-5,7-dimethyl-3,4-dihydrocoumarin (3cg). Mp 176.8–177.6 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.16 (s, 3H, Me), 2.34 (s, 3H, Me), 2.97 (dd, J=3.0, 15.6 Hz, 1H, CH), 3.03 (dd, J=5.7, 15.6 Hz, 1H, CH), 3.79 (s, 3H, OMe), 4.30 (dd,

J=3.0, 5.7 Hz, 1H, CH), 5.53 (s, 1H, OH), 6.50–6.53 (m, 2H, ArH), 6.77–6.83 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 18.56, 21.02, 37.68, 38.00, 55.83, 109.25, 114.71, 115.33, 119.82, 120.34, 127.28, 132.24, 136.57, 138.68, 144.89, 146.91, 151.97, 167.69. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.46; H, 6.08.

4.2.19. 6,7-Methylenedioxy-4-(4-methylphenyl)-3,4-dihydrocoumarin (3db). Mp 131.6–132.4 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (s, 3H, Me), 2.93 (dd, J=15.9, 7.8 Hz, 1H, CH), 3.01 (dd, J=15.8, 6.15 Hz, 1H, CH), 4.17 (t, J=6.9 Hz, 1H, CH), 5.93 (s, 2H, CH_2), 6.38 (s, 1H, ArH), 6.64 (s, 1H, ArH), 7.03 (d, J=8.1 Hz, 2H, ArH), 7.15 (d, J=8.0 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 20.97, 37.01, 40.24, 99.06, 101.64, 107.26, 118.26, 127.31, 129.77, 137.37, 137.39, 144.37, 146.16, 147.43, 167.66. Anal. Calcd for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.38; H, 4.99.

4.2.20. 1,2-Dihydro-1-(2,3,4-trimethoxyphenyl)-3*H*-naphtho[2,1-*b*]pyran-3-one (3fa). Mp 178.0–178.4 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.08 (dd, J=17.0, 3.6 Hz, 1H, CH), 3.15 (dd, J=15.9, 6.6 Hz, 1H, CH), 3.75 (s, 3H, OMe), 3.90 (s, 3H, OMe), 4.09 (s, 3H, OMe), 5.23 (app. d, J=4.2 Hz, 1H, CH), 6.35 (d, J=8.7 Hz, 1H, ArH), 6.40 (d, J=8.7 Hz, 1H, ArH), 7.32 (d, J=9.0 Hz, 1H, ArH), 7.40–7.49 (m, 2H, ArH), 7.76 (d, J=8.1 Hz, 1H, ArH), 7.85 (d, J=8.7 Hz, 2H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 31.59, 36.44, 55.72, 60.63, 60.98, 107.13, 117.34, 117.64, 121.89, 122.98, 125.05, 125.95, 127.27, 128.56, 129.58, 130.87, 130.97, 142.11, 150.03, 150.69, 153.22, 167.44. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.30; H, 5.48.

4.2.21. 1,2-Dihydro-1-(3,4,5-trimethoxyphenyl)-3*H*-naphtho[2,1-*b*]pyran-3-one (3ea). Mp 181.9–182.6 °C (CH_2Cl_2/hexane). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.10–3.24 (m, 2H, CH_2), 3.72 (s, 6H, OMe), 3.77 (s, 3H, OMe), 4.87–4.90 (m, 1H, CH), 6.33 (s, 2H, ArH), 7.33–7.53 (m, 3H, ArH), 7.81–7.88 (m, 3H, ArH). ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 37.56, 37.97, 56.06, 60.72, 103.96, 117.42, 117.51, 123.02, 125.31, 127.50, 128.75, 130.04, 131.00, 131.07, 136.30, 137.40, 149.71, 153.72, 167.14. Anal. Calcd for $C_{22}H_{20}O_5$: C, 72.51; H, 5.53. Found: C, 72.15; H, 5.55.

4.2.22. 3-(4-Hydroxyphenyl)-3-(4-methoxyphenyl)propionic acid (5). ^{1}H NMR (CD_3OD, 300 MHz) δ 2.93 (d, J=7.8 Hz, 2H, CH_2), 3.73 (s, 3H, OMe), 4.35 (t, J=8.0 Hz, 1H, CH), 6.68 (app. d, J=6.5 Hz, 2H, ArH), 6.80 (app. d, J=6.6 Hz, 2H, ArH), 7.04 (d, J=8.1 Hz, 2H, ArH), 7.13 (d, J=8.4 Hz, 2H, ArH). ^{13}C NMR (CD_3OD, 75.5 MHz) δ 42.12, 46.92, 55.65, 114.79, 116.15, 129.60, 136.54, 137.86, 156.80, 159.57, 175.94. Anal. Calcd for $C_{16}H_{16}O_4$: C, 70.58; H, 5.92. Found: C, 70.29; H, 6.01.

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Facile and convenient synthesis of functionalized propargylic alcohols and amines: an $InBr_3$–Et_3N reagent system promotes the alkynylation of aldehydes and *N*,*O*- or *N*,*S*-acetals

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Abstract—The use of a novel $InBr_3$–Et_3N reagent system to promote the alkynylation of not only a variety of aromatic/heterocyclic or bulky aliphatic aldehydes but also *N*,*O*- or *N*,*S*-acetals is described. The use of *N*-silyl-*N*,*O*-acetals and 1-alkynes could lead to the direct production of primary propargylic amines in good yields.

1. Introduction

The synthesis of functionalized propargylic alcohols and amines has been widely studied because a number of such derivatives constitute some of the basic units in natural products and related biologically active substances.[1] The nucleophilic addition of alkynylmetals containing Ce,[2] B,[3] and V[4] to carbonyl compounds, and the addition of alknylalminium[5] to aminals has been typically used for this purpose in the past. A practical procedure, in which the combined use of a Lewis acid, such as $Sn(OTf)_2$,[6] GaI_3,[7] $Zn(OTf)_2$,[8] and $ZnCl_2$[9] and a Lewis base, such as an amine promotes or catalyzes the alkynylation of not only carbonyl compounds but also enamines and imine, was recently developed. On the other hand, because of the interesting chemical properties of indium halides, such as their high stability under aqueous conditions, and strong tolerance to oxygen- and nitrogen containing functional groups, a number of groups have developed synthetic methodologies that involve high regio- or chemoselectivity,[10] and we previously reported that a system comprised of indium halide and an amine effectively promotes the alkynylation of aldehydes under relatively mild conditions, leading to the corresponding propargylic alcohols.[11,12] Herein, we report on a reinvestigation of the reaction conditions and some additional details of the scope and limitations of the alkynylation of carbonyl compounds by the indium(III) salt–amine reagent system leading to the corresponding propargylic alcohols. We also report herein that, unlike conventional alkynylations using enamines,[13] aminals,[14] and imines,[8,15] by employing *N*,*O*-acetals, this reagent system can be used to directly produce propargylic amines, especially, with *N*-silyl-*N*,*O*-acetal, to afford primary propargylic amines in good yields.

2. Results and discussion

We initially examined the reaction of phenylacetylene (**1a**) with benzaldehyde (**2a**) in the presence of indium halide and triethylamine as a model system. Thus, when the acetylene (2 equiv) was treated with Et_3N (2 equiv) and $InCl_3$ (2 equiv) at room temperature in dichloromethane for 1 h, followed by the addition of benzaldehyde, the corresponding propargylic alcohol **3a** was produced in 33% yield (run 1). To optimize the alkynylation, we then ran the reaction using several different solvents and other indium trihalides. The results are summarized in Table 1. Consequently, we found that, when the reaction was conducted in Et_2O instead of CH_2Cl_2, the product yield was improved to 50% (run 2). In contrast, in the cases of THF, and PhMe, the yields were decreased (runs 3 and 4). It is particularly noteworthy that, when $InBr_3$ was used as a promoter, the reaction was completed within 2 h and **3a** was produced in a near quantitative yield (run 5). On the other hand, InI_3 was not effective for this reaction (run 6). It was also found that decreasing of amount of $InBr_3$ to 1.5 equiv reduced the product yield and it was necessary to prolong the reaction time (run 7). As expected, in the absence of indium halide, no alkynylation took place (run 8).

Keywords: Alkynylation; Propargylic alcohols; Propargylic amines; Indium bromide; Acetal.
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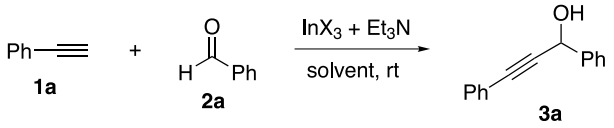
Table 1. Optimization of the alkynylation of benzaldehyde (**2a**) with phenylacetylene (**1a**)[a]

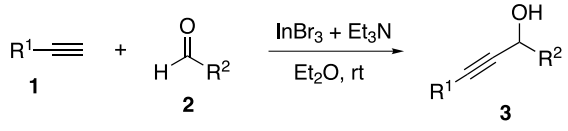


Run	InX_3	Solvent	Time (h)	Yield (%)[b]
1	$InCl_3$	CH_2Cl_2	24	33
2	$InCl_3$	Et_2O	24	50
3	$InCl_3$	THF	24	4
4	$InCl_3$	PhMe	24	Trace
5	$InBr_3$	Et_2O	2	95[c]
6	InI_3	Et_2O	24	26
7[d]	$InBr_3$	Et_2O	6	61
8	None	Et_2O	10	ND[e]

[a] Phenylacetylene (2 equiv), indium halide (2 equiv), Et_3N (2 equiv), and benzaldehyde (0.4 mmol) in 2 mL of solvent.
[b] NMR yields based on benzaldehyde.
[c] Isolated yield.
[d] Phenylacetylene (1.5 equiv), $InBr_3$, and Et_3N was used.
[e] ND, Not detected.

To clarify the general applicability of this alkynylation, the reaction of various benzaldehyde derivatives and aliphatic/aromatic aldehydes with four types of 1-alkynes was carried out under the optimized conditions and the results are listed in Table 2. The use of benzaldehyde derivatives containing an electron-withdrawing substituent, such as halogens, cyano, and nitro groups required only a short time for a complete reaction, and the corresponding propargylic alcohols were produced in excellent yields ranging from 83 to 99% (runs 1–4, 7, 16, and 19). Similarly, benzaldehydes containing an electron-donating group also underwent the expected alkynylation in good yields (runs 5 and 6). In the case of *p*-methoxybenzaldehyde, however, refluxing was required to obtain a satisfactory yield (run 5). Steric effects of substituent groups at the position did not affect the product yield (run 7). When aliphatic aldehydes were used, the alkynylation of bulky aldehydes such as pival- and isobutyraldehyde gave the corresponding alcohols in good to moderate yields (runs 8 and 9). However, an easily enolizable aldehyde, such as butyraldehyde produced only a small amount of the alkynylated product **3k** along with a 22% yield of the side-reaction product, formed by aldol condensation of the aldehyde (run 10). This result shows that the abstraction of an α-hydrogen on the aldehyde by the in-situ formed anionic intermediate proceeds faster than the nucleophilic addition of the resulting intermediate to the aldehyde, thus leading to enolization of the aldehyde. Interestingly, the present method could be applied to alkynylation reactions using heteroaromatic aldehydes containing pyridine, thiophene, and furan skeletons (runs 13–15, and 17). For example, when phenylacetylene or 1-octyne was treated with the heteroaromatic aldehyde, 3-pyridinecarboxaldehyde, the corresponding heterocyclic propargyl alcohols **3n** and **3r** were produced in satisfactory yields (runs 13 and 17). In contrast, the alkynylation of ketones, for example, cyclohexanone was somewhat sluggish (>50 h), and the yield of product **3u** (<40%) was low. Furthermore, a reaction using acetic anhydride, benzoic anhydride, and esters was not successful.

Table 2. Reaction of terminal alkynes with various aldehydes leading to propargyl alcohols[a]



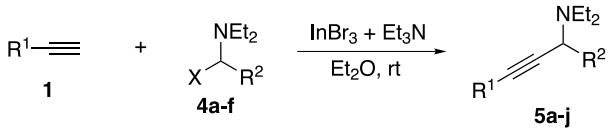
Run	Alkyne	Aldehyde	Time (h)	Yield of **3** (%)[b]
	R^1	R^2		
1	Ph	*p*-Cl–C_6H_4	5	**3b** 90
2	Ph	*p*-F–C_6H_4	5	**3c** 92
3	Ph	*p*-CN–C_6H_4	1.5	**3d** 97
4	Ph	*p*-NO_2–C_6H_4	0.5	**3e** 87
5[c]	Ph	*p*-MeO–C_6H_4	24	**3f** 70
6	Ph	*p*-Me–C_6H_4	15	**3g** 80
7	Ph	*o*-Br–C_6H_4	3	**3h** 83
8[c]	Ph	*t*-Bu	24	**3i** 88
9	Ph	*i*-Pr	24	**3j** 44
10	Ph	*n*-Pr	24	**3k** 11
11	Ph	PhCH=CH	20	**3l** 46
12	Ph	2-Naphthyl	24	**3m** 61
13	Ph	3-Pyridyl	1	**3n** 99
14	Ph	2-Thienyl	24	**3o** 57
15	Ph	2-Furyl	12	**3p** 93
16	C_6H_{13}	*p*-CN–C_6H_4	18	**3q** 99
17	C_6H_{13}	3-Pyridyl	12	**3r** 40
18	*t*-Bu	Ph	24	**3s** 67
19[c]	Me_3Si	*p*-CN–C_6H_4	24	**3t** 93

[a] General procedure: alkyne (0.8 mmol), aldehyde (0.4 mmol), $InBr_3$ (0.8 mmol), Et_3N (0.8 mmol) in Et_2O (2 mL).
[b] Isolated yield based on aldehyde **2**.
[c] Reaction was carried out at 40 °C.

We then applied the reaction to the preparation of propargylic amine derivatives with *N*,*O*-acetals. Thus, the reaction of four types of 1-alkynes **1** with appropriate *N*,*O*-acetals **4** was carried out under the conditions described above, and the results are shown in Table 3. Generally, when alkynes and *N*,*O*-acetal containing a phenyl group **4a** were used, the reaction proceeded faster than that of aldehydes to give the corresponding propargylic amine **5a** and **5b** in good yields (runs 1 and 2). In the case of heterocyclic *N*,*O*-acetal **4b**, the reaction also proceeded, producing the corresponding products in mild to good yields (runs 4–7). On the other hand, when the reaction was carried out with *N*,*O*-acetals involving furan and thiophene rings **4c** and **4d**, the yields were rather low (runs 8 and 9). However, the employment of *N*,*S*-acetals **4e** and **4f** instead of the *N*,*O*-acetal solved the problem and the desired product was produced in moderate yields, as the result of the higher activity of thiolate anion as a leaving group than methoxy anion.

Finally, on the basis of our previous work,[16] we attempted the preparation of primary propargylic amine derivatives, since a simple and direct preparation of primary propargylic amine is lacking.[17] Thus, the reaction of three types of 1-alkynes with *N*-silyl-*N*,*O*-acetal **6** was carried out under optimized conditions, the results of which are listed in Table 4. All three reactions proceeded smoothly to afford the corresponding primary amines in satisfactory yields. We isolated the latter two products, the amide product of which could be achieved by a one-pot synthesis using benzyl chloride to prevent the loss of product during the work-up (runs 2 and 3).

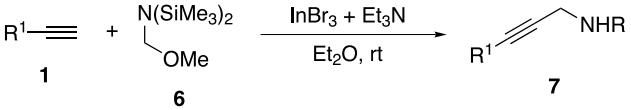
Table 3. Reaction of terminal alkynes with *N*,*O*- or *N*,*S*-acetals leading to propargylic amines[a]



Run	Alkyne **1**	Acetal **4**		Time (h)	Yield of **5** (%)[b]
	R^1	X	R^2		
1	Ph	MeO	Ph	0.2	**5a** 94
2	C_6H_{13}	MeO	Ph	0.2	**5b** 78
3	Me_3Si	MeO	Ph	10	**5c** 54
4[c]	Ph	MeO	3-Pyridyl	0.2	**5d** 65
5[c]	C_6H_{13}	MeO	3-Pyridyl	3	**5e** 42
6[c]	*t*-Bu	MeO	3-Pyridyl	24	**5f** 69
7[c]	Me_3Si	MeO	3-Pyridyl	24	**5g** 81
8	Ph	PhS	2-Furyl	3	**5h** 24 (12)[d]
9	Ph	PhS	2-Thienyl	24	**5i** 56 (ND)[e]

[a] General procedure: alkyne (1 mmol), *N*,*O*- or *N*,*S*-acetal (0.5 mmol), $InBr_3$ (1 mmol), Et_3N (1 mmol) in Et_2O (3 mL).
[b] Isolated yields based on acetal **4**.
[c] Reaction was carried out at 40 °C.
[d] Reaction was carried out with *N*,*O*-acetal **4c**.
[e] Reaction was carried out with *N*,*O*-acetal **4d**.

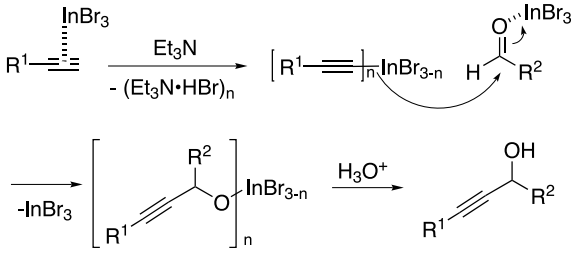
Table 4. Reaction of terminal alkynes with *N*-silyl-*N*,*O*-acetal **6**



Run	Alkyne **1**	Time (h)	Yield (%) of **7**[a]
	R^1		
1	Ph	1	**7a** 66 (R=H)
2[b]	C_6H_{13}	5	**7b** 54 (R=PhCO)
3[b]	*t*-Bu	5	**7c** 52 (R= PhCO)

[a] Isolated yields.
[b] Products **7b** and **7c** were isolated as amide products by using benzoyl chloride. See Section 4.4.

A plausible mechanism for the alkynylation of an aldehyde is shown in Scheme 1. $InBr_3$ initially coordinate with an alkyne π-bond, which increases the acidity of the terminal hydrogen, followed by the facile abstraction of a proton by a mild base, such as triethylamine, to form an intermediate such as an indium acetylide. The intermediate then attacks the aldehyde, which was activated by the Lewis acidic $InBr_3$, subsequently leading to the final propargylic alcohol by the usual work-up. In cases of *N*,*O*- or *N*,*S*-acetals, the reaction path also would proceeds similarly and, in such systems, the indium plays a dual role, first to coordinate with the alkyne π-bond to facilitate the abstraction of a terminal hydrogen, and also to activate the aldehydes and acetals.[18] Unfortunately, when the reaction was conducted in the presence of a catalytic amount of indium salt, the product yield was decreased significantly, probably due to the difficulty of regenerating the indium(III) salt.[18e]



Scheme 1.

3. Conclusion

In summary, we demonstrated that the $InBr_3$–Et_3N reagent system promotes the facile reaction of 1-alkynes with a variety of aldehydes under mild conditions leading to the production of functionalized propargylic alcohols in good to excellent yields. We also found that this reagent system can be used in alkynylation reactions of heteroaromatic aldehydes producing the corresponding heterocyclic propargylic alcohols in excellent yields, and can be widely applied to the one-pot preparation of primary or tertiary propargylic amine derivatives and amide derivatives with *N*,*O*- or *N*,*S*-acetals. Further investigations of the mechanism of this reaction are currently in progress.

4. Experimental

4.1. General methods

Column chromatography was performed using Silica gel 60 (Merck). Diethyl ether was distilled from sodium–benzophenone before use. Dichloromethane was distilled from P_2O_5 and dried over MS4A. The other organic solvents and materials were dried and distilled prior to use. Commercially available $InCl_3$, $InBr_3$, and InI_3 were used without further purification. *N*,*N*-diethyl-α-(methoxy-3-pyridyl)-methanamine (**4a**), *N*,*N*-diethyl-α-methoxy-benzenemethanamine (**4b**), *N*,*N*-diethyl-α-(methoxy-2-furyl)-methanamine (**4c**), *N*,*N*-diethyl-α-(methoxy-2-thienyl)-methanamine (**4d**), *N*,*N*-diethyl-α-(thiophenyl-2-furyl)-methanamine (**4e**), and *N*,*N*-diethyl-α-(thiophenyl-2-thienyl)-methanamine (**4f**) were prepared according to previously reported procedures.[19,20] All reactions were carried out under an argon atmosphere, unless otherwise noted. ^1H NMR spectra were measured at 500 MHz using tetramethylsilane as an internal standard. ^{13}C NMR

spectra were measured at 125 MHz using the chloroform peak (77.0 ppm) as an internal standard. High-resolution mass spectra were measured on a JEOL JMS-700 MStation using NBA (3-nitrobenzylalcohol) as a matrix.

4.2. General procedure for the alkynylation of aldehydes or a ketone

To a Et_2O (2 mL) solution of phenylacetylene (**1a**, 81.7 mg, 0.800 mmol) and Et_3N (81.0 mg, 0.800 mmol) were added a Et_2O solution of $InBr_3$ (284 mg, 0.800 mmol) and the reaction mixture was stirred at room temperature under argon. After 1 h, benzaldehyde (or a ketone) (**2a**, 42.5 mg, 0.400 mmol) was added to the solution via a syringe. The mixture was stirred at the same temperature until the reaction was complete, as shown by TLC (hexane–AcOEt=95/5) or GC. After the reaction, a mixture of CH_2Cl_2 (10 mL) and 1 N HCl (5 mL) was added to the reaction mixture, and the organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2/hexane–AcOEt=95/5) to give afford propargylic alcohol **3a** (79 mg, 95% yield) and, if necessary, further purified by a Recycling Preparative HPLC equipped with a GPC column (chloroform as the eluent).

4.2.1. 1,3-Diphenyl-2-propyn-1-ol (3a).[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.44 (br s, 1H), 5.64 (s, 1H), 7.22–7.24 (m, 4H), 7.28–7.30 (m, 2H), 7.36–7.37 (m, 2H), 7.53–7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.5, 86.0, 89.1, 122.3, 126.6, 126.7, 128.1, 128.4, 131.5, 137.5, 140.6; MS (EI) *m/z* 208 (M^+).

4.2.2. 4-Chloro-α-(phenylethynyl)-benzenemethanol (3b).[7] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.74 (br s, 1H), 5.64 (s, 1H), 7.29–7.35 (m, 5H), 7.45 (d, 2H, J=7.5 Hz), 7.52 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.2, 86.8, 88.2, 122.1, 128.0, 128.3, 128.4, 128.7, 131.7, 134.1, 139.0; MS (EI) *m/z* 242 (M^+), 207.

4.2.3. 4-Fluoro-α-(phenylethynyl)-benzenemethanol (3c).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.63 (br s, 1H), 5.65 (s, 1H), 7.00 (t, 2H, J=7.5 Hz), 7.30–7.31 (m, 3H), 7.45 (d, 2H, J=5.5 Hz), 7.57 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.3, 86.8, 88.4, 115.3, 115.5, 128.3, 128.5, 128.6, 131.7, 136.4, 162.6 (d, J_{C-F}=245 Hz); MS (EI) *m/z* 226 (M^+).

4.2.4. 4-Cyano-α-(phenylethynyl)-benzenemethanol (3d).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.19 (br s, 1H), 5.71 (s, 1H), 7.27–7.32 (m, 3H), 7.41–7.42 (m, 2H), 7.61 (d, 2H, J=8.0 Hz), 7.68 (d, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 64.0, 87.2, 87.5, 111.7, 118.5, 121.7, 127.1, 128.3, 128.8, 131.6, 132.3, 145.6.

4.2.5. 4-Nitro-α-(phenylethynyl)-benzenemethanol (3e).[7] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.13 (br s, 1H), 5.77 (s, 1H), 7.29–7.32 (m, 3H), 7.41 (d, 2H, J=7.5 Hz), 7.74 (d, 2H, J=7.5 Hz), 8.18 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.8, 87.4, 87.5, 121.6, 123.7, 127.3, 128.3, 128.9, 131.6, 147.4, 147.6; MS (EI) *m/z* 253 (M^+).

4.2.6. 4-Methoxy-α-(phenylethynyl)-benzenemethanol (3f).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (br s, 1H), 3.80 (s, 3H), 5.62 (s, 1H), 6.91 (d, 2H, J=8.0 Hz), 7.29–7.31 (m, 3H), 7.45 (d, 2H, J=8.0 Hz), 7.52 (d, 2H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 55.3, 64.6, 86.4, 88.9, 113.9, 122.4, 128.1, 128.2, 128.5, 131.7, 133.0, 159.7; MS (EI) *m/z* 238 (M^+), 207.

4.2.7. 4-Methyl-α-(phenylethynyl)-benzenemethanol (3g).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 4H (including OH)), 5.64 (s, 1H), 7.20 (d, 2H, J=7.5 Hz), 7.30–7.32 (m, 3H), 7.48–7.49 (m, 2H), 7.50 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 64.9, 86.4, 88.8, 122.4, 126.6, 128.2, 128.4, 129.3, 131.7, 137.7, 138.2; MS (EI) *m/z* 222 (M^+), 207.

4.2.8. 2-Bromo-α-(phenylethynyl)-benzenemethanol (3h).[22] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 2.61 (br s, 1H), 5.9 (s, 1H), 7.15 (t, 1H, J=7.5 Hz), 7.25 (s, 3H), 7.30 (t, 1H, J=7.5 Hz), 7.40 (dd, 2H, J=2.0, 7.5 Hz), 7.51 (d, 1H, J=7.5 Hz), 7.77 (dd, 1H, J=2.0, 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 64.7, 86.8, 87.6, 122.3, 122.8, 127.9, 128.3, 128.6, 129.9, 130.0, 131.7, 133.0, 139.5.

4.2.9. 4,4-Dimethyl-1-phenyl-1-pentyn-3-ol (3i).[7] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 9H), 2.27 (br s, 1H), 4.17 (s, 1H), 7.22–7.24 (m, 3H), 7.34–7.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.3, 36.1, 71.8, 85.6, 88.9, 122.7, 128.2, 128.3, 131.6; MS (EI) *m/z* 188 (M^+), 131.

4.2.10. 4-Methyl-1-phenyl-1-pentyn-3-ol (3j).[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (d, 6H, J=6.5 Hz), 1.84 (br s, 1H), 1.91 (m, 1H), 4.32 (s, 1H), 7.23–7.25 (m, 3H), 7.36–7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 18.1, 34.7, 68.4, 85.5, 88.8, 122.7, 128.2, 128.3, 131.6; MS (EI) *m/z* 174 (M^+), 131.

4.2.11. 1-Phenyl-1-hexyn-3-ol (3k).[24] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, 3H, J=7.5 Hz), 1.51 (br s, 1H), 1.52–1.53 (m, 2H), 1.74–1.80 (m, 2H), 4.58 (t, 1H, J=7.5 Hz), 7.28–7.29 (m, 3H), 7.39–7.41 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 18.5, 40.0, 62.8, 84.8, 90.1, 122.6, 128.2, 128.3, 131.6; MS (EI) *m/z* 174 (M^+), 131.

4.2.12. 1,5-Diphenyl-4-penten-1-yn-3-ol (3l).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.25 (br s, 1H), 5.30 (d, 1H, J=0.6 Hz), 6.40 (dd, 1H, J=15.0, 0.6 Hz), 6.84 (d, 1H, J=15.0 Hz), 7.27–7.34 (m, 6H), 7.43 (d, 2H, J=7.0 Hz), 7.48 (d, 2H, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.4, 86.4, 87.9, 122.3, 126.8, 128.0, 128.1, 128.2, 128.3, 128.5, 131.7, 132.0, 136.0; MS (EI) *m/z* 234 (M^+), 105.

4.2.13. α-(Phenylethynyl)-2-naphthalenemethanol (3m).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.61 (br s, 1H), 6.33 (s, 1H), 7.30–7.32 (m, 3H), 7.47–7.57 (m, 5H), 7.84–7.93 (m, 3H), 8.38 (d, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 63.3, 87.2, 88.5, 122.4, 123.9, 124.6, 125.2, 125.8, 126.4, 128.2, 128.5, 128.6, 129.3, 130.5, 131.7, 134.0, 135.6; MS (EI) *m/z* 258 (M^+).

4.2.14. α-(Phenylethynyl)-3-pyridinemethanol (3n).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.43 (br s, 1H), 5.74 (s, 1H), 7.24–7.31 (m, 4H), 7.41–7.42 (m, 2H), 7.99 (d, 1H, J=8.0 Hz), 8.55 (d, 1H, J=8.0 Hz), 8.83 (d, 1H, J=8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 62.3, 86.7, 88.2, 122.2,

123.6, 128.2, 128.6, 131.6, 134.9, 137.2, 147.7, 148.6; MS (EI) *m/z* 209 (M^+), 180.

4.2.15. 3-Phenyl-1-(2-thienyl)-2-propyn-1-ol (3o).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (br s, 1H), 5.87 (s, 1H), 6.98 (d, 1H, J=5.0 Hz), 7.24 (d, 1H, J=5.0 Hz), 7.30–7.32 (m, 4H), 7.47 (d, 2H, J=5.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 60.7, 86.0, 88.0, 122.1, 125.6, 126.1, 126.7, 128.3, 128.7, 131.7, 144.6; MS (EI) *m/z* 214 (M^+), 184.

4.2.16. α-(Phenylethynyl)-2-furanmethanol (3p).[23] ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (br s, 1H), 5.62 (s, 1H), 6.31 (s, 1H), 6.45 (s 1H), 7.25–7.27 (m, 3H), 7.40 (s, 1H), 7.42 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 58.6, 85.7, 86.1, 107.8, 110.3, 122.0, 128.2, 128.7, 131.7, 143.0, 152.9; MS (EI) *m/z* 198 (M^+), 141.

4.2.17. 4-(4-Cyanophenyl)-1-hydroxy-non-2-yne (3q). Yellow oil; IR (neat) 3325 (br), 2185 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, 3H, J=7.5 Hz), 1.27–1.30 (m, 3H including OH), 1.34–1.36 (m, 2H), 1.49–1.52 (m, 2H), 2.20–2.25 (m, 4H), 5.48 (m, 1H), 7.64 (d, 4H, J=1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.7, 22.5, 28.4, 28.5, 31.2, 63.9, 78.9, 88.8, 111.8, 118.7, 127.2, 132.3, 146.2; MS (EI) *m/z* 241 (M^+); HRMS (FAB): Calcd for $C_{16}H_{19}NO$: 241.1467, Found 241.1468.

4.2.18. 1-Hydroxy-1-(3-pyridinyl)-non-2-yne (3r). Yellow oil; IR (neat) 3495 (br), 2248 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, 3H, J=7.0 Hz), 1.20–1.24 (m, 4H), 1.29–1.35 (m, 2H), 1.44–1.50 (m, 2H), 2.21 (q, 2H, J=7.0 Hz), 3.85 (br s, 1H), 5.45 (s, 1H), 7.24 (m, 1H), 7.84 (d, 1H, J=7.5 Hz), 8.44 (d, 1H, J=0.4 Hz), 8.64 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.7, 22.4, 28.4, 28.5, 31.2, 62.3, 79.2, 88.2, 123.3, 134.5, 137.2, 148.1, 148.9; MS (EI) *m/z* 217 (M^+); HRMS (FAB): Calcd for $C_{14}H_{19}NO$: 217.1467, Found: 217.1465.

4.2.19. 4,4-Dimethyl-1-phenyl-2-pentyn-1-ol (3s).[9] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (s, 9H), 2.09 (br s, 1H), 5.42 (s, 1H), 7.29 (d, 2H, J=7.5 Hz), 7.31–7.37 (m, 2H), 7.53 (d, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.4, 30.8, 64.6, 78.3, 95.8, 126.9, 128.1, 128.4, 141.3; MS (EI) *m/z* 188 (M^+), 131.

4.2.20. 4-[1-Hydroxy-3-(trimethylsilyl)-2-propynyl]-benzonitrile (3t).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.15 (s, 9H), 2.22 (br s, 1H), 5.46 (s, 1H), 7.42 (d, 1H, J=7.5 Hz), 7.58 (d, 1H, J=7.5 Hz), 7.75 (d, 1H, J=7.5 Hz), 8.18 (d, 1H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.34, 64.2, 92.8, 104.8, 127.3, 127.5, 130.1, 132.6, 145.7.

4.2.21. 1-(Phenylethynyl)-cyclohexanol (3u).[21] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.54–1.67 (m, 8H), 1.90–1.93 (m, 2H), 7.23–7.25 (m, 3H), 7.36–7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.4, 25.2, 40.0, 69.1, 84.3, 92.7, 122.8, 128.1, 128.2, 131.6.

4.3. General procedure for the alkynylation of *N,O*- or *N,S*-acetal

A Et_2O solution (3 mL) of Et_3N (101.2 mg, 1.000 mmol), 1-alkyne (1.00 mmol), and $InBr_3$ (354.5 mg, 1.000 mmol) was stirred at room temperature for 1 h, followed by the addition of *N,O*- or *N,S*-acetal **4** (0.5 mmol) via a syringe. The reaction mixture was stirred until the reaction reached completion, as evidenced by TLC (hexane–AcOEt=9/1) or GC. After the reaction, a saturated $NaHCO_3$ aqueous solution was added to the mixture, and the organic layer was extracted with Et_2O. The combined organic layer was dried over Na_2CO_3, filtered, and concentrated in vacuum. The crude product was purified by flash silica gel chromatography (hexane–AcOEt=9/1) to give the corresponding propargylic amine **5**.

4.3.1. *N,N*-Diethyl-α-(phenylethynyl)-benzenemethanamine (5a).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.06 (t, 6H, J=7.5 Hz), 2.52 (q, 2H, J=7.5 Hz), 2.61 (q, 2H, J=7.5 Hz), 5.03 (s, 1H), 7.30–7.33 (m, 6H), 7.48 (dd, 2H, J=7.5, 1.5 Hz), 7.66 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 44.5, 57.0, 86.1, 87.4, 123.4, 127.2, 128.0, 128.1, 128.2, 128.3, 131.7, 139.9; MS (EI) *m/z* 263 (M^+).

4.3.2. *N,N*-Diethyl-α-1-octynyl-benzenemethanamine (5b).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=7.0 Hz), 1.03 (t, 6H, J=7.5 Hz), 1.30–1.32 (m, 4H), 1.44–1.45 (m, 2H), 1.55–1.57 (m, 2H), 2.29–2.30 (m, 2H), 2.44 (q, 2H, J=7.5 Hz), 2.53 (q, 2H, J=7.5 Hz), 4.80 (s, 1H), 7.24–7.25 (m, 1H), 7.30–7.31 (m, 2H), 7.62 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 14.0, 18.7, 21.1, 22.5, 28.5, 29.0, 31.3, 44.4, 56.5, 75.9, 87.5, 126.8, 127.8, 128.3, 137.6, 140.5.

4.3.3. *N,N*-Diethyl-α-[(trimethylsilyl)ethynyl]-benzenemethanamine (5c).[11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.19 (s, 9H), 1.02 (t, 6H, J=7.5 Hz), 2.43 (q, 2H, J=7.5 Hz), 2.53 (q, 2H, J=7.5 Hz), 4.80 (s, 1H), 7.25 (d, 1H, J=7.5 Hz), 7.29–7.31 (m, 3H), 7.60 (d, 2H, J=7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.32, 13.2, 44.1, 91.8, 101.9, 126.6, 126.9, 127.7, 128.0, 137.4.

4.3.4. *N,N*-Diethyl-α-(phenylethynyl-3-pyridyl)-methanamine (5d). Yellow oil; IR (neat) 3049, 2202 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.04 (t, 6H, J=7.1 Hz), 2.48–2.61 (m, 4H), 2.40–2.53 (m, 4H), 5.02 (s, 1H), 7.18–7.25 (m, 2H), 7.29 (t, 2H, J=3.2 Hz), 7.47 (t, 2H, J=3.2 Hz), 7.94 (d, 1H, J=7.8 Hz), 8.49 (d, 1H, J=3.7 Hz), 8.89 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.6, 44.6, 55.1, 84.5, 88.2, 122.91, 122.94, 127.1, 127.5, 128.2, 128.3, 129.0, 131.8, 135.6, 135.9, 148.5, 149.9; MS (EI): *m/z* 264; HRMS (FAB): Calcd for $C_{18}H_{20}N_2$: 264.1626, Found: 264.1621.

4.3.5. *N,N*-Diethyl-α-(1-octynyl-3-pyridyl)-methanamine (5e). Yellow oil; IR (neat) 2977, 2213 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, 3H, J=6.6 Hz), 1.03 (t, 6H, J=7.1 Hz), 1.31 (d, 4H, J=6.6 Hz), 1.44 (s, 2H), 1.56 (q, 2H, J=6.4 Hz), 2.30 (t, 2H, J=6.4 Hz), 2.53–2.42 (m, 4H), 4.81 (s, 1H), 7.27 (d, 1H, J=7.8 Hz), 7.91 (d, 1H, J=7.8 Hz), 8.49 (d, 1H, J=7.8 Hz), 8.84 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 13.9, 18.7, 22.5, 28.5, 28.9, 31.2, 40.4, 54.5, 74.5, 88.5, 122.7, 135.8, 135.9, 148.3, 150.0; MS (EI): *m/z* 272; HRMS (FAB): Calcd for $C_{18}H_{28}N_2$: 272.2252, Found: 272.2245.

4.3.6. *N,N*-Diethyl-α-(*t*-butylethynyl-3-pyridyl)-methanamine (5f). Pale yellow oil; IR (neat) 2912, 2207 cm^{-1}; ^{1}H

NMR (500 MHz, $CDCl_3$) δ 1.03 (t, 6H, J=7.1 Hz), 1.30 (t, 9H, J=13.7 Hz), 2.40–2.53 (m, 4H), 4.79 (s, 1H), 7.27 (d, 1H, J=7.8 Hz), 7.90 (d, 1H, J=7.8 Hz), 8.49 (d, 1H, J=7.8 Hz), 8.85 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 27.6, 31.3, 44.4, 54.4, 72.8, 97.2, 122.7, 135.9, 148.3, 150.1; MS (EI): *m/z* 244; HRMS (FAB): Calcd for $C_{16}H_{24}N_2$ (M+H): 245.2018, Found: 245.2021.

4.3.7. *N*,*N*-Diethyl-α-[(trimethylsilyl)ethynyl-3-pyridyl]-methanamine (5g). Yellow oil; IR (neat) 2215 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.20 (d, 9H, J=14.7 Hz), 1.02 (t, 6H, J=7.1 Hz), 2.43–2.51 (m, 4H), 4.82 (s, 1H), 7.22–7.25 (m, 1H), 7.89 (d, 1H, J=7.9 Hz), 8.49 (s, 1H), 8.83 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 0.30, 13.4, 44.3, 55.1, 92.8, 100.5, 122.8, 135.1, 135.7, 148.4, 149.9; MS (EI): *m/z* 260; HRMS (FAB): Calcd for $C_{15}H_{24}N_2Si$ (M+H): 261.1787, Found: 261.1773.

4.3.8. *N*,*N*-Diethyl-α-(phenylethynyl-2-furyl)-methanamine (5h). Brown oil; IR (neat) 3066, 2281 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.09 (t, 6H, J=7.3 Hz), 2.59 (dd, 2H, J=7.0, 6.5 Hz), 2.70 (dd, 2H, J=7.3, 7.0 Hz), 5.07 (s, 1H), 6.33 (s, 1H), 6.47 (s, 1H), 7.30 (d, 3H, J=3.0 Hz), 7.40 (s, 1H), 7.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.2, 22.7, 29.7, 44.9, 51.9, 85.8, 109.0, 110.1, 122.9, 129.3, 131.8, 142.4, 152.4; MS (EI): *m/z* 253; HRMS (FAB): Calcd for $C_{17}H_{19}NO$: 253.1467, Found: 253.1471.

4.3.9. *N*,*N*-Diethyl-α-(phenylethynyl-2-thienyl)-methanamine (5i). Brown oil; IR (neat) 3071, 2289 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (t, 6H, J=7.3 Hz), 2.55 (dd, 2H, J=6.9, 6.9 Hz), 2.71 (dd, 2H, J=7.3, 7.3 Hz), 5.17 (s, 1H), 6.95 (t, 1H, J=3.7, 4.6 Hz), 7.25 (s, 2H), 7.32 (d, 3H, J=3.2 Hz), 7.49 (d, 2H, J=3.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 19.2, 44.7, 53.4, 85.7, 86.1, 123.1, 125.1, 125.6, 126.2, 128.1, 128.3, 131.8, 139.9, 145.7; MS (EI): *m/z* 269; HRMS (FAB): Calcd for $C_{17}H_{19}NS$: 269.1238, Found: 269.1245.

4.3.10. 3-Phenyl-2-propynylamine (7a).[17b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.49 (br s, 2H), 3.61 (s, 2H), 7.26 (m, 3H), 7.37 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 32.1, 82.3, 90.1, 123.1, 127.9, 128.2, 131.4; MS (EI) *m/z* 131 (M^+).

4.4. General procedure for amidation of primary propargylic amine

A Et_2O solution (3 mL) of Et_3N (101.2 mg, 1.000 mmol), 1-alkyne **1** (1.00 mmol), and $InBr_3$ (354.5 mg, 1.000 mmol) was stirred at room temperature for 1 h, followed by the addition of *N*-silyl-*N*,*O*-acetal[25] **6** (102 mg, 0.500 mmol) via a syringe. The reaction mixture was stirred until the reaction reached completion, as evidenced by GC. After completion of the reaction, the volatile components were removed under reduced pressure, and the reaction vessel was refilled with argon gas and subsequently CH_2Cl_2 (3 mL). Benzoyl chloride (127 μL, 1.10 mmol) was then added, followed by stirring for 1 h at room temperature. After the reaction, a saturated aqueous solution of $NaHCO_3$ was added to the mixture, and the organic layer was extracted with CH_2Cl_2. The combined organic layer was dried over Na_2CO_3, filtered, and concentrated in vacuum. The crude product was purified by flash column chromatography (SiO_2/hexane–AcOEt=9/1) to give the corresponding amide **7**.

4.4.1. *N*-(2-Nonynyl)-benzamide (7b). Colorless oil; IR (neat) 3465, 2931, 2199, 1675 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.85 (t, 2H, J=6.4 Hz), 1.44 (m, 9H), 2.16 (s, 2H), 4.20 (s, 2H), 7.41 (t, 2H, J=7.8 Hz), 7.48 (d, 1H, J=7.8 Hz), 7.77 (d, 2H, J=7.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 18.7, 22.5, 28.5, 30.3, 30.9, 31.3, 75.3, 84.5, 126.9, 128.5, 131.6, 134.1, 166.9; MS (EI): *m/z* 243 (M^+); HRMS (FAB): Calcd for $C_{16}H_{21}NO$ (M+H): 244.1701, Found: 244.1722.

4.4.2. *N*-(4,4-Dimethyl-2-pentynyl)-benzamide (7c). Colorless oil; IR (neat) 2977, 2218, 1670 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.19 (t, 9H, J=14.2 Hz), 4.21 (d, 2H, J=5.0 Hz), 7.42 (d, 2H, J=7.3 Hz), 7.48 (d, 1H, J=7.3 Hz), 7.76 (d, 2H, J=7.3 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 27.3, 30.3, 30.4, 73.7, 92.7, 126.9, 128.6, 131.6, 134.1, 166.9; MS (EI): *m/z* 215 (M^+); HRMS (FAB): Calcd for $C_{14}H_{17}NO$ (M+H): 216.1388, Found: 216.1404.

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Solid-phase synthesis of hydroxypiperazine derivatives using phenethylamine linker by oxidation–Cope elimination

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Abstract—A general method is reported for the parallel solid-phase synthesis of hydroxypiperazine derivatives based on the oxidation–Cope elimination of polymer-bound phenethylamine linker with *m*-CPBA. The key intermediate of phenethylamine *N*-oxide resins was separable on solid-phase for subsequent β-elimination, from which the desired hydroxypiperazine products could be obtained in high purities and yields without any significant contamination at 90 °C for 2 h. The utility of the methodology for solid-phase synthesis of general hydroxylamines was also investigated using the same linker. The progress of reactions could be monitored on polymer bound intermediates by ATR-FTIR spectroscopy on single bead. The desired products were obtained in good six-step overall yields upon cleavage from the resins and were characterized by LC/MS, ^{1}H NMR, and ^{13}C NMR spectroscopy.

1. Introduction

Solid-phase synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Hydroxylamines provide scaffold, on which pharmacophore can be arranged to yield potent and selective drugs.[2] Therefore, many hydroxylamine derivatives have been reported, since a variety of hydroxylamine derivatives possess drug-like characteristics and exhibit biological activities similar to their corresponding amines as a bioisostere.[3] Especially, hydroxypiperazine, a kind of hydroxylamine, showed good antimicrobial activity.[4] However, hydroxylamine derivatives have scarcely been reported in the research field of drug-like library construction by solid-phase synthesis, as compared with their tertiary amine analogues.[5] As only example, Kurth reported about solid-phase synthesis of hydroxylamines using REM (polymer-bound benzyl arylate) resin by β-elimination strategy, which is a good example of traceless linker.[6] The β-elimination strategy as a traceless cleavage method is very useful for construction of tertiary amine libraries and *N*,*N*-disubstituted hydroxylamines derivatives using REM resin. However, the synthesis of hydroxylamines on REM resin was accomplished through premature elimination reaction during the oxidation procedure with *meta*-chloroperbenzoic acid (*m*-CPBA) to generate *N*-oxide intermediate at room temperature. As the results of in situ β-elimination of *N*-oxide intermediate, were contaminated with *meta*-chlorobenzoic acid (*m*-CBA) and excess *m*-CPBA. Consequently further purification steps such as extraction and column chromatography were needed to obtain pure hydroxylamines after cleavage from the REM resins. To solve this problem, therefore, we tried to find more stable linker for the solid-phase synthesis of hydroxylamine derivatives under *m*-CPBA oxidation condition at room temperature because we needed to develop a facile and rapid solid-phase approach for construction of drug-like hydroxypiperazine derivatives as a part of our research on drug discovery program.[7]

Herein, we would like to report a solid-phase synthesis of hydroxypiperazine derivatives using phenethylamine linker. The polymer bound phenethylamine *N*-oxide, produced by oxidation reaction with *m*-CPBA on the phenethylamine resin, served as key intermediate. And further β-elimination reaction on this phenethylamine *N*-oxide resin under thermal condition, generated the desired various hydroxypiperazine derivatives with high purities. And we also attempted to develop the methodology of solid-phase synthesis of general hydroxylamine derivatives using the same linker.

Keywords: Solid-phase; Hydroxypiperazine; Phenethylamine linker; Oxidation–Cope.
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Our initial studies were concentrated to the design of thermally more stable linker than REM resin under *m*-CPBA oxidation condition. To this end, we decided to examine *N*-oxide formation from polymer bound phenethylamine under the same condition in hope that Cope elimination reaction would not occur at room temperature but take place at a higher temperature. The pK_a value of β-proton in REM resin **2** is about 25. On the other hand, the value of phenethylamine resin **1** is about 40, much higher than that of REM resin as shown in Figure 1.[8] That is to say, the phenethylamine *N*-oxide linker was expected to need much higher energy for β-elimination reaction, compared with REM resin. Fortunately we confirmed that the results of the experiment coincided with our expectation.

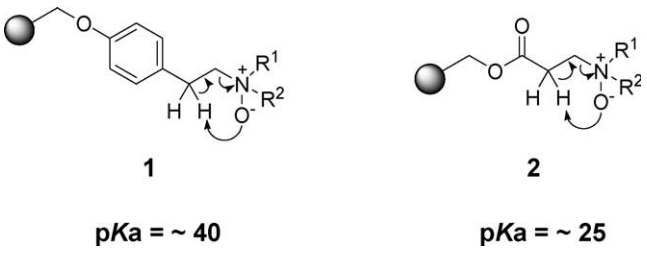


Figure 1. Comparision of stability toward β-elimination reaction.

As the first step, we selected Merrifield resin **3** as a polymer support for the preparation of phenethylamine, since the chloride group in the Merrifield resin **3** is suitable for the introduction of 4-hydroxyphenethyl alcohol through ether formation under the condition of sodium methoxide in *N*,*N*-dimethylacetamide (DMA) at 50 °C. The hydroxyl group of phenethyl alcohol resin **4** was changed to bromide in the presence of triphenylphosphine in carbon tetrabromide to give phenethylbromide resin, the formation, of which was confirmed by the disappearance of the hydroxyl group stretching frequency at 3350 cm^{-1} (Fig. 2, A and B). The phenethylbromide resin **5** was transformed to the polymer bound piperazine **6** by a nucleophilic substitution reaction with piperazine in the presence of triethylamine as a base in *N*,*N*-dimethylformamide (DMF) at 50 °C. To perform further derivatization on the piperazine resin **6**, we examined the reaction with various electrophiles, such as acid halides and sulfonyl halides, to introduce amide and sulfonamide functional groups on the nitrogen atom (N^a) of piperazine resin **6**. The completion of the reaction was confirmed by a negative chloranil test[9] with the substituted (N^a) phenethylpiperazine resins **7**. And we could successfully obtain the desired various phenethylpiperazine *N*-oxide resins **8** from the substituted (N^a) phenethylpiperazine resins **7** by oxidation reaction with *m*-CPBA at room temperature. Finally, to confirm formation of the final products **9**, we performed the β-elimination reaction of the polymer bound *N*-oxide resins **8** in toluene at 90 °C for 2 h, and we could obtain the desired various hydroxypiperazine derivatives in high purities and yields without any significant impurities from the key intermediate *N*-oxide resins **8**. The key intermediates, the phenethylpiperazine *N*-oxide resins **8**, were prepared in a six-step procedure starting from the Merrifield resin **3**, as shown in Scheme 1. As listed in Table 1, variously substituted (N^a) hydroxypiperazine derivatives were successfully synthesized in high six-step overall yields from Merrifield resin **3** with high purities by oxidation–Cope elimination of the phenethylpiperazine *N*-oxide resin **8**. The progress of these reactions could be monitored by ATR-FTIR spectroscopy on single beads (Fig. 2, C–E).

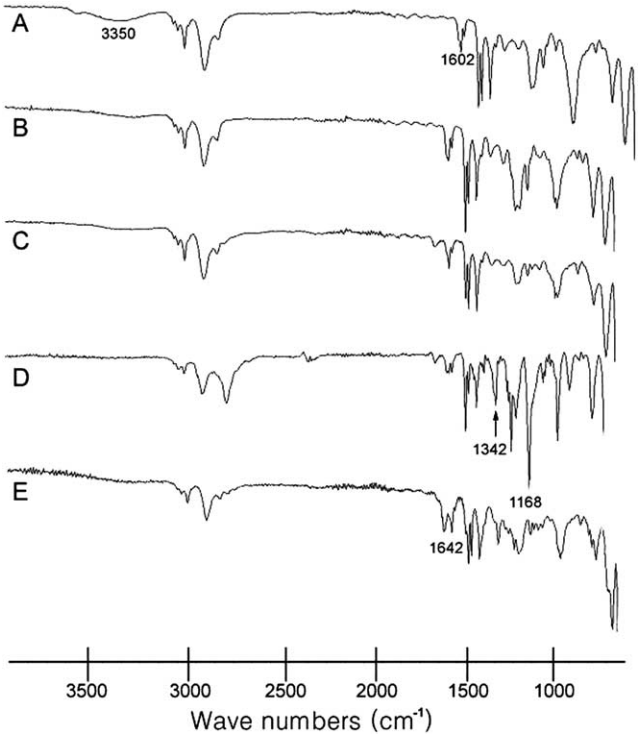
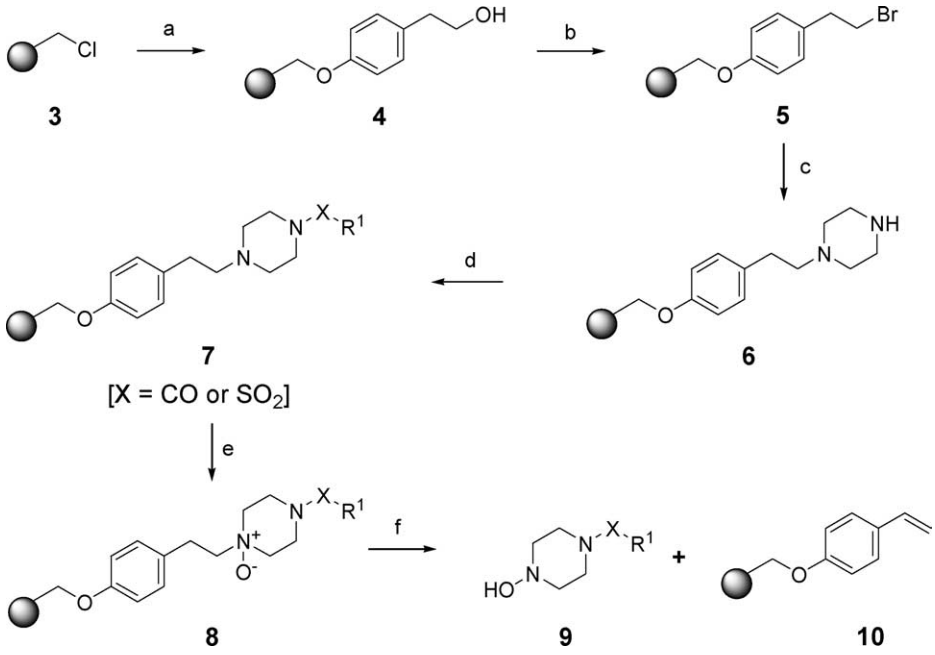


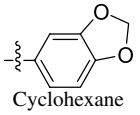
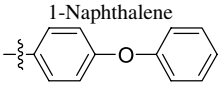
Figure 2. ATR-FTIR spectra on single bead of resin **4** (A), **5** (B), **6** (C), **7c** (D) and **7h** (E).

Further, we attempted to develop the methodology for solid-phase synthesis of general hydroxylamine derivatives using the same linker. The phenethylbromide resin **5** was transformed to the polymer bound secondary amines **11** by a nucelophilic substitution reaction with various primary aliphatic and aromatic amines in the presence of triethylamine as base in DMF at 50 °C. The secondary phenethylamine resins **11** were changed to the polymer bound tertiary amines **12** by reductive alkylation with various aldehyde and boran–pyridine complex. The completion of this step was also checked by a negative chloranil test. With the tertiary phenethylamine resins **12**, we examined the oxidation reaction with *m*-CPBA to obtain the desired phenethylamine *N*-oxide resins **13**. And we could successfully obtain the desired phenethylamine *N*-oxide resins **13** as the key intermediate. Finally, to confirm formation of the final products **14**, we carried out thermal reaction with the polymer bound *N*-oxide resins **13** for β-elimination reaction in toluene at 90 °C for 2 h, as shown in Scheme 2. By using this sequence of reactions, we could obtain the desired hydroxylamine derivatives **14** in relatively good six-step overall yields and purities from Merrifield resin **3**. However, the yields of most of the desired hydroxylamine derivatives **14** by this multistep synthetic method on solid phase were lower than those of hydroxypiperazines **9**. The reason was assumed that substituted hydroxyamines **14** were partly oxidized to the corresponding nitrone compounds **15** under the standard condition. In fact, we could identify



Scheme 1. Reagents and conditions: (a) 4-hydroxyphenethyl alcohol, NaOMe, DMA, 50 °C, 18 h; (b) CBr_4, PPh_3, CH_2Cl_2, rt, 12 h; (c) piperazine, TEA, DMF, 50 °C, 18 h; (d) acid halide or sulfonyl halide, TEA, DMF, rt, 18 h; (e) *m*-CPBA, CH_2Cl_2, rt, 2 h; (f) toluene, 90 °C, 2 h.

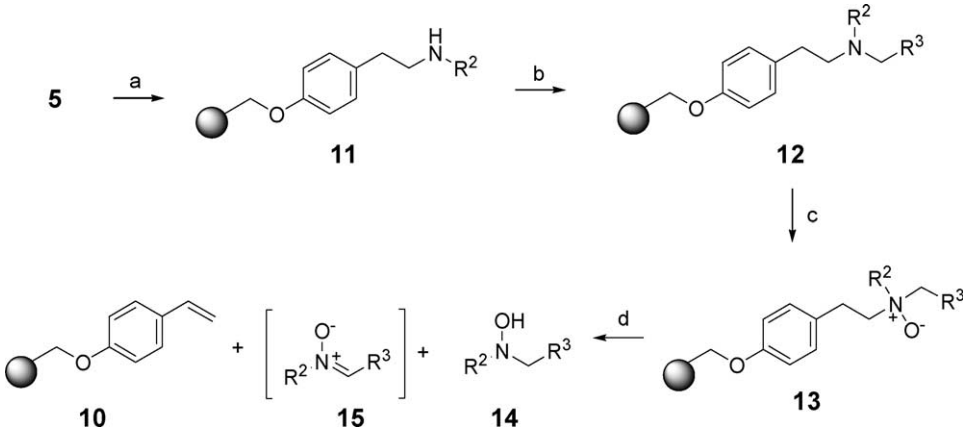
Table 1

Product	X	R^1	Purity[a] (%)	Yield[b] (%)	Product	X	R^1	Purity (%)	Yield (%)
9a	–SO_2–	4-MeO-Ph	99	50	**9g**	–CO–	4-MeO-Ph	98	39
9b	–SO_2–	4-NO_2-Ph	94	57	**9h**	–CO–	4-NO_2-Ph	99	49
9c	–SO_2–	4-Cl-Ph	97	45	**9i**	–CO–		97	24
9d	–SO_2–	2,4,6-Triisopropyl-Ph	95	33	**9j**	–CO–	Cyclohexane	97	55
9e	–SO_2–	1-Naphthalene	96	57	**9k**	–CO–	1-Naphthalene	99	29
9f	–SO_2–	4-*tert*-Bu-Ph	93	55	**9l**	–CO–		97	24

[a] Calculated from integrated peak areas recorded by LC/MS of the crude products.
[b] Six-step overall yields from Merrifield resin **3** (loading capacity of the resin **3** in 1.6 mmol/g).

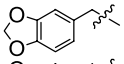
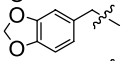
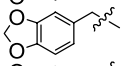
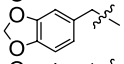
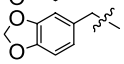
the nitrones **15** by LC/MS spectroscopy of the crude products (Table 2).

In summary, we succeeded in the solid-phase synthesis of hydroxypiperazines **9** and hydroxylamines **14** by using phenethylamine *N*-oxide resins **8**, **13** as the key intermediate. The key intermediates of *N*-oxide resins **8**, **13** were separable on solid phase for subsequent β-elimination



Scheme 2. Reagents and conditions: (a) amine, TEA, 50 °C, 18 h; (b) aldehyde, boran–pyridine complex, DMF/EtOH (4:1), rt, 3 days; (c) *m*-CPBA, CH_2Cl_2, rt, 2 h; (d) toluene, 90 °C, 2 h.

Table 2

Product	R^2	R^3	Purity (%)		Yield (%)[a]	Product	R^2	R^3	Purity (%)		Yield (%)
14a	Bn	Ph	82[b]	93[c]	40	**14f**		Ph	92	95	33
14b	Bn	4-F-Ph	81	97	38	**14g**		4-F-Ph	86	97	34
14c	Bn	4-NO_2-Ph	49	96	17	**14h**		4-MeO-Ph	88	88	23
14d	Bn	4-^{t}Bu-Ph	82	92	35	**14i**		4-^{t}Bu-Ph	74	93	24
14e[d]	Bn	Isopropyl	68	—	22	**14j**[d]		Isopropyl	55	—	20

[a] Six-step overall yields from Merrifield resin **3** after purification (loading capacity of the resin **3** in 1.6 mmol/g).
[b] Calculated from integrated peak areas recorded by LC/MS of the isolated products.
[c] Calculated from integrated peak areas recorded by LC/MS of the crude products.
[d] *Compounds*. **14e** and **14j** compounds could be not isolated from mixture of the hydroxylamine and nitrone.

reaction, from which the desired hydroxypiperazine and hydroxylamine products **9**, **14** could be obtained without any significant contamination at 90 °C. Especially, the hydroxypiperazine derivatives could be obtained in high six-step overall yields with high purities from Merrifield resin **3** without any purification step after the thermal cleavage step. With the high yields and purities, this method is the versatile approach to develop combinatorial libraries of hydroxypiperazine and hydroxylamine derivatives useful for the synthesis of biologically interesting compounds, which is a subject for our current research.

2. Experimental

2.1. Materials and methods

The polystyrene Merrifield resin (1.6 mmol/g, 1% cross-linking, 100–200 mesh) was obtained from NovaBiochem. Solvents were purchased from Merck and were anhydrous and HPLC grade. Reactions, filtrations, and washings were carried out on a MiniBlock (Bohdan). Solvent evaporation was performed on a GeneVac Atlas HT-4 centrifugal evaporator. Crude products were purified by parallel chromatography using QuadFlash silica-cartridges (Biotage Catalog no. QK0-1107-1504L). All of the intermediate resins were monitored by ATR-FTIR (SensIR Technology). The structures of final products were confirmed by ^{1}H NMR and ^{13}C NMR (Bruker AMX-500 FT NMR), and LC/MS spectroscopy. LC/MS data were recorded on a Waters ZQ electrospray mass spectrometer (EI) equipped with PDA (200–600 nm) detection using XTerraMS column (C_{18}, 5 μM, 4.6×100 mm) from Waters (UK). Typical gradient were 5–95% MeCN/H_2O containing 0.1% trifluoroacetic acid.

2.2. Procedure for the synthesis of the phenethyl alcohol resin 4

Sodium methoxide (1.30 g, 24.0 mmol) was added to a solution of 4-hydroxyphenethyl alcohol (3.32 g, 24.0 mmol) in cold DMA (80 mL) at 0 °C. The solution was stirred at room temperature for 2 h and Merrifield resin **3** (5 g, 8.0 mmol, loading 1.6 mmol/g: chloromethylated 1% vinylbenzene–styrene copolymer) was added. The resulting suspension was stirred for 18 h at 50 °C. The phenethyl alcohol resin **4** was filtered and washed with DMF (2× 100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.3. Procedure for the synthesis of the phenethylbromide resin 5

To a suspension of phenethyl alcohol resin **4** (5 g, 8.0 mmol) in dry DCM (dichloromethane: 60 mL) was added triphenylphosphine (10.49 g, 40 mmol), followed by slow addition of carbon tetrabromide (13.27 g, 40 mmol) in dry DCM at 0 °C. The suspension was shaken for 12 h at room temperature under Ar gas. The phenethylbromide resin **5** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.4. Procedure for the synthesis of the polymer-bound piperazine resin 6

The phenethylbromide resin **5** (2.0 g, 3.2 mmol) was suspended in dry DMF (30 mL), and piperazine (1.4 g, 16.0 mmol) and TEA (2.23 mL, 16.0 mmol) were successively added. The mixture was shaken for 18 h at 50 °C. The polymer-bound piperazine resin **6** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.5. Procedure for the synthesis of the resin 7a

The polymer-bound piperazine resin **6** (100 mg, 0.16 mmol) was swollen in DMF (4 mL) and TEA (0.07 mL, 0.45 mmol) followed by addition of 4-methoxybenzene-sulfonyl chloride (92 mg, 0.45 mmol). After the reaction was shaken for 18 h at room temperature, the sulfonyl piperazine resin **7a** was filtered and washed with DMF (2×20 mL), DCM (2×20 mL) and MeOH (2×20 mL) and dried under high vacuum.

2.6. Representative procedure for the oxidation and Cope elimination steps 9a

To the pre-swollen sulfonyl piperazine resin **7a** (100 mg, 0.16 mmol) in DCM (4 mL) was added *m*-CPBA (158 mg, 0.64 mmol, ~70%) at 0 °C. The resin was agitated for 2 h at

room temperature and washed with 3% TEA/DMF (3×20 mL), DMF (3×20 mL), MeOH (3×20 mL), and then DCM (20 mL). After drying under high vacuum for 30 min, the resin **8a** was heated in 4 mL of toluene at 90 °C for the Cope elimination during 2 h. The resin was filtered off and washed with toluene (2×3 mL) and DCM (2×3 mL). The combined filtrate was concentrated under high vacuum and afforded the desired sulfonylpiperazine derivatives with high purities.

2.6.1. 4-(4-Methoxybenzenesulfonyl)piperazin-1-ol 9a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=7.0 Hz), 7.00 (d, 2H, J=7.0 Hz), 3.88 (s, 3H), 3.53 (m, 2H), 3.16 (m, 2H), 2.48–2.42 (m, 1H), 1.80 (br s, 2H), 1.70 (br s, 3H), 1.51 (m, 2H), 1.25 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.23, 129.86, 127.14, 114.35, 56.36, 55.65, 44.09; LC/MS (ESI) m/z 273 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{16}N_2O_4S$, 272.0831; found, 272.0828.

The following compounds were synthesized using the above protocol.

2.6.2. 4-(4-Nitrobenzenesulfonyl)piperazin-1-ol 9b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, 2H, J=8.6 Hz), 7.96 (d, 2H, J=8.6 Hz), 3.57 (br, 2H), 3.21 (br, 2H), 2.85 (br, 4H); LC/MS (ESI) m/z 288 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{10}H_{13}N_3O_5S$, 287.0576; found, 287.0579.

2.6.3. 4-(4-Chlorobenzenesulfonyl)piperazin-1-ol 9c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, 2H, J=8.5 Hz), 7.52 (d, 2H, J=8.5 Hz), 3.52 (m, 2H), 3.18 (m, 2H), 2.84 (t, 2H, J=8.9 Hz), 2.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.71, 134.30, 129.53, 129.10, 56.21, 43.83; LC/MS (ESI) m/z 277 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{10}H_{13}ClN_2O_3S$, 276.0335; found, 276.0339.

2.6.4. 4-(2,4,6-Triisopropylbenzenesulfonyl)piperazin-1-ol 9d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.14 (m, 1H), 3.52 (m, 2H), 3.22 (m, 2H), 3.06 (t, 2H, J=10.8 Hz), 2.90 (m, 1H), 2.72 (t, 2H, J=10.1 Hz), 1.26 (s, 9H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.54, 151.89, 129.33, 124.00, 56.63, 42.58, 34.19, 29.34, 24.87, 23.54; LC/MS (ESI) m/z 369 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{19}H_{32}N_2O_3S$, 368.2134; found, 368.2135.

2.6.5. 4-(Naphthalene-1-sulfonyl)piperazin-1-ol 9e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.99–7.92 (m, 3H), 7.75–7.63 (m, 3H), 3.61 (br, 2H), 2.16 (br, 2H), 2.80 (br, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.99, 132.82, 132.22, 129.39, 129.25, 129.12, 129.00, 127.97, 127.70, 122.84, 56.35, 44.06, 29.71; LC/MS (ESI) m/z 293 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{16}N_2O_3S$, 292.0882; found, 292.0883.

2.6.6. 4-(4-*tert*-Butylbenzenesulfonyl)piperazin-1-ol 9f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, 2H, J=8.4 Hz), 7.54 (d, 2H, J=8.4 Hz), 3.56 (br, 2H), 3.18 (br, 2H), 2.82 (br, 2H), 2.71 (br, 2H), 1.33 (s, 9H); LC/MS (ESI) m/z 299 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{22}N_2O_3S$, 298.4011; found, 298.4014.

2.6.7. (4-Hydroxypiperazin-1-yl)-(4-methoxyphenyl) methanone 9g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, 2H, J=7.2 Hz), 6.92 (d, 2H, J=7.2 Hz), 3.84 (s, 3H), 3.22 (br, 4H), 2.67 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.36, 160.97, 129.15, 113.81, 57.50, 55.38; LC/MS (ESI) m/z 237 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{16}N_2O_3$, 236.1161; found, 236.1163.

2.6.8. (4-Hydroxypiperazin-1-yl)-(4-nitrophenyl)methanone 9h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (d, 2H, J=8.0 Hz), 7.58 (d, 2H, J=8.0 Hz), 3.29 (br, 2H), 3.14 (br, 4H), 2.63 (br, 2H); LC/MS (ESI) m/z 252 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{13}N_3O_4$, 251.0906; found, 251.0906.

2.6.9. Benzo[1,3]dioxol-5-yl-(4-hydroxypiperazin-1-yl) methanone 9i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dd, 1H, J=7.9, 1.6 Hz), 6.90 (d, 1H, J=1.6 Hz), 6.83 (d, 1H, J=7.9 Hz), 6.00 (s, 2H), 4.41–4.10 (m, 1H), 3.21 (m, 5H), 2.66 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.71, 134.30, 129.53, 129.10, 56.21, 43.83; LC/MS (ESI) m/z 251 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{14}N_2O_4$, 250.0954; found, 250.0956.

2.6.10. Cyclohexyl-(4-hydroxypiperazin-1-yl)methanone 9j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (m, 1H), 3.86 (m, 1H), 3.29–3.21 (m, 3H), 2.93 (t, 1H, J=10.9 Hz), 2.60 (m, 2H), 2.48–2.42 (m, 1H), 1.80 (br s, 2H), 1.70 (br s, 3H), 1.51 (m, 2H), 1.25 (m, 3H); LC/MS (ESI) m/z 213 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{20}N_2O_2$, 212.2887; found, 212.2886.

2.6.11. (4-Hydroxypiperazin-1-yl)naphthalen-1-yl-methanone 9k. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90–7.87 (m, 3H), 7.56–7.38 (m, 4H), 3.40 (br, 4H), 2.98 (br, 2H), 2.82 (br, 2H); LC/MS (ESI) m/z 257 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{16}N_2O_2$, 256.1212; found, 256.1215.

2.6.12. (4-Hydroxypiperazin-1-yl)-(4-phenoxyphenyl) methanone 9l. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41–7.36 (m, 4H), 7.17 (m, 1H), 7.05 (d, 2H, J=7.7 Hz), 7.00 (d, 2H, J=8.6 Hz), 4.48–4.37 (m, 1H), 3.91–3.84 (m, 1H), 3.22 (m, 5H), 2.67 (m, 2H); LC/MS (ESI) m/z 299 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{17}H_{18}N_2O_3$, 298.1317; found, 298.1317.

2.7. Procedure for the synthesis of polymer-bound secondary amine resins 11a

The phenethylbromide resin **5** (2 g, 3.2 mmol) was suspended in dry DMF (30 mL), and benzyl amine (1.75 mL, 16.0 mmol) and triethyl amine (2.23 mL, 16.0 mmol) were successively added. The mixture was shaken for 18 h at 50 °C. Secondary amine resin **11a** was filtered and washed with DMF (2×100 mL), DCM (2×100 mL) and MeOH (2×100 mL), and dried under high vacuum.

2.8. Procedure for the reductive alkylation of polymer-bound secondary amine resin 12a

Secondary amine resin **11a** (100 mg, 0.16 mmol) was swollen in DMF/EtOH (4:1, 4 mL) and followed by addition of benzaldehyde (0.13 mL, 1.28 mmol) and

borane–pyridine complex (0.13 mL, 1.28 mmol). After the reaction was shaken for three days at room temperature, the tertiary amine resin **12a** was filtered and washed with DMF (2×20 mL), DCM (2×20 mL) and MeOH (2×20 mL) and dried under high vacuum.

2.9. Procedure for the oxidation and Cope elimination steps 14a

To pre-swollen tertiary amine resin **12a** (100 mg, 0.16 mmol) in DCM (4 mL) was added the *m*-CPBA (158 mg, 0.64 mmol, ~70%) at 0 °C. The resin was agitated for 3 h at room temperature and washed with 3% TEA(triethylamine)/DMF (3×20 mL), DMF (3×20 mL), MeOH (3×20 mL), and then DCM (20 mL). After drying under high vacuum for 30 min, the resin **13a** was heated in 4 mL of toluene at 90 °C for the Cope elimination during 2 h. The resin was filtered off and washed with toluene (2×3 mL) and DCM (2×3 mL).

The combined filtrate was evaporated and purified by silica gel column chromatography.

2.9.1. *N*,*N*-Dibenzylhydroxylamine 14a. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.26 (m, 10H), 3.81 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.48, 129.52, 128.34, 127.42, 64.04; LC/MS (ESI) *m*/*z* 214 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{15}NO$, 213.1154; found, 213.1155.

The following compounds were synthesized using the above protocol.

2.9.2. *N*-Benzyl-*N*-(4-fluorobenzyl)hydroxylamine 14b. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34–7.29 (m, 7H), 7.01 (t, 2H, J=8.7 Hz), 3.82 (s, 2H), 3.79 (s, 2H); LC/MS (ESI) *m*/*z* 232 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{14}FNO$, 231.1059; found, 231.1062.

2.9.3. *N*-Benzyl-*N*-(4-nitrobenzyl)hydroxylamine 14c. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, 2H, J=8.5 Hz), 7.55 (d, 2H, J=8.5 Hz), 7.39–7.33 (m, 5H), 3.98 (s, 4H); LC/MS (ESI) *m*/*z* 259 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{14}H_{14}N_2O_3$, 258.1004; found, 258.1003.

2.9.4. *N*-Benzyl-*N*-(4-*tert*-butylbenzyl)hydroxylamine 14d. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.32 (m, 6H), 7.27–7.25 (m, 3H), 3.79 (s, 2H), 1.29 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.33, 137.56, 134.38, 129.48, 129.26, 128.31, 127.37, 125.25, 64.00, 63.67, 34.50, 31.37; LC/MS (ESI) *m*/*z* 270 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{18}H_{23}NO$, 269.1780; found, 269.1781.

2.9.5. *N*-Benzyl-*N*-isopropylhydroxylamine 14e. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.33 (m, 5H), 3.79 (s, 2H), 2.50 (d, 2H, J=7.0 Hz), 1.93 (m,1H), 0.93 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 130.2, 129.1, 128.1, 68.4, 65.6, 26.3, 20.9; LC/MS (ESI) *m*/*z* 180 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{17}NO$, 179.1310; found, 179.1312.

2.9.6. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-benzylhydroxylamine 14f. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 5H), 6.87 (d, 1H, J=0.9 Hz), 6.79 (dd, 1H, J=7.9, 0.9 Hz), 6.76 (d, 1H, J=7.9 Hz), 5.93 (s, 2H), 3.83 (s, 2H), 3.76 (s, 2H); LC/MS (ESI) *m*/*z* 258 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{15}NO_3$, 257.1052; found, 257.1050.

2.9.7. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-fluorobenzyl) hydroxylamine 14g. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32–7.29 (m, 2H), 7.01 (t, 2H, J=8.6 Hz), 6.85 (s, 1H), 6.78 (d, 1H, J=7.8 Hz), 6.75 (d, 1H, J=7.8 Hz), 5.93 (s, 2H), 3.77 (s, 2H), 3.74 (s, 2H); LC/MS (ESI) *m*/*z* 276 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{15}H_{14}FNO_3$, 275.0958; found, 275.0961.

2.9.8. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-methoxybenzyl)hydroxylamine 14h. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28–7.25 (m, 2H), 6.87–6.86 (m, 3H), 6.78–6.75 (m, 2H), 5.92 (d, 2H, J=7.8 Hz), 3.79–3.78 (m, 5H), 3.75 (s, 2H); LC/MS (ESI) *m*/*z* 288 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{11}H_{16}N_2O_4S$, 287.1158; found, 287.1159.

2.9.9. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-(4-*tert*-butylbenzyl)hydroxylamine 14i. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, 2H, J=8.2 Hz), 7.27 (d, 2H, J=8.2 Hz), 6.87 (d, 1H, J=0.8 Hz), 6.78 (dd, 1H, J=7.9, 0.8 Hz), 6.75 (d, 2H, J=7.9 Hz), 5.93 (s, 2H), 3.79 (s, 2H), 3.73 (s, 2H), 1.30 (s, 9H); LC/MS (ESI) *m*/*z* 314 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{19}H_{23}NO_3$, 313.1678; found 313.1676.

2.9.10. *N*-Benzo[1,3]dioxol-5-ylmethyl-*N*-isopropylhydroxylamine 14j. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, 1H, J=1.1 Hz), 6.79 (dd, 1H, J=7.9, 1.1 Hz), 6.76 (d, 1H, J=7.9 Hz), 5.94 (s, 2H), 3.71 (s, 2H), 2.48 (d, 2H, J=6.9 Hz), 1.96–1.89 (m, 1H), 0.94 (s, 3H), 0.92 (s, 3H); LC/MS (ESI) *m*/*z* 224 $[M+H]^+$; HRMS (ES): $[M]^+$ calcd for $C_{12}H_{17}NO_3$, 223.1208; found, 223.1207.

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Stereoselective Mannich-type reaction of chlorotitanium α-phenylseleno esters enolates with aromatic aldimines

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Abstract—The stereoselective Mannich-type reaction of α-phenylseleno chlorotitanium enolates with aromatic aldimines is described. The corresponding α-phenylseleno-β-amino esters were obtained in good yields and with moderate to good diastereoselectivity. A rationale for the predominant *syn* selectivity based on a chelated cyclic transition state is suggested. The obtained compounds are useful synthetic tools and direct precursors of new α-phenylseleno-β-lactams.

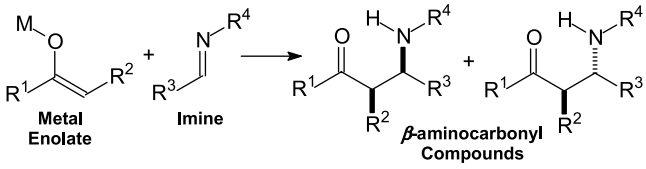
1. Introduction

β-Amino acids and their derivatives,[1] although far less abundant in nature than their α-amino analogues, are an important class of building blocks for the synthesis of natural products and therapeutics that exhibit cytotoxic properties including antifungal and antibiotics agents.[2] For example, β-amino acids are the key precursors in the synthesis of medicinally important β-lactam antibiotics[3] and β-peptides, which exhibit a remarkably stable secondary structures and high resistance to peptidases.[4] Recently, interest in α-seleno-β-amino esters has increased considerably due to their utility as precursors of modified β-amino esters and oligopeptides.[5]

Among the different methods found in the literature for the stereoselective synthesis of β-amino acids, enolate addition to imines (the Mannich-type reaction) has received special attention and much efforts employing a range of metal enolates[6] including the neutral silyl enolates[7] have been devoted to its development in a stereoselective manner.

The Mannich-type reaction provides an opportunity to control the relative stereochemistry of two stereogenic centers generated during the course of the reaction at both α- and β-positions of the β-aminocarbonyl system (Scheme 1).

Due to the importance of organoselenium compounds as building blocks in organic synthesis,[8] we have dedicated efforts to develop new methods for their preparation and their applications in organic reactions.[9] The presence of the organoselenium functional group also provides an entry into radical chemistry.[8]



Scheme 1. The Mannich-type reaction.

2. Results and discussion

In connection with our research interest on the reactivity of organoselenium compounds bearing an ester function,[10] their use as intermediates in organic synthesis[11] and taking into account the previous reports of stereoselective addition of chlorotitanium enolates to imines,[12] we would like to report herein our results on the Mannich-type reaction between a α-phenylseleno chlorotitanium enolates and aromatic aldimines, which affords preferentially the *syn* α-phenylseleno-β-amino esters in reasonable to good diastereoselectivity. Although there are examples of classical aldol reaction to prepare α-phenylseleno-β-hydroxy ketones or esters[13] as well as a few different methods to prepare α-phenylseleno-β-amino esters,[5a,14] to our best knowledge, this is the first example of a Mannich-type

Keywords: Mannich reaction; Phenylseleno esters; α-Seleno-β-amino esters; Stereoselective.
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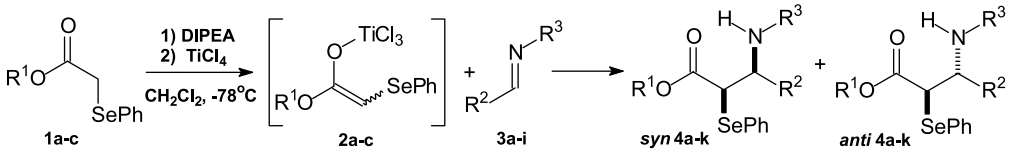


Scheme 2. Stereoselective preparation of *syn* α-phenylseleno-β-amino esters **4a–k**.

reaction of α-phenylseleno chlorotitanium enolates with aromatic aldimines (see Scheme 2).

Our initial studies were focused on the development of an optimum set of reaction conditions. The α-phenylseleno ethyl ester **1a** was readily enolized in CH_2Cl_2 with $TiCl_4$ (1 equiv) and diisopropylethylamine (DIPEA, 1 equiv) at −78 °C. After the addition of aldimine **3a** (1 equiv) the desired product **4a** was obtained in 37% yield as a mixture in 90:10 ratio of the *syn* and *anti* diastereoisomers, respectively (Table 1, entry 1).

The effect of the temperature in this reaction is noteworthy on the diastereoselectivity. When the reaction was performed at −50 °C or at −23 °C, a decrease of selectivities were observed (entries 2 and 3). Experiments carried out in presence of 1.2 and 1.5 equiv of both $TiCl_4$ and *i*-Pr_2NEt also resulted in low yields of desired products, although with the same preferential selectivity for the *syn*-isomer (entries 4 and 5). The use of 2 equiv of both $TiCl_4$ and *i*-Pr_2NEt allowed an appreciable improvement on the yields without affecting the diastereoselectivity (entry 6). At higher stoichiometry of $TiCl_4$ and *i*-Pr_2NEt, no improvement on the yield and on the diastereoselectivity was observed (entry 7). This best-achieved condition (2 equiv of $TiCl_4$ and *i*-Pr_2NEt) was extended for the reactions of α-phenylseleno ester enolates **2a–c** with the aromatic aldimines **3a–i**. The results are summarized in Table 1.

All reactions showed reasonable yields and diastereoselectivity; even the reactions performed with electron-rich aldimines (entries 8, 9, 12 and 16) were successful, except the reaction of enolate **2a** with the benzylidene benzylamine **3i** were unsuccessful and none of desired product was isolated (entry 18).

The influence of the R^1 group in the α-phenylseleno esters **1a–c** in the reactions with the aldimine **3a** showed that the diastereoselectivity seems not to be significantly affected by the bulkiness of R^1 (Et, *i*-Pr, Me; entries 6, 13 and 15, respectively).

The diastereomeric ratios were determined by the ^1H NMR spectroscopy based on the relative integration curves of the distinguishable β-hydrogens for the *syn*- and *anti*-isomers in the crude mixture. Although the relative stereochemistry of acyclic α-phenylseleno-β-amino carbonyl compounds can not be unambiguously determined based on the chemical shifts or by the values of coupling constants, a comparison with the similar α-phenylseleno-β-amino-carbonyl derivatives can be made. In this way, the relative stereochemistry of compounds **4a–k** was assigned by the correlation of the chemical shifts and coupling constant data with similar compounds already described in the literature.[14]

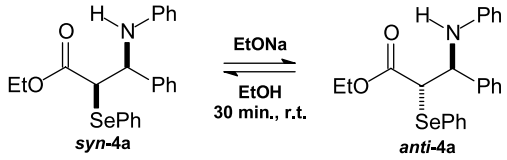
For the analogous α-phenylseleno-β-alkylamino esters, the H_β hydrogen of the *syn*-isomer appears at higher chemical shift related to the *anti*-isomer. Additionally, the vicinal coupling constant $^3J_{H\alpha-H\beta}$ for the *syn*-isomer shows smaller value than the *anti*-isomer.[14] These chemical correlations are in agreement with the major isomer obtained by us and the relative stereochemistry of the major isomer was suggested as being syn.[15]

Table 1. α-Phenylseleno-β-amino esters produced via Scheme 2

Entry	Ester **1**		Aldimine **3**			Equiv	Temperature (°C)	**4**	Yield (%)[a]	*syn*/*anti* ratio[b]
		R^1		R^2	R^3	$TiCl_4$				
1	**1a**	C_2H_5	**3a**	Ph	Ph	1	−78	**4a**	37	90:10
2	**1a**	C_2H_5	**3a**	Ph	Ph	1	−50	**4a**	43	75:25
3	**1a**	C_2H_5	**3a**	Ph	Ph	1	−23	**4a**	45	50:50
4	**1a**	C_2H_5	**3a**	Ph	Ph	1.2	−78	**4a**	47	90:10
5	**1a**	C_2H_5	**3a**	Ph	Ph	1.5	−78	**4a**	53	90:10
6	**1a**	C_2H_5	**3a**	Ph	Ph	2	−78	**4a**	68	90:10
7	**1a**	C_2H_5	**3a**	Ph	Ph	3.0	−78	**4a**	67	90:10
8	**1a**	C_2H_5	**3b**	4-(CH_3)–C_6H_4	Ph	2	−78	**4b**	79	83:17
9	**1a**	C_2H_5	**3c**	4-(CH_3O)–C_6H_4	Ph	2	−78	**4c**	87	83:17
10	**1a**	C_2H_5	**3d**	4-(Cl)–C_6H_4	Ph	2	−78	**4d**	77	75:25
11	**1a**	C_2H_5	**3e**	4-(Cl)–C_6H_4	4-(Cl)–C_6H_4	2	−78	**4e**	72	83:17
12	**1a**	C_2H_5	**3f**	Ph	4-(CH_3O)–C_6H_4	2	−78	**4f**	73	70:30
13	**1b**	*i*-C_3H_7	**3a**	Ph	Ph	2	−78	**4g**	71	83:17
14	**1b**	*i*-C_3H_7	**3d**	4-(Cl)–C_6H_4	Ph	2	−78	**4h**	74	83:17
15	**1c**	CH_3	**3a**	Ph	Ph	2	−78	**4i**	65	83:17
16	**1a**	C_2H_5	**3g**	3,4-(O–CH_2–O)-C_6H_3	Ph	2	−78	**4j**	74	90:10
17	**1a**	C_2H_5	**3h**	2-Furyl	Ph	2	−78	**4k**	67	66:34
18	**1a**	C_2H_5	**3i**	Ph	Bn	2	−78	**4l**	—	—

[a] Isolated yields of the pure products.
[b] Diastereoselectivity determined by ^1H NMR (400 MHz).

In an equilibration experiment, the 3:1 diastereomeric mixture of compound **4a** enriched in the diastereoisomer, which shows the H_β hydrogen at higher chemical shift in the ^1H NMR spectra (4.96 ppm, $^3J_{H\alpha-H\beta}=5.2$ Hz), was submitted under basic conditions (EtOH/EtO^-Na^+) for 30 min at room temperature. After this time, it was extracted with ethyl acetate and the crude mixture analyzed by ^1H NMR spectroscopy. It was possible to observe a change in the diastereomeric ratio to 2:1 favoring the diastereoisomer, which shows the H_β hydrogen in up-field (4.59 ppm, $^3J_{H\alpha-H\beta}=9.0$ Hz). These data are compatible for the equilibration experiment to the expected thermodynamically more stable *anti*-isomer, reinforcing our initial attribution of the relative stereochemistry *syn* to the major isomer obtained previously (Scheme 3).



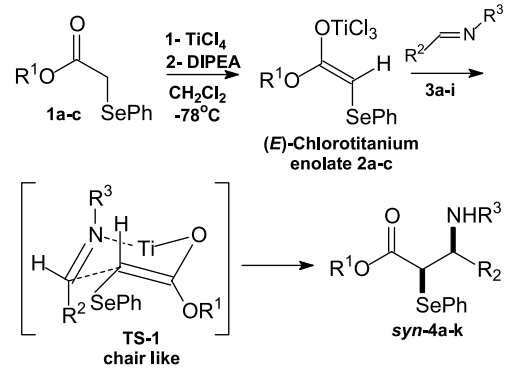
Scheme 3. Equilibration experiment of diastereomeric mixture of compound **4a**.

The nature of the geometry of the chlorotitanium enolates is uncertain[16] and demands caution in proposing models of stereoselection. However, to the diastereoselective aldol reactions, it is well established as a thumb's rule that the (*Z*)-geometry of the metal enolate is associated with the preferential formation of *syn*-aldols while the (*E*)-enolates afford the *anti*-aldols[17,18] through a cyclic chelated six-membered chair-like transition state so called the Zimmerman–Traxler model.[19]

The previous reported results for the use of chlorotitanium α-phenylseleno enolates in aldol condensation,[13a] and more recently for the conjugated additions[13b] were in agreement with that rule. In fact, for both cases, the (*Z*)-geometry of α-seleno chlorotitanium enolates was established on basis of NOESY experiments recorded on a sample of the enolate generated in CD_2Cl_2 at −40 °C in an NMR tube. A recent report by Tiecco and co-workers assigned by NMR a (*Z*) geometry to the titanium enolate generated from methyl phenylselenoacetate, 1.1 equiv of $TiCl_4$ and 2 equiv of Et_3N at − 78 °C.[13c]

On the other hand, in the Mannich-type reaction, due to the more thermodynamically stable (*E*)-aldimines be restricted to only one binding mode[20] a rationale through the chair-like Zimmerman–Traxler model **TS-1** associate the (*E*)-geometry of the chlorotitanium enolate **2a–c** to the preferential formation of the *syn*-α-phenylseleno-β-amino esters as depicted in the Scheme 4.

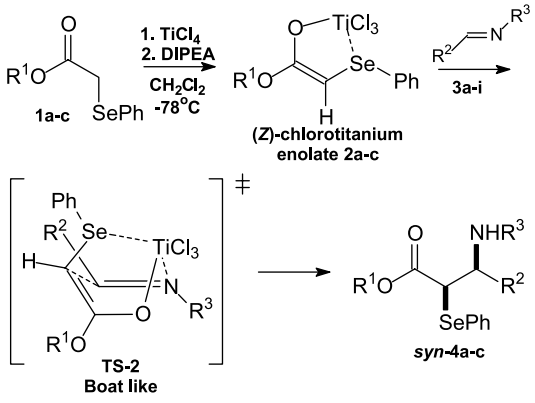
In order to gain some information about the nature of the geometry of the α-phenylseleno chlorotitanium enolates **2a** generated in presence of 2 equiv of both $TiCl_4$ and DIPEA, we carried out the condensation with benzaldehyde following the Toru's procedure,[13a] which afforded a 3:1 mixture favouring the *syn*-α-phenylseleno-β-hydroxy ester.



Scheme 4. The *syn*-isomer by the chair-like model **TS-1**.

This experiment indicates that under these conditions the geometry of the enolate should also be (*Z*).

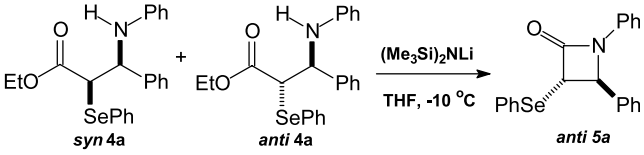
However, we do not exclude the possibility of the participation of a (*Z*)-chlorotitanium enolate. Some authors have proposed this possibility assuming the formation of the *syn*-isomer through a bidentate boat-like transition-state,[21] **TS-2** (Scheme 5).



Scheme 5. The *syn*-isomer from the boat-like model, **TS-2**.

Thus, both the transition states **TS-1** (chair-like) and **TS-2** (boat-like) can be responsible for the formation of the major *syn*-isomers. If the relative orientation of the (*E*)-aldimine is reversed in **TS-1** or **TS-2**, a chelated transition state complex is not possible and the *anti*-isomer takes place.

In order to test their potential use in the synthesis of β-lactams, the α-phenylseleno-β-amino ester **4a** (a diastereoisomer mixture, *syn*/*anti* ratio 90:10) was transformed into the α-phenylseleno-β-lactam **5a** (scheme 6). The ^1H NMR spectrum of the crude reaction showed the presence of only one diastereoisomer with respect to the relative configuration between both chiral centers. Comparison of



Scheme 6. Synthesis of the β-lactam **5a** from of the α-phenylseleno-β-amino ester **4a**.

the observed $J_{3,4}$ coupling constants in the ^{1}H NMR spectrum with those reported in the literature[14,23] ($J_{3,4}$= 5.8 Hz for the *syn*-isomer and $J_{3,4}$=2.2 Hz for the *anti*-isomer) allowed us to propose an *anti* relative configuration between the two adjacent chiral centers. The formation of the *anti*-isomer is in accordance with a previous strong base-promoted cyclization of α-phenylseleno-β-amino esters, where a dianionic intermediate was proposed for the *syn*/*anti* equilibration.[14] Thus, the trans-α-phenylseleno-β-lactams were prepared starting from either the *syn* or the *anti* diastereoisomers by treatment with 2 equiv of *t*-BuLi.[14]

3. Conclusions

In conclusion, the results demonstrate that the Mannich-type condensation of α-phenylseleno chlorotitanium enolates with aromatic aldimines affords preferentially the *syn*-α-phenylseleno-β-amino esters in reasonable to good diastereoselectivity and good yields. The obtained β-amino esters exhibit interesting synthetic properties and proved to be direct precursor of important β-lactamic structures.

4. Experimental

All reactions were performed in flame-dried glassware under a positive pressure of argon. Air and moisture sensitive reagents and solvents were transferred via syringe, and were introduced into reaction vessels though a rubber septum. CH_2Cl_2 was distilled from calcium hydride under argon. $TiCl_4$ and *i*-$PrNEt_2$ were purchased from commercial sources and were distilled before use. All the reactions were monitored by thin-layer chromatography (TLC) carried out using Merck 60 F_{254} plates with a 0.25 mm thickness. Column chromatography was carried out using Merck silica gel 60 (230–400 mesh). All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, on a Bruker DPX 400 instrument, using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in ppm down-field from internal tetramethylsilane or $CHCl_3$, and J values are given in Hz. Infrared spectra were recorded on a Nicollet-Magna spectrometer. Elemental analyses were carried out on a Perkin-Elmer 2400. Starting aldimines were easily prepared from the corresponding aromatic aldehydes and anilines in CH_2Cl_2.[24]

4.1. Synthesis of the α-phenylseleno esters 1a–c

The α-phenylseleno esters **1a–c** were prepared starting from the diphenyl diselenide using standard procedures.[10d,25]

4.1.1. Ethyl 2-(phenylseleno)acetate (1a).[10d] Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15 (t, 3H, J=7 Hz), 3.46 (s, 2H), 4.07 (q, 2H, J=7 Hz), 7.21–7.27 (m, 3H), 7.52–7.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 27.2, 60.8, 127.4, 128.8, 128.9, 132.5, 170.4.

4.1.2. Methyl 2-(phenylseleno)acetate (1b).[25b] Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.47 (s, 2H), 3.61 (s, 3H), 7.21–7.25 (m, 3H), 7.53–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 27.6, 58.9, 127.4, 127.5, 128.7, 132.0, 170.5.

4.1.3. *i*-Propyl 2-(phenylseleno)acetate (1c).[10d] Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (d, 6H, J=6.2 Hz), 3.44 (s, 2H), 4.94 (sept, 1H, J=6.2 Hz), 7.23–7.26 (m, 3H), 7.55–7.57 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3, 27.5, 68.5, 127.4, 128.5, 129.0, 132.7, 169.9.

4.2. Representative procedure for the Mannich-type reaction of α-phenylseleno esters with aldimines

4.2.1. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-phenylpropanoate (4a). To a solution of ethyl 2-(phenylseleno)-acetate **1a** (0.223 g, 1 mmol) in CH_2Cl_2 (4 mL) was added $TiCl_4$ (0.21 mL, 2 mmol). After 10 min *i*-Pr_2NEt (0.35 mL, 2 mmol) at −78 °C was added and the mixture was stirred for 1 h. The color changed from red to deep violet. A solution of benzylidene aniline **3a** (0.362 g, 2 mmol) in CH_2Cl_2 (2 mL) was added to reaction mixture. The reaction was stirred for 8 h at −78 °C. Saturated aq NH_4Cl (10 mL) was then added, and the mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel 50 g, hexane/ethyl acetate= 95:5) to give pure *syn*-**4a** (0.288 g, 68%). Both isomers have nearly the same R_f values. The *syn*/*anti* ratio was determined to be 90:10 by the ^{1}H NMR (400 MHz) analysis of the crude product. *syn*-**4a**: Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J=7.2 Hz), 3.92 (q, 2H, J=7.2 Hz), 4.07 (d, 1H, J= 5.2 Hz), 4.96 (d, 1H, J=5.2 Hz), 6.55–6.61 (m, 3H), 7.00–7.24 (m, 10H), 7.4 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.7, 59.5, 61.0, 113.6, 117.8, 126.9, 127.2, 127.7, 128.4, 128.7, 128.9, 129.1, 135.0, 139.8, 146.6, 172.2. IR cm^{-1} (neat) 3385, 3046, 3018, 2979, 2927, 1712, 1598, 1502, 1250, 1097, 1016, 811, 740, 692. GC/MS: *m*/*z* (rel intensity) 425 (M^+, 0.52), 182 (100), 77 (38). Anal. Calcd for $C_{23}H_{23}NO_2Se$: C, 65.09; H, 5.46; N, 3.30. Found: C, 64.81; H, 5.28; N, 3.12.

4.2.2. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-(4-methylphenyl) propionate (4b). Compound *syn*-**4b**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.97 (t, 3H, J=7.2 Hz), 2.24 (s, 3H), 3.95 (q, 2H, J=7.2 Hz), 4.05 (d, 1H, J=5.2 Hz), 4.96 (d, 1H, J=5.2 Hz), 6.57 (d, 2H, J=8.0 Hz), 6.64 (t, 1H, J=7.2 Hz), 7.03–7.10 (m, 4H), 7.15 (d, 2H, J=8.0 Hz), 7.24–7.29 (m, 3H), 7.57 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 20.9, 49.7, 59.2, 61.0, 113.6, 117.7, 126.6, 128.2, 129.0, 129.0, 129.2, 134.9, 136.0, 136.8, 137.2, 146.5, 172.3. IR cm^{-1} (neat) 3394, 3051, 3013, 2975, 2913, 1712.49, 1598, 1502, 1240, 1207, 1016, 735, 683. GC/MS: *m*/*z* (rel intensity) 439 (M^+, 0.32), 196 (100), 77 (28). Elemental Anal. Calcd for $C_{24}H_{25}NO_2Se$: C, 65.74; H, 5.74; N, 3.19. Found: C, 65.55; H, 5.87; N, 3.21.

4.2.3. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-(4-methoxyphenyl) propionate (4c). Oil; major diastereoisomer (*syn*-**4c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (t, 3H, J=7.2 Hz), 3.72 (s, 3H), 3.96 (q, 2H, J=7.2 Hz), 4.05 (d, 1H, J=5.6 Hz), 4.94 (d, 1H, J=5.6 Hz), 6.57 (d, 2H, J= 8.0 Hz), 6.65 (t, 1H, J=7.2 Hz), 6.78 (d, 2H, J=8.0 Hz), 7.09 (t, 2H, J=8.0 Hz), 7.19 (d, 2H, J=8.0 Hz), 7.23–7.30 (m, 3H), 7.57 (d, 2H, J=7.8 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.9, 55.1, 59.0, 61.1, 113.6, 114.1, 117.7, 122.1, 127.8, 128.2, 129.0, 130.1, 131.8, 135.0,

146.5, 158.9, 172.3. Minor diastereoisomer (*anti*-**4c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (t, 3H, J=7.2 Hz), 3.65 (s, 3H), 3.97 (q, 2H, J=7.2 Hz), 4.11 (d, 1H, J=9.2 Hz), 4.54 (d, 1H, J=9.2 Hz), 6.47 (d, 2H, J=8.0 Hz), 6.65 (d, 2H, J=8.0 Hz), 7.18–7.31 (m, 8H), 7.57 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.9, 55.2, 58.9, 61.0, 113.6, 113.9, 118.7, 127.9, 128.2, 128.7, 129.0, 129.1, 131.8, 134.9, 146.5, 158.9, 172.4. IR cm^{-1} (neat) 3384, 3052, 2979, 2960, 2834, 1715, 1600, 1244, 1135, 825, 742. GC/MS: *m*/*z* (rel intensity) 455 (M^+, 0.19), 212 (100), 77 (26). Elemental Anal. Calcd for $C_{24}H_{25}NO_3Se$: C, 63.43; H, 5.55; N, 3.08. Found: C, 63.67; H, 5.11; N, 3.47.

4.2.4. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-(4-chlorophenyl)propionate (4d). Compound *syn*-**4d**. Oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J=7.2 Hz), 3.97 (q, 2H, J=7.2 Hz), 4.02 (d, 1H, J=5.2 Hz), 4.93 (d, 1H, J=5.2 Hz), 6.55 (d, 2H, J=7.6 Hz), 6.68 (t, 1H, J=7.2 Hz), 7.22–7.32 (m, 9H), 7.56 (d, 2H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.5, 59.1, 61.3, 113.6, 118.1, 128.2, 128.5, 128.7, 129.1, 129.2, 133.4, 135.1, 136.1, 138.5, 146.2, 172.1. IR cm^{-1} (neat) 3380, 3046, 2975, 2927, 1722, 1602, 1369, 1021, 735. GC/MS: *m*/*z* (rel intensity) 459 (M^+, 0.50), 216 (100), 77 (42). Elemental Anal. Calcd for $C_{23}H_{22}NO_2ClSe$: C, 60.21; H, 4.83; N, 3.05. Found: C, 60.24; H, 4.77; N, 2.99.

4.2.5. Ethyl 3-[(4-chlorophenyl)amino]-2-(phenylseleno)-3-(4-chlorophenyl)propionate (4e). Oil; major diastereoisomer (*syn*-**4e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J=7.2 Hz), 3.95 (q, 2H, J=7.2 Hz), 4.01 (d, 1H, J=5.2 Hz), 4.86 (d, 1H, J=5.2 Hz), 6.45 (d, 2H, J=8.0 Hz), 7.03 (d, 2H, J=8.0 Hz), 7.17–7.31 (m, 7H), 7.56 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.1, 59.2, 61.3, 114.6, 122.6, 126.3, 128.1, 128.5, 128.5, 128.7, 129.0, 129.1, 135.1, 136.1, 138.0, 144.8, 170.1. Minor diastereoisomer (*anti*-**4e**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, J=7.2 Hz), 3.85 (d, 1H, J=9.2 Hz), 3.96 (q, 2H, J=7.2 Hz), 4.47 (d, 1H, J=9.2 Hz), 6.39 (d, 2H, J=8.0 Hz), 7.03 (d, 2H, J=8.0 Hz), 7.17–7.31 (m, 7H), 7.51 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 51.1, 57.7, 61.2, 115.1, 122.6, 128.1, 128.4, 128.5, 128.7, 129.1, 135.1, 136.1, 138.0, 138.3, 144.9, 172.0. IR cm^{-1} (neat) 3365, 3056, 2984, 2927, 1707, 1602, 1488, 1240, 1097, 1016, 807, 735. GC/MS: *m*/*z* (rel intensity) 493 (M^+, 0.65), 250 (100), 252 (61), 77 (15). Elemental Anal. Calcd for $C_{23}H_{21}NO_2Cl_2Se$: C, 56.00; H, 4.29; N, 2.84. Found: C, 56.10; H, 4.15; N, 2.78.

4.2.6. Ethyl 3-[(4-methoxyphenyl)amino]-2-(phenylseleno)-3-phenylpropanoate (4f). Oil; major diastereoisomer (*syn*-**4f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J=7.2 Hz), 3.64 (s, 3H), 3.95 (q, 2H, J=7.2 Hz), 4.07 (d, 1H, J=5.6 Hz), 4.91 (d, 1H, J=5.6 Hz), 6.54 (d, 2H, J=8.0 Hz), 6.67 (d, 2H, J=8.0 Hz), 7.18–7.29 (m, 8H), 7.55 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.9, 55.1, 59.0, 61.0, 113.6, 113.9, 117.7, 127.8, 128.2, 128.7, 129.0, 129.0, 131.8, 134.9, 146.5, 158.9, 172.3. Minor diastereoisomer (*anti*-**4f**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, 3H, J=7.2 Hz), 3.64 (s, 3H), 3.95 (q, 2H, J=7.2 Hz), 4.09 (d, 1H, J=9.2 Hz), 4.53 (d, 1H, J=9.2 Hz), 6.49 (d, 2H, J=8.0 Hz), 6.67 (d, 2H, J=8.0 Hz), 7.18–7.29 (m, 8H), 7.55 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 49.9, 55.1, 59.0, 61.0, 113.6, 113.9, 118.7, 127.8, 128.2, 128.7, 129.0, 129.1, 131.8, 134.9, 146.5, 158.9, 172.3. IR cm^{-1} (neat) 3379, 3052, 3021, 2970, 2929, 1705, 1602, 1510, 1249, 1146, 860, 696. GC/MS: *m*/*z* (rel intensity) 455 (M^+, 0.57), 212 (100), 77 (40). Elemental Anal. Calcd for $C_{24}H_{25}NO_3Se$: C, 63.43; H, 5.55; N, 3.08. Found: C, 65.71; H, 5.66; N, 3.29.

4.2.7. *i*-Propyl 3-(phenylamino)-2-(phenylseleno)-3-phenylpropanoate (4g). Oil; major diastereoisomer (*syn*-**4g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J=6.4 Hz), 1.01 (d, 3H, J=6.4 Hz), 4.00 (d, 1H, J=5.6 Hz), 4.83 (sept, 1H, J=6.4 Hz), 4.94 (d, 1H, J=5.6 Hz), 6.55 (d, 2H, J=8.0 Hz), 6.67 (t, 1H, J=7.2 Hz), 7.26–7.34 (m, 9H), 7.57 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 21.4, 49.6, 58.9, 69.0, 113.5, 118.0, 128.2, 128.3, 128.7, 128.8, 129.1, 133.3, 134.9, 136.0, 138.5, 146.2, 171.7. Minor diastereoisomer (*anti*-**4g**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J=6.4 Hz), 1.01 (d, 3H, J=6.4 Hz), 3.86 (d, 1H, J=9.6 Hz), 4.55 (d, 1H, J=9.6 Hz), 4.78 (sept, 1H, J=6.4 Hz), 6.49 (d, 2H, J=8.0 Hz), 6.67 (t, 1H, J=7.2 Hz), 7.06–7.12 (m, 9H), 7.53 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 21.4, 49.6, 58.0, 68.9, 114.1, 118.5, 128.2, 128.6, 128.8, 129.0, 133.3, 134.9, 136.0, 138.5, 146.2, 170.0. IR cm^{-1} (neat) 3385, 3046, 3018, 2979, 2927, 1712, 1598, 1250, 1097, 740, 692. GC/MS: *m*/*z* (rel intensity) 439 (M^+, 0.17), 149 (100), 167 (36), 57 (51). Elemental Anal. Calcd for $C_{24}H_{25}NO_2Se$: C, 65.75; H, 5.75; N, 3.19. Found: C, 65.51; H, 5.66; N, 3.29.

4.2.8. *i*-Propyl 3-(phenylamino)-2-(phenylseleno)-3-(4-chlorophenyl)propionate (4h). Oil; major diastereoisomer (*syn*-**4h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (d, 3H, J=6.4 Hz), 0.98 (d, 3H, J=6.4 Hz), 4.05 (d, 1H, J=5.2 Hz), 4.82 (sept, 1H, J=6.4 Hz), 4.98 (d, 1H, J=5.2 Hz), 6.58 (d, 2H, J=8.0 Hz), 6.65 (q, 1H, J=7.2 Hz), 7.18–7.29 (m, 10), 7.54–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.2, 50.0, 59.4, 68.8, 113.5, 117.6, 126.7, 127.5, 128.2, 128.5, 129.0, 129.1, 134.8, 135.9, 139.9, 146.5, 171.9. Minor diastereoisomer (*anti*-**4h**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, J=6.4 Hz), 0.99 (d, 3H, J=6.4 Hz), 3.93 (d, 1H, J=9.6 Hz), 4.60 (d, 1H, J=9.6 Hz), 4.75 (sep, 1H, J=6.4 Hz), 6.52 (d, 2H, J=8.0 Hz), 6.64 (q, 1H, J=7.2 Hz), 7.04–7.38 (m, 12H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.3, 52.2, 58.7, 63.7, 114.0, 118.1, 127.4, 127.7, 128.4, 128.7, 128.9, 129.1, 134.9, 135.9, 140.2, 146.5, 170.0. IR cm^{-1} (neat) 3392, 3052, 3016, 2960, 1720, 1604, 1506, 1349, 1253, 1135, 743, 701. GC/MS: *m*/*z* (rel intensity) 473 (M^+, 0.58), 216 (100), 218 (38), 77 (30). Elemental Anal. Calcd for $C_{24}H_{24}NO_2ClSe$: C, 60.96; H, 5.12; N, 2.96. Found: C, 61.39; H, 5.06; N, 2.95.

4.2.9. Methyl 3-(phenylamino)-2-(phenylseleno)-3-phenylpropanoate (4i). Oil; major diastereoisomer (*syn*-**4i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.43 (s, 3H), 4.09 (d, 1H, J=5.6 Hz), 4.97 (d, 1H, J=5.6 Hz), 6.57 (d, 2H, J=8.0 Hz), 6.63 (m, 1H), 7.15–7.24 (m, 10H), 7.54 (d, 2H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.6, 51.9, 59.5, 113.6, 117.8, 126.6, 127.1, 127.5, 128.5, 128.9, 129.0, 134.9, 136.0, 139.7, 146.3, 172.5. Minor diastereoisomer (*anti*-**4i**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.98 (d, 1H, J=9.6 Hz), 4.61 (d, 1H, J=9.6 Hz), 6.51 (d, 2H, J=8.0 Hz), 6.63 (m, 1H), 7.04–7.17 (m, 10H), 7.54 (d, 2H,

J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 49.6, 50.9, 58.5, 114.0, 118.1, 126.6, 127.1, 128.3, 128.5, 128.7, 128.9, 134.9, 136.0, 146.3, 172.5. IR cm^{-1} (neat) 3387, 3053, 2978, 2961, 2835, 1716, 1601, 1519, 1245, 1030, 827, 687. GC/MS: *m/z* (rel intensity) 411 (M^+, 0.59), 182 (100), 77 (46), 104 (22). Elemental Anal. Calcd for $C_{22}H_{21}NO_2Se$: C, 64.38; H, 5.16; N, 3.40. Found: C, 64.39; H, 4.93; N, 3.41.

4.2.10. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-[(3,4-methylenedioxy)phenyl]propanoate (4j). Oil; major diastereoisomer (*syn*-**4j**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.02 (t, 3H, J=7.2 Hz), 3.90–4.05 (m, 3H), 4.88 (d, 1H, J=5.6 Hz), 5.86 (s, 2H), 6.51–6.75 (m, 5H), 6.86 (s, 1H), 7.04–7.10 (m, 2H), 7.23—7.28 (m, 3H), 7.53–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 49.9, 58.2, 61.1, 100.9, 107.0, 108.1, 113.6, 117.7, 120.2, 128.3, 128.7, 128.9, 129.0, 134.0, 134.9, 146.4, 146.9, 147.8, 172.2. Minor diastereoisomer (*anti*-**4j**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 3H, J=7.2 Hz), 3.85–4.00 (m, 3H), 4.50 (d, 1H, J=9.2 Hz), 5.87 (s, 2H), 6.55–6.76 (m, 5H), 6.83 (s, 1H), 7.04–7.10 (m, 2H), 7.23–7.28 (m, 3H), 7.53–7.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.9, 51.9, 59.3, 61.1, 100.9, 107.3, 108.2, 114.0, 118.2, 120.9, 128.3, 128.7, 128.9, 129.1, 134.2, 136.0, 146.7, 146.9, 147.8, 172.8. IR cm^{-1} (neat) 3397, 3050, 2995, 2911, 2650, 1703, 1602, 1511, 1240, 1050, 746. GC/MS: *m/z* (rel intensity) 469 (M^+, 0.18), 226 (100), 77 (23). Elemental Anal. Calcd for $C_{24}H_{23}NO_4Se$: C, 61.54; H, 4.95; N, 2.99. Found: C, 61.32; H, 4.77; N, 3.15.

4.2.11. Ethyl 3-(phenylamino)-2-(phenylseleno)-3-(furan-2-yl)propanoate (4k). Oil; major diastereoisomer (*syn*-**4k**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7.2 Hz), 3.89 (q, 2H, J=7.2 Hz), 4.01 (d, 1H, J=5.6 Hz), 4.96 (d, 1H, J=5.6 Hz), 6.22 (d, 1H, J=1.2 Hz), 6.61 (d, 1H, J=8.0 Hz), 6.73 (t, 1H, J=7.2 Hz), 7.09–7.32 (m, 8H), 7.57 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 47.5, 53.1, 61.2, 107.9, 110.2, 114.1, 114.2, 118.6, 128.7, 129.0, 129.1, 136.2, 141.9, 146.4, 152.6, 170.3. Minor diastereoisomer (*anti*-**4k**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, 3H, J=7.2 Hz), 3.89 (q, 2H, J=7.2 Hz), 4.21 (d, 1H, J=8.8 Hz), 4.87 (d, 1H, J=8.8 Hz), 6.22 (d, 1H, J=1.2 Hz), 6.61 (d, 1H, J=8.0 Hz), 6.73 (t, 1H, J=7.2 Hz), 7.09–7.32 (m, 8H), 7.57 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.8, 49.0, 54.3, 61.5, 107.9, 110.2, 114.1, 114.1, 118.6, 128.7, 129.0, 129.1, 136.2, 141.9, 146.4, 152.6, 170.3. IR cm^{-1} (neat) 3399, 3130, 3090, 3001, 2590, 1720, 1610, 1509, 1401, 1298, 1007, 789. GC/MS: *m/z* (rel intensity) 415 (M^+, 0.10), 172 (100), 77 (23). Elemental Anal. Calcd for $C_{21}H_{21}NO_3Se$: C, 60.87; H, 5.11; N, 3.38. Found: C, 60.46; H, 5.32; N, 3.04.

4.2.12. Procedure for the equilibration experiment of the α-phenylseleno-β-amino ester 4a. To a solution of the diastereomeric (*syn*/*anti* 3:1) α-phenylseleno-β-amino ester **4a** (212 mg, 0.5 mmol) in EtOH (2 mL) at room temperature under inert atmosphere (argon) and magnetic stirring, EtONa (1 M in EtOH, 1 mL) was added and the mixture was stirred (2×5 mL) for 30 min. The crude mixture was extracted with ethyl acetate and washed with 5 mL of a saturated solution of NH_4Cl. The solvent was evaporated under vacuum and 190 mg of the crude diastereomeric mixture was obtained in 90% yield. The crude mixture was analyzed by ^{1}H NMR which shown the *syn*/*anti* ratio as 1:2. *anti*-**4a**: Oil, ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, 3H, J=7.2 Hz), 3.92 (q, 2H, J=7.2 Hz), 3.83 (d, 1H, J=9.2 Hz), 4.60 (d, 1H, J=9.2 Hz), 6.55–6.61 (m, 3H), 7.00–7.24 (m, 10H), 7.4 (d, 2H, J=8.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 13.7, 48.7, 57.5, 61.0, 113.6, 117.8, 126.9, 127.2, 127.8, 128.4, 128.7, 128.9, 129.0, 135.0, 139.8, 146.6, 172.2.

4.2.13. Synthesis of the β-lactam 5a from of the α-phenylseleno-β-amino ester 4a. General procedure.[22] To a solution of α-phenylseleno-β-amino ester **4a** (212 mg, 0.5 mmol) in anhydrous THF (10 mL) at −10 °C under inert atmosphere (argon) and magnetic stirring, 1 mmol of $(Me_3Si)_2NLi$ (0.5 M in THF) was added dropwise. After 90 min, the reaction was quenched with saturated aqueous NH_4Cl and mixture was extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave a residue, which was purified by column chromatography (silica gel 50 g, hexane/ethyl acetate=90:10) affording the *anti* α-phenylseleno β-lactam: *anti*-1-phenyl-3-phenylseleno-4-phenyl-azetidin-2-one[26] **5a** in 57% yield as a white solid. Mp 109–110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.28 (d, 1H, J=2.4 Hz), 4.79 (d, 1H, J=2.4 Hz). 7.16–7.31 (m, 13H), 7.63–7.68 (m, 2H). ^{13}NMR ($CDCl_3$, 100 MHz): δ 53.1, 63.0, 117.0, 124.0, 125.8, 126.3, 128.5, 128.7 128.9, 129.1, 129.2, 135.1, 136.5, 137.2, 164.0. IR cm^{-1} (neat) 3090, 3031, 2901, 2503, 1743, 1605, 1503, 1391, 1105, 790. GC/MS: *m/z* (rel intensity) 379 (M^+, 6.96), 180 (100), 77 (91), 260 (55), 51 (45). Elemental Anal. Calcd for $C_{21}H_{17}NOSe$: C, 66.67; H, 4.53; N, 3.70. Found: C, 66.82; H, 4.55; N, 3.63.

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26. The ^{1}H NMR (400 MHz) analysis of the crude product showed only the *anti* diastereoisomer.

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Deallyloxy- and debenzyloxycarbonylation of protected alcohols, amines and thiols via a naphthalene-catalysed lithiation reaction

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Abstract—The naphthalene-catalysed lithiation of Alloc- and Cbz-protected alcohols, amines and thiols in THF at 0 °C led, after quenching with methanol, to the recovery of the free alcohols, amines and thiols in short reaction times and with very good yields. The selectivity for the removal of the Alloc- or the Cbz- group in a polyfunctionalised substrate has been studied. The selective reductive cleavage of a benzylic carbon–oxygen bond was achieved in the presence of an allylic carbon–oxygen or carbon–nitrogen bond. This method represents a great improvement in comparison with the previously reported deprotection procedures by dissolving metals, since it avoids the use of the toxic liquid ammonia and, therefore, the need to perform the reaction at low temperatures.

1. Introduction

The allyloxycarbonyl (Alloc) and the benzyloxycarbonyl (Cbz) are among the most useful protecting groups for alcohols, amines and, to a lesser extent, thiols.[1] They have shown a wide application in organic synthesis, especially in the fields of peptides,[2] nucleotides,[3] and carbohydrates.[4] These blocking groups present the advantages that are easily introduced (generally by acylation with allyl[5a] or benzyl chloroformate[5b] in the presence of a base), deactivate the nucleophilic properties of the protected heteroatom and can readily be removed when needed. The Alloc group can be cleaved by sodium in liquid ammonia,[6] nickel tetracarbonyl or several palladium complexes in the presence of an external nucleophile in order to prevent the liberated functional group from adding to the intermediate π-allyl complex.[7] Concerning the Cbz group, several methods have been reported for its removal: palladium-catalysed hydrogenolysis, reduction by electrolysis, dissolving metals or alkali metal borohydrides, basic hydrolysis, treatment with strong acids, boron trihalides or trimethylsilyl halides.[8] A mild deprotection of allylic and benzylic carbamates using tetrabutylammonium fluoride has recently been reported.[9] However, some of these methods require the use of toxic reagents or expensive transition metal complexes and, in some cases, side reactions have been observed with other functional groups present in the molecule to be deprotected.[8b]

Our research group has extensively been studying an arene-catalysed lithiation methodology.[10,11] The use of an excess of lithium powder and a catalytic amount of an arene [mainly naphthalene or 4,4′-di-*tert*-butylbiphenyl (DTBB)] has allowed us to generate simple organolithium compounds starting from non-halogenated materials,[12] and functionalised organolithium compounds[13] by chlorine–lithium exchange or by ring opening of heterocycles.[14] The application of this lithiation process to the reductive cleavage of several allylic and benzylic carbon-heteroatom bonds has led to methods for removal of some blocking groups from protected alcohols, amines and thiols.[15] In a previous study, we were able to generate allylic and benzylic organolithium reagents by reductive cleavage of carbon–oxygen and carbon–nitrogen bonds in carbonates and carbamates.[16] These results prompted us to test the application of our lithiation methodology to the removal of the Alloc and Cbz groups. In this paper we report the lithium-mediated naphthalene-catalysed reductive cleavage of these two groups from several protected alcohols, amines and thiols in short reaction times under very mild reaction conditions, avoiding the use of the toxic liquid ammonia.

2. Results and discussion

All protected substrates **1**–**3** (Scheme 1, Table 1) were prepared from commercially available alcohols (for **1**),

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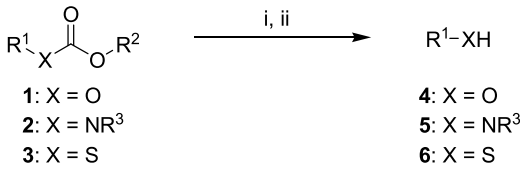

Scheme 1. Reagents and conditions: (i) Li, $C_{10}H_8$ (8 mol%), THF, 0 °C; (ii) H_2O.

amines (for **2**) or thiols (for **3**) and the corresponding allyl or benzyl chloroformate under basic reaction conditions.

Benzyl 1-decyl carbonate **1ab** (Scheme 1 and Table 1, entry 2) was chosen as a model substrate. The reaction of compound **1ab** with an excess of lithium powder (1:9 molar ratio) and a catalytic amount of naphthalene (1:0.16 molar ratio; 8 mol%) in THF at 0 °C for 2 h gave, after quenching the excess of lithium with methanol, the expected 1-decanol **4a** in 86% yield (Table 1, entry 2). The reaction was repeated at −30 and −78 °C, but yields did not improve. Therefore, the temperature of 0 °C was chosen because of the simpler experimental set-up (reaction cooled in an ice-bath).

Next, the process was extended to some other Cbz-protected alcohols. Benzylic carbonates derived from 2-octanol (**1b**) and 3,7-dimethyl-3-octanol (**1d**) were submitted to the naphthalene-catalysed lithiation reaction under the same experimental conditions and gave the corresponding free alcohols **4b** and **4d** in excellent yields (Table 1, entries 3 and 5). However, the lithiation of benzyl geranyl carbonate **1e** under the same conditions only led to a 12% yield of geraniol, probably due to a competitive cleavage of the allylic geranyl-oxygen bond leading to the corresponding hydrocarbon.[17] The selective removal of the Cbz group was achieved when the lithiation of **1e** was performed at −78 °C, which led to a 71% yield of geraniol (Table 1, entry 6). The Alloc group of carbonates **1aa**, **1c** and **1f** could also be effectively cleaved under the typical lithiation conditions, affording the deprotected alcohols **4a** and **4c** and phenol **4f**, respectively, in yields ranging from 58 to 80% (Table 1, entries 1, 4 and 7).

Having proved that our procedure was efficient for the removal of both Alloc and Cbz groups from carbonates, a competition experiment was performed in order to check if any of these groups could be selectively cleaved in the presence of the other one. 1,9-Nonanediol was mono-protected with the Cbz group on one hydroxyl and the Alloc group was introduced on the remaining hydroxyl. The naphthalene-catalysed lithiation of the obtained dicarbonate **1g** led to the recovery of the free diol **4g** in almost quantitative yield (Table 1, entry 8), showing that there was no chemoselectivity in the process. Attempts to get some selectivity at −78 °C did not change the result, the diol **4g** being obtained again.

Our methodology was successfully applied to the deallyloxy- and debenzyloxycarbonylation of protected secondary amines and thiols (Scheme 1 and Table 1, entries 9–16). Both the Alloc and the Cbz groups could easily be removed from the protected dioctylamines **2aa** and **2ab**, respectively, in very good yields (Table 1, entries 9 and 10). The Cbz group could selectively be eliminated in the protected diallylamine **2b**, which contains two allylic carbon–nitrogen bonds that could also be cleaved under the lithiation reaction conditions (Table 1, entry 11).[18] *N*-Methylaniline **5c** was obtained in an excellent yield in the lithiation of substrate **2c** (Table 1, entry 12). We also tried the debenzyloxycarbonylation of a protected primary amine, but it failed. Octylamine was protected with the Cbz group and the removal of the latter was attempted following the same procedure previously used by us in the deprotection of tritylated primary amines,[15c] consisting in deprotonation with *n*-butyllithium and treatment with trimethylsilyl chloride before performing the lithiation step. Although the starting material disappeared, neither octylamine nor *N*-(trimethylsilyl)octylamine were detected in the crude reaction mixture (GC–MS). Concerning sulfur-containing substrates, the lithiation of the allylic and benzylic

Table 1. Deallyloxy- or debenzyloxycarbonylation of compounds **1–3** via a naphthalene-catalysed lithiation. Preparation of compounds **4–6**

Entry	Substrate				Time (h)	Product	
	No.	X	R^1	R^2		No.	Yield (%)[a]
1	**1aa**	O	$Me(CH_2)_9$	$CH_2{=}CHCH_2$	2.0	**4a**	80
2	**1ab**	O	$Me(CH_2)_9$	$PhCH_2$	2.0	**4a**	86
3	**1b**	O	$Me(CH_2)_5CH(Me)$	$PhCH_2$	5.0	**4b**	>99
4	**1c**	O	*c*-C_6H_{11}	$CH_2{=}CHCH_2$	1.5	**4c**	74
5	**1d**	O	$Pr^i(CH_2)_3C(Me)(Et)$	$PhCH_2$	5.0	**4d**	81
6	**1e**	O	Geranyl	$PhCH_2$	2.5	**4e**	71[b]
7	**1f**	O	2,4,6-$Me_3C_6H_2$	$CH_2{=}CHCH_2$	1.0	**4f**	58
8	**1g**	O	$CbzO(CH_2)_9$	$CH_2{=}CHCH_2$	2.0	**4g**[c]	>99
9	**2aa**	$Me(CH_2)_7N$	$Me(CH_2)_7$	$CH_2{=}CHCH_2$	2.0	**5a**	86
10	**2ab**	$Me(CH_2)_7N$	$Me(CH_2)_7$	$PhCH_2$	5.0	**5a**	71
11	**2b**	$CH_2{=}CHCH_2N$	$CH_2{=}CHCH_2$	$PhCH_2$	1.0	**5b**	62
12	**2c**	MeN	Ph	$PhCH_2$	1.0	**5c**	98
13	**3aa**	S	$Me(CH_2)_9$	$CH_2{=}CHCH_2$	2.0	**6a**	78
14	**3ab**	S	$Me(CH_2)_9$	$PhCH_2$	1.0	**6a**	82
15	**3b**	S	*c*-C_6H_{11}	$PhCH_2$	1.0	**6b**	62
16	**3c**	S	Ph	$CH_2{=}CHCH_2$	1.0	**6c**	96

[a] Yield determined by quantitative GLC, using commercially available compound **4–6** and *n*-dodecane (internal standard) in the determination of response factors.
[b] The reaction was performed at −78 °C.
[c] Compound **4g** = 1,9-nonanediol.

thiocarbonates **3a**–**3c**, derived from primary, secondary and aromatic thiols, led to the formation of the parent thiols in moderate to excellent yields (Table 1, entries 13–16). The moderate yield obtained with benzyl cyclohexyl thiocarbonate **3b** could be attributed to some oxidation of the obtained cyclohexanethiol to the corresponding disulfide during the work-up, since the latter was detected in the crude reaction mixture (GC–MS).

Concerning a possible reaction mechanism, we assume that the reductive cleavage of the allylic (for Alloc) or benzylic (for Cbz) carbon–oxygen bond takes place first, leading to allyl- or benzyllithium and the corresponding alkyl lithium carbonate (from **1**), carbamate (from **2**) or thiocarbonate (from **3**). Then, the latter carbonic acid derivatives decarboxylate to give the corresponding lithium alkoxide (from **1**), amide (from **2**) or sulfide (from **3**). The final quench with excess of methanol renders the expected alcohols **4**, amines **5** or thiols **6**, respectively, and the hydrocarbons propene (by protonolysis of allyllithium) or toluene (by protonolysis of benzyllithium). The latter was always detected (GC–MS) in all the reactions with Cbz-protected substrates, which is in favour of the proposed reaction mechanism.

3. Conclusion

In conclusion, we have reported here a very efficient procedure to remove the Alloc and the Cbz groups from protected alcohols, amines and thiols under mild reaction conditions. The methodology is applicable to aliphatic and aromatic substrates. This deprotection procedure works very efficiently even for branched alcohols and thiols. Concerning amines, this reductive cleavage is only applicable to carbamates bearing two substituents at the nitrogen atom. This method has shown to be a very good alternative to the reported methods to remove this two popular protecting groups, since it uses safer reagents and simpler experimental set-up conditions.

4. Experimental

4.1. General

All moisture sensitive reactions were carried out under argon atmosphere. Commercially available anhydrous THF (99.9%, water content $\leq$0.006%, Acros) was used as solvent in all the reactions. All reagents used for the synthesis of protected substrates **1**–**3** and naphthalene were commercially available (Acros, Aldrich) and were used without further purification. Lithium powder was prepared according to the procedure described in Ref. 19. Commercially available *n*-butyllithium was titrated with a 1 M solution of *sec*-butanol in xylene using 1,10-phenanthroline as indicator.[20] All glassware was dried in an oven at 100 °C and cooled to room temperature under Ar before use. Column chromatography was performed with Merck silica gel 60 (0.040–0.063 μm, 240–400 mesh). Thin-layer chromatography (TLC) was performed on precoated silica gel plates (Merck 60, F254, 0.25 mm). Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker ARX-300 spectrophotometer using $CDCl_3$ (unless otherwise stated) as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra (EI) were obtained at 70 eV on a Hewlett Packard HP-5890 GC/MS instrument equipped with a HP-5972 selective mass detector. Infrared (FT-IR) spectra were obtained on a Nicolet-Nexus spectrophotometer. The purity of volatile compounds and the chromatographic analyses (GC) were determined with a Shimadzu GC-9A instrument equipped with a flame-ionization detector and a 2 m column (1.5% OV17 9_A SUS Chrom 103 80/1000), using nitrogen as carrier gas.

4.2. Synthesis of the carbonates 1a–1f, carbamates 2 and thiocarbonates 3. General procedure

n-BuLi (6.3 mL of a 1.6 M solution of *n*-BuLi in hexane, 10.0 mmol) was dropwise added to a stirred solution of the corresponding alcohol (for **1a**–**1f**), amine (for **2**) or thiols (for **3**) (10.0 mmol) in anhydrous THF (10 mL) under Ar at 0 °C. Ten minutes after the addition had been completed, allyl or benzyl chloroformate (10.0 mmol) was added during ca. 5 min. After stirring for 2 h at the same temperature, the crude reaction mixture was adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) afforded the expected Alloc- and Cbz-protected compounds **1a**–**1f**, **2** and **3** in pure form. Their corresponding physical, spectroscopic and analytical data follow.

4.2.1. Allyl 1-decyl carbonate (1aa).[21] Colourless oil; yield: 22%; R_f 0.88 (hexane/ethyl acetate: 9/1); ν (film) 1747 (C=O), 1256 cm^{-1} (CO); δ_H 0.88 (3H, t, J=6.8 Hz, Me), 1.00–1.51 [14H, m, Me(CH_2)$_7$], 1.53–1.82 (2H, m, CH_2CO), 4.12 (2H, t, J=6.6 Hz, CH_2CH_2O), 4.63 (2H, d, J=6.9 Hz, $CHCH_2O$), 5.21–5.44 (2H, m, CH_2=C), 5.84–6.03 (1H, m, CH=CH_2); δ_C 14.1 (Me), 22.6, 28.6, 29.2, 29.3, 29.5, 30.9 (2C), 31.8 [Me(CH_2)$_8$], 68.0, 68.2 (2×CO), 118.8 (CH_2=C), 131.5 (CH=C), 155.1 (C=O); *m*/*z* (DIP) 242 (M^+, <1%), 203 (10), 141 (80), 140 (47), 112 (25), 111 (25), 99 (27), 98 (16), 97 (39), 85 (100), 84 (25), 83 (49), 82 (17), 71 (84), 70 (37), 69 (43), 68 (12), 57 (90), 56 (31), 55 (48), 43 (54), 42 (11), 41 (30).

4.2.2. Benzyl 1-decyl carbonate (1ab).[22] Colourless oil; yield: 61%; R_f 0.38 (hexane); ν (film) 3071, 3034, 1587 (HC=C), 1746 (C=O), 1261 cm^{-1} (CO); δ_H 0.88 (3H, t, J=6.9 Hz, Me), 1.18–1.44 [14H, m, Me(CH_2)$_7$], 1.58–1.73 (2H, m, CH_2CO), 4.13 (2H, t, J=6.8 Hz, CH_2CH_2O), 5.15 (2H, s, $PhCH_2$), 7.26–7.43 (5H, m, ArH); δ_C 14.1 (Me), 22.6, 25.6, 28.6, 29.15, 29.2, 29.5 (2C), 31.8 [Me(CH_2)$_8$], 68.3 (CH_2CO), 69.4 ($PhCH_2$), 128.3 (2C), 128.4, 128.5 (2C), 135.3 (ArC), 155.2 (C=O); *m*/*z* (DIP) 292 (M^+, <1%), 286 (14), 273 (11), 272 (27), 271 (100), 257 (47), 239 (26), 195 (12), 194 (14), 193 (64), 149 (66), 135 (16), 129 (20), 128 (11), 116 (10), 111 (11), 97 (18), 89 (17), 85 (16), 83 (19), 73 (19), 71 (22), 69 (19), 61 (10), 60 (13), 57 (46), 56 (61), 55 (27), 43 (38), 41 (24).

4.2.3. Benzyl 2-octyl carbonate (1b).[23] Colourless oil; yield: 70%; R_f 0.58 (hexane/ethyl acetate: 9:1); ν (film) 3093, 3055, 3034, 1498 (HC=C), 1734 (C=O), 1263 cm^{-1} (CO); δ_H 0.87 (3H, t, J=6.5 Hz, $MeCH_2$), 1.17–1.75 [10H,

m, $(CH_2)_5$], 1.27 (3H, d, $J=6.1$ Hz, *Me*CH), 4.68–4.85 (1H, m, CHO), 5.14 (2H, s, PhCH_2), 7.24–7.47 (5H, m, ArH); δ_C 14.0 (*Me*CH_2), 19.8 (*Me*CO), 22.5, 25.15, 25.2, 29.0, 31.6 [$(CH_2)_5$], 69.2 (Ph*C*H_2), 75.6 (Me*C*O), 128.2 (2C), 128.3, 128.5 (2C), 135.4 (ArH), 154.8 (C=O); *m/z* (DIP) 264 (M^+, 2%), 180 (14), 152 (56), 151 (26), 112 (13), 111 (11), 110 (10), 108 (58), 107 (70), 92 (19), 91 (100), 90 (13), 79 (26), 77 (11), 71 (30), 69 (10), 65 (14), 57 (30), 55 (10), 43 (19), 41 (13).

4.2.4. Allyl cyclohexyl carbonate (1c). Colourless oil; yield: 44%; R_f 0.40 (hexane/ethyl acetate: 9:1); ν (film) 1742 (C=O), 1651 (HC=C), 1254 cm^{-1} (CO); δ_H 1.06–2.11 (10H, m, 5×CH_2 ring), 4.47–4.73 (1H, m, CHO), 4.62 (2H, d, $J=4.5$ Hz, CH_2O), 5.15–5.42 (2H, m, CH_2=C), 5.80–6.04 (1H, m, CH=C); $\delta_C=23.0$, 25.2 (2C), 31.6 (2C) (5×CH_2 ring), 68.1 (CH_2O), 89.2 (CHO), 118.7 (*C*H_2=C), 131.8 (*C*H=C), 154.5 (C=O); *m/z* (DIP) 184 (M^+, 5%), 183 (30), 149 (15), 143 (12), 141 (15), 137 (12), 135 (18), 127 (18), 125 (21), 123 (15), 113 (17), 112 (12), 111 (39), 109 (21), 99 (26), 98 (16), 97 (48), 96 (14), 95 (28), 91 (12), 85 (78), 84 (21), 83 (83), 82 (28), 81 (32), 71 (75), 70 (25), 69 (55), 67 (29), 57 (100), 56 (21), 55 (72), 43 (55), 41 (64); HRMS: $M^+-C_4H_5O_2$, found 99.0813. $C_6H_{11}O$ requires 99.0810.

4.2.5. Benzyl 3,7-dimethyl-3-octyl carbonate (1d). Colourless oil; yield: 87%; R_f 0.68 (hexane/ethyl acetate: 9:1); ν (film) 3088, 3066, 3034, 1580, 1498 (HC=C), 1740 (C=O), 1263 cm^{-1} (CO); δ_H 0.75–0.99 (9H, m, 2×*Me*CH and *Me*CH_2), 1.07–1.61 [7H, m, C*H*Me and $(CH_2)_3$], 1.41 (3H, s, MeC), 1.63–1.96 (2H, m, CH_2Me), 5.09 (2H, s, PhCH_2), 7.24–7.50 (5H, m, ArH); δ_C 8.0, 22.5, 23.0, 27.8 (4×Me), 21.2, 30.6, 37.6, 39.1 [$(CH_2)_3$ and CH_2Me], 68.6 (Ph*C*H_2), 87.1 (CO), 128.1 (2C), 128.2, 128.5 (2C), 135.8 (ArC), 153.3 (C=O); *m/z* (DIP) 292 (M^+, <1%), 181 (16), 180 (11), 140 (29), 91 (100), 85 (12), 71 (13), 70 (17), 57 (13), 43 (11); HRMS: M^+, found 292.2064. $C_{18}H_{28}O_3$ requires 292.2038.

4.2.6. Benzyl geranyl carbonate (1e).[24] Colourless oil; yield: 26%; R_f 0.50 (hexane/ethyl acetate: 9:1); ν (film) 3082, 3055, 3033, 1596, 1498 (HC=C), 1744 (C=O), 1255 cm^{-1} (CO); δ_H 1.60, 1.68, 1.71 (3H each, 3s, 3×Me), 1.99–2.12 [4H, m, $(CH_2)_2$], 4.54–4.74 (2H, m, CHCH_2O), 4.99–5.20 (3H, m, C*H*=CMe_2 and PhCH_2), 5.33–5.46 (1H, m, C*H*CH_2O), 7.29–7.42 (5H, m, ArH); δ_C 16.5, 17.7, 25.7 (3×Me), 26.2, 39.5 [$(CH_2)_2$], 66.5 (CH*C*O), 69.6 (Ph*C*H_2), 117.8, 123.6 (2×*C*H=CMe), 131.7, 135.3 (2×*C*=CH), 128.2 (2C), 128.25, 128.5 (2C), 142.8 (ArC), 155.1 (C=O); *m/z* 288 (M^+, <1%), 136 (29), 135 (12), 121 (26), 108 (12), 107 (18), 93 (41), 92 (20), 91 (100), 80 (15), 79 (15), 77 (15), 69 (81), 68 (50), 67 (16), 65 (10).

4.2.7. Allyl 2,4,6-trimethylphenyl carbonate (1f). Colourless oil; yield: 64%; R_f 0.55 (hexane/ethyl acetate: 9:1); ν (film) 3088, 3068, 1650, 1607, 1486 (HC=C), 1759 (C=O), 1245 cm^{-1} (CO); δ_H 2.59, 2.69 (6H and 3H, respectively, 2s, 3×Me), 5.18 (2H, d, $J=5.8$ Hz, CHCH_2O), 5.67–5.92, (2H, m, CH_2=C), 6.32–6.52 (1H, m, C*H*=CH_2), 7.29 (2H, s, 2×ArH); δ_C 16.0 (2C), 20.7 (3×Me), 69.0 (CH_2O), 119.2 (*C*H_2=C), 131.3 (*C*H=CH_2), 129.3 (2C), 129.6 (2C), 135.6, 146.2 (ArC), 153.0 (C=O); *m/z* (DIP) 220 (M^+, 8%), 136 (23), 135 (100), 97 (17), 91 (33), 85 (28), 83 (15), 71 (35), 70 (12), 69 (16), 57 (44), 56 (12), 55 (18), 43 (26), 41 (37); HRMS: M^+, found 220.1098. $C_{13}H_{16}O_3$ requires 220.1099.

4.2.8. *N*-(Allyloxycarbonyl)dioctylamine (2aa).[25] Colourless oil; yield: 41%; R_f 0.60 (hexane/ethyl acetate: 9:1); ν (film) 3082, 1649 (HC=C), 1705 (C=O), 1237 cm^{-1} (CO); δ_H 0.88 (6H, t, $J=6.6$ Hz, 2×Me), 1.14–1.38, 1.41–1.61 [20H and 4H, respectively, 2m, 2×Me(CH_2)$_6$], 3.06–3.30 (4H, m, 2×CH_2N), 4.59 (2H, d, $J=5.3$ Hz, CH_2O), 5.20, 5.31 (1H each, 2d, $J=10.1$, 17.2 Hz, respectively, CH_2=C), 5.81–6.02 (1H, m, CH=C); δ_C 14.1 (2C, 2×Me), 22.6 (2C), 26.8 (2C), 29.2 (2C), 29.3 (2C), 29.4 (2C), 31.8 (2C) [2×Me(*C*H_2)$_6$], 46.9 (2C, 2×CN), 65.6 (CO), 118.8 (*C*H_2=C), 133.4 (*C*H=C), 155.1 (C=O); *m/z* (DIP) 325 (M^+, <1%), 269 (27), 268 (100), 241 (16), 240 (86), 142 (26), 71 (28), 57 (28), 43 (13).

4.2.9. *N*-(Benzyloxycarbonyl)dioctylamine (2ab).[26] Colourless oil; yield: 68%; R_f 0.56 (hexane/ethyl acetate: 9:1); ν (film) 3065, 3032, 1498 (HC=C), 1704, 1643 (C=O), 1237 cm^{-1} (CO); δ_H 0.88 (6H, t, $J=7.0$ Hz, 2×Me), 1.07–1.38, 1.40–1.66 [20H and 4H, respectively, 2m, 2×Me(CH_2)$_6$], 3.13–3.32 (4H, m, 2×CH_2N), 5.12 (2H, s, PhCH_2), 7.07–7.46 (5H, m, ArH); δ_C 14.1 (2C, 2×Me), 22.6 (2C), 26.8 (2C), 29.2 (2C), 29.3 (2C), 29.4 (2C), 31.8 (2C) [2×Me(*C*H_2)$_6$], 46.9, 47.5 (2×CN), 66.7 (CO), 127.65 (2C), 127.7, 128.3 (2C), 137.1 (ArC), 156.1 (C=O); *m/z* (DIP) 375 (M^+, 5%), 269 (24), 268 (100), 240 (35), 232 (42), 170 (25), 142 (20), 91 (74), 71 (33), 57 (31), 43 (14).

4.2.10. *N*-(Benzyloxycarbonyl)diallylamine (2b).[27] Colourless oil; yield: 65%; R_f 0.23 (hexane/ethyl acetate: 9:1); ν (film) 3082, 3060, 3028, 1651, 1591, 1503 (HC=C), 1744, 1702 (C=O), 1241 cm^{-1} (CO); δ_H 3.77–3.99 (4H, m, 2×CH_2N), 5.15 (2H, s, PhCH_2), 5.01–5.25 (4H, m, 2×CH_2=C), 5.67–5.86 (2H, m, 2×C*H*=CH_2), 7.26–7.50 (5H, m, ArH); δ_C 46.2, 49.1 (2×CN), 67.1 (Ph*C*H_2), 116.7, 117.1 (2×*C*H_2=C), 127.7 (2C), 128.4 (2C), 128.5, 136.8 (ArC), 133.4 (2C, 2×*C*H=CH_2), 156.0 (C=O); *m/z* (DIP) 231 (M^+, 3%), 181 (12), 180 (37), 151 (33), 107 (57), 92 (31), 91 (100), 79 (36), 77 (17), 65 (17).

4.2.11. *N*-(Benzyloxycarbonyl)-*N*-methylaniline (2c).[28] Colourless oil; yield: 62%; R_f 0.28 (hexane/ethyl acetate: 9:1); ν (film) 3088, 3063, 3032, 1598, 1497 (HC=C), 1749, 1708 (C=O), 1298 cm^{-1} (CO); δ_H 3.31 (3H, s, Me), 5.15 (2H, s, PhCH_2), 6.99–7.51 (10H, m, ArH); δ_C 38.4 (Me), 67.2 (Ph*C*H_2), 126.6 (2C), 126.8, 127.6, 127.8 (2C), 128.3 (2C), 128.8 (2C), 136.6, 138.9 (ArC), 155.4 (C=O); *m/z* (DIP) 241 (M^+, 58%), 197 (65), 196 (17), 181 (11), 120 (28), 106 (14), 92 (28), 91 (100), 77 (28), 65 (24).

4.2.12. *O*-Allyl *S*-(1-decyl) thiocarbonate (3aa). Colourless oil; yield: 81%; R_f 0.33 (hexane); ν (film) 3082, 1648 (HC=C), 1744, 1713 (C=O), 1138 cm^{-1} (CO); δ_H 0.88 (3H, t, $J=6.6$ Hz, Me), 1.15–1.46, 1.55–1.71 [14H and 2H, respectively, 2m, Me(CH_2)$_8$], 2.86 (2H, t, $J=7.3$ Hz, CH_2S), 4.71 (2H, d, $J=5.8$ Hz, CH_2O), 5.28, 5.37 (1H each, 2d, $J=10.5$, 17.2 Hz, respectively, CH_2=C), 5.83–6.03, (1H, m, CH=C); δ_C 14.1 (Me), 22.6, 28.7,

29.1, 29.3, 29.4, 29.5, 29.7, 31.0, 31.9 [(CH_2)$_9$], 67.6 (CO), 118.9 (H_2C=C), 131.6 (CH=C), 171.1 (C=O); *m/z* (DIP) 258 (M^+, <1%), 201 (49), 174 (10), 173 (68), 172 (29), 140 (16), 99 (17), 97 (18), 85 (92), 83 (20), 71 (79), 69 (23), 57 (100), 55 (37), 43 (61), 42 (14), 41 (32); HRMS: M^+, found 258.1654. $C_{14}H_{26}O_2S$ requires 258.1654.

4.2.13. *O*-Benzyl *S*-(1-decyl) thiocarbonate (3ab). Colourless oil; yield: 62%; R_f 0.33 (hexane); ν (film) 3099, 3065, 3033, 1498 (HC=C), 1744, 1710 (C=O), 1134 cm^{-1} (CO); δ_H 0.88 (3H, t, J=6.6 Hz, Me), 1.14–1.45, 1.50–1.71 [14H and 2H, respectively, 2m, Me(CH_2)$_8$], 2.86 (2H, t, J=7.5 Hz, CH_2S), 5.22 (2H, s, PhCH_2), 7.18–7.44, (5H, m, ArH); δ_C 14.1 (Me), 22.7, 28.7, 29.1, 29.3, 29.4, 29.5, 29.7, 31.1, 31.9 [(CH_2)$_9$], 68.7 (CO), 128.3 (2C), 128.4, 128.6 (2C), 135.3 (ArC), 171.3 (C=O); *m/z* (DIP) 264 (M^+, 7%), 201 (16), 181 (49), 180 (30), 179 (16), 174 (11), 173 (88), 172 (12), 165 (12), 97 (21), 92 (59), 91 (100), 85 (26), 83 (15), 77 (11), 71 (23), 69 (17), 65 (20), 57 (32), 55 (28), 43 (34), 41 (30); HRMS: M^+, found 308.1809. $C_{18}H_{28}O_2S$ requires 308.1810.

4.2.14. *O*-Benzyl *S*-cyclohexyl thiocarbonate (3b). Colourless oil; yield: 74%; R_f 0.25 (hexane); ν (film) 3099, 3064, 3032, 1591, 1503 (HC=C), 1705 (C=O), 1132 cm^{-1} (CO); δ_H 1.10–2.10 (10H, m, 5×CH_2 ring), 3.28–3.43 (1H, m, CHS), 5.21 (2H, s, PhCH_2), 7.15–7.43 (5H, m, ArH); δ_C 25.4, 25.8 (2C), 33.1 (2C) (5×CH_2 ring), 44.4 (CS), 68.4 (CO), 128.2 (2C), 128.3, 128.5 (2C), 135.3 (ArC), 170.8 (C=O); *m/z* (DIP) 250 (M^+, 9%), 181 (28), 180 (17), 92 (70), 91 (100), 83 (17), 81 (18), 79 (13), 77 (24), 65 (34), 55 (28), 41 (22); HRMS: M^+, found 250.1024. $C_{14}H_{18}O_2S$ requires 250.1028.

4.2.15. *O*-Allyl *S*-phenyl thiocarbonate (3c). Colourless oil; yield: 57%; R_f 0.70 (hexane/ethyl acetate: 9:1); ν (film) 3078, 3055, 1636, 1583, 1479 (HC=C), 1726 (C=O), 1135 cm^{-1} (CO); δ_H 4.72 (2H, d, J=5.8 Hz, CH_2O), 5.28, 5.31 (1H each, 2d, J=10.5, 17.2 Hz, respectively, CH_2=C), 5.78–6.01 (1H, m, CH=CH_2), 6.93–7.74 (5H, m, ArH); δ_C 68.2 (CO), 117.6 (CH_2=C), 129.6, 129.8 (2C), 134.8 (2C), 135.9 (ArC), 133.5 (C=CH_2), 169.4 (C=O); *m/z* (DIP) 194 (M^+, 2%), 165 (15), 150 (15), 149 (77), 137 (10), 135 (64), 125 (15), 124 (69), 123 (100), 111 (13), 110 (39), 109 (50), 97 (14), 91 (17), 85 (13), 83 (12), 79 (11), 77 (22), 71 (14), 69 (17), 65 (16), 57 (22), 55 (13), 51 (13), 45 (26), 43 (12), 41 (21); HRMS: M^+, found 194.0415. $C_{10}H_{10}O_2S$ requires 194.0402.

4.3. Preparation of diprotected nonane-1,9-diol 1g

n-BuLi (6.3 mL of a 1.6 M solution of *n*-BuLi in hexane, 10.0 mmol) was dropwise added to a stirred solution of nonane-1,9-diol (1.635 g, 10.0 mmol) in anhydrous THF (10 mL) at 0 °C. Five minutes after the addition had been completed, benzyl chloroformate (1.5 mL, 10.0 mmol) was added during ca. 5 min. After stirring for 10 min at the same temperature, the same amount of *n*-BuLi as above was dropwise added, the reaction mixture was stirred for 5 min and allyl chloroformate (1.1 mL, 10.0 mmol) was added during ca. 5 min. The reaction was then stirred for 5 min, the cooling bath was removed and stirring was continued at room temperature for 2 h. The crude reaction mixture was adsorbed on basic aluminium oxide, transferred to a short column of basic aluminium oxide and eluted with hexane. Evaporation of the solvent (15 Torr) gave the pure diprotected diol **1g** in 26% yield. The corresponding physical, spectroscopic and analytical data follow.

4.3.1. Benzyl 9-(allyloxycarbonyloxy)-1-nonyl carbonate (1g). Colourless oil; yield: 26%; R_f 0.50 (hexane/ethyl acetate: 9:1); ν (film) 3060, 3028, 1645, 1497 (HC=C), 1747 (C=O), 1259 cm^{-1} (CO); δ_H 1.13–1.74 [14H, m, (CH_2)$_7$CO], 4.13 (2H, t, J=6.6 Hz, 1×$CH_2C\mathit{H}_2O$), 4.57–4.68 (4H, m, CH_2CH and 1×$CH_2C\mathit{H}_2O$), 5.17 (2H, s, PhCH_2), 5.28, 5.39 (1H each, 2d, J=10.3, 17.7 Hz, respectively, CH_2=C), 5.85–6.01 (1H, m, H_2C=CH), 7.31–7.42 (5H, m, ArH); δ_C 14.1 (2C), 23.3 (2C), 25.7 (2C), 39.0 [(CH_2)$_7$CO], 68.3 (2C), 69.6, 74.3 (4×CO), 118.8 (CH_2=C), 128.3 (2C), 128.5, 128.6 (2C), 131.7 (ArC), 131.5 (CH=CH_2), 155.2 (2C, 2×C=O); *m/z* (DIP) 378 (M^+, 1%), 125 (14), 108 (16), 107 (79), 92 (11), 91 (100), 83 (31), 81 (15), 69 (56), 57 (15), 55 (27), 41 (27); HRMS: M^+, found 378.2050. $C_{21}H_{30}O_6$ requires 378.2042.

4.4. Naphthalene-catalysed lithiation of compounds 1–3. Preparation of products 4–6. General procedure

A solution of the protected substrate **1**–**3** (1.0 mmol) in THF (2 mL) was dropwise added to a green suspension of lithium powder (63 mg, 9.0 mmol) and naphthalene (20 mg, 0.16 mmol) in THF (5 mL), under Ar, at 0 °C. After stirring at the same temperature for the time indicated in Table 1, methanol (5 mL) was carefully added, the cooling bath was removed and the reaction was stirred till it reached room temperature. The yields of the deprotected products were determined by quantitative GLC. Commercially available alcohols **4**, amines **5**, thiols **6**, *n*-dodecane (internal standard) and *n*-hexadecane (internal standard for **4f**) were used in the determination of response factors. Compounds **4**–**6** (commercially available) were characterised by comparison of their physical and spectroscopic data with authentic samples.

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DTBB-catalysed lithiation of 1,2-bis(phenylsulfanyl)ethene: does 1-lithio-2-phenylsulfanylethene really exist?

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Abstract—The reaction of (*Z*)- or (*E*)-1,2-bis(phenylsulfanyl)ethene (**1**) with an excess of lithium and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB, 2.5 mol%) in the presence of a carbonyl compound as electrophile (Barbier conditions) in THF at −78 °C leads, after hydrolysis with water at temperatures ranging between −78 °C and rt, to a mixture of the corresponding (*Z*/*E*)-unsaturated 1,4-diols **2**, the diastereomers ratio being independent of the stereochemistry of the starting materials. Allylic alcohols **3** are the main by-products, resulting from a lithium–hydrogen exchange on some of the lithiated intermediates along the whole process. A mechanistic explanation for the observed behaviour is given.

1. Introduction

Among functionalised organolithium compounds,[1] the corresponding sp^3-hybridised β-substituted derivatives **I** are extremely unstable even at very low temperature, so they decompose very easily by β-elimination giving an olefin.[2] There are two main ways to stabilise intermediates of type **I**: (a) locating a negative charge at the heteroatom (as in **II**) in order to inhibit the ability of the group Y^- to act as a leaving one,[3] and (b) bonding the lithium atom to a sp^2-hybridised carbon atom (as in **III**), which can stabilise better the negative charge. Concerning the heteroatom, only oxygen- or nitrogen-containing intermediates of type **II** and **III** have been reported so far. For instance, chlorovinyllithiums (**IV**) were generated with essentially 0% yield even at very low temperatures.[3] For oxygen-containing derivatives, while (*Z*)-ethoxyvinyllithium (**V**) can be generated at low temperature by bromine–lithium[4] or tin–lithium exchange,[5] the corresponding (*E*)-analogue decomposes easily (even at −50 °C) to give acetylene.[6] As expected, the stability of this type of intermediates is increased notably when an anionic group is located at the β-position (such as in intermediate **VI**, prepared by bromine–lithium exchange)[7] or when a chelating heteroatom is in an adequate position (such as in compound **VII**, generated by direct deprotonation),[8] in the last case the coordination by the oxygen atom exerting an important stabilising effect.[9] In the case of nitrogen-containing intermediates of type **III**, the corresponding (*Z*)-derivatives **VIII** have been prepared by direct deprotonation[10] or by bromine–lithium exchange,[11] only one example of an (*E*)-derivative **IX** having been described so far, to the best of our knowledge.[12] However, as far as we know, only two examples of sulfur-containing derivatives of type **III** have been reported in the literature, the dilithium compound **X** (prepared by double tin–lithium exchange from the corresponding stannathiacyclopentene)[13] and **XI** (generated by direct deprotonation).[14] On the other hand, dilithium intermediates of the type **XII** (not accessible from the corresponding dihalo compounds) are interesting reagents in synthetic organic chemistry because in the reaction with electrophiles they are able to introduce two electrophilic fragments in one only synthetic operation (Chart 1).[15] In this paper we want to report the arene-catalysed lithiation[16–18] of 1,2-bis(phenylsulfanyl)ethenes with the aim of generating dilithium intermediates of type **XII**, involving monolithiated species of type **III** with **X**=PhS. This last intermediate has not only the drawback of decomposing by β-elimination (the PhS^- is a good leaving group), but also it can deprotonate intra or intermolecularly a carbon–hydrogen bond at the α-position with respect to the sulfur atom (for instance in the starting materials).

2. Results and discussion

The reaction of (*Z*)-1,2-bis(phenylsulfanyl)ethene [(*Z*)-**1**

Keywords: DTBB-catalysed lithiation; Sulfur–lithium exchange; Dilithium synthons; Unsaturated 1,4-diols.
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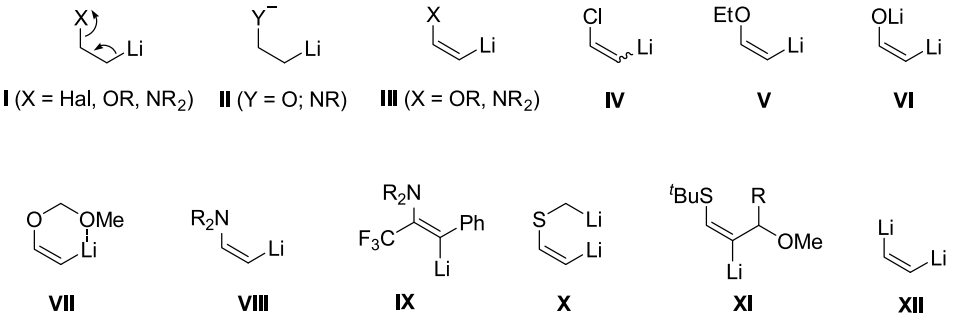
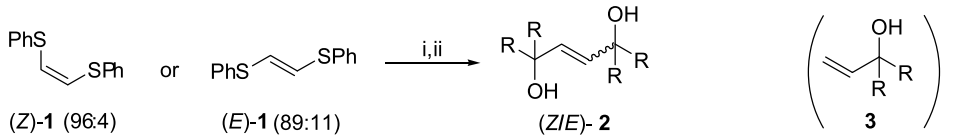


Chart 1.



Scheme 1. Reagents and conditions: (i) Li, DTBB (cat.), R_2CO=Et_2CO, $^nPr_2CO$, $(n\text{-}C_5H_{11})_2CO$, $^iPr_2CO$, $(CH_2)_5CO$, THF, −78 °C; (ii) H_2O, −78 °C to rt.

(96:4)] with an excess of lithium (1:7 mol ratio; theoretical 1:4 mol ratio) and a catalytic amount of 4,4′-di-*tert*-butylbiphenyl (DTBB; 1:0.1 mol ratio; 2.5% mol) in the presence of a ketone as electrophile (1:3 mol ratio) in THF at −78 °C gave, after hydrolysis with water, the corresponding diols **2** as a (*Z*/*E*)-mixture of diastereomers with low to modest isolated yields (Scheme 1, Chart 2 and Table 1, entries 1–5). In general, the main by-product in the crude reaction mixture was the corresponding allylic alcohols **3**.

As can be seen in Scheme 1, one important aspect concerning the stereochemistry has to do with the final proportion of (*Z*/*E*)-diastereomers depending on the geometry of the starting material **1**. Thus, starting from an enriched material (*Z*)-**1** (96:4) or (*E*)-**1** (89:11) and 3-pentanone, the same (*Z*/*E*)-ratio was observed in both cases: 0.47/1 (Table 1, entries 1 and 6). The same behaviour was observed with cyclohexanone, so a 0.67/1 (*Z*/*E*)-ratio was obtained for both starting materials (Table 1, entries 5 and 7). These results clearly indicate that some equilibration takes place through the whole reaction. Initially a sulfur–lithium exchange occurs, which in principle works with retention of the configuration,[19] but once intermediates **XIII** are formed an equilibrium can take place,[20] so the corresponding mixture of diastereomers is obtained independently of the starting material. Two important problems are associated to intermediates **XIII**: (a) the (*E*)-diastereomer suffers easy β-elimination to yield acetylene, even at low temperature,[4a] and (b) a lithium–hydrogen exchange can take place from intermediates **XIII** giving either phenyl vinyl thioether (abstracting a proton from the reaction medium, probably from THF[21]) or a new intermediate **XVII** (by intra or intermolecular deprotonation). Anyhow, once intermediates **XIII** have survived, they react with a carbonyl compound also with retention to yield alkoxides **XIV**, which suffer again a sulfur–lithium exchange to give the corresponding organolithium intermediates **XV** with the same stereochemistry. This type of intermediates are configurationally stable[22] and do not undergo equilibration, so the corresponding final products **XVI** arise from the reaction of compounds **XV** with the same electrophile present in the reaction medium with retention of the configuration. Final hydrolysis of these dialkoxides **XVI** gives the expected diols **2**. Another important problem with dianions of type **XV** is their instability by abstracting a proton from the reaction medium to give the most abundant by-products, the allylic alcohols **3** through the corresponding alkoxides **XVIII** (Chart 3). As can be seen, from the former considerations, it is easy to explain the low yields obtained in the lithiation of compounds **1** and in situ reaction with carbonyl compounds.

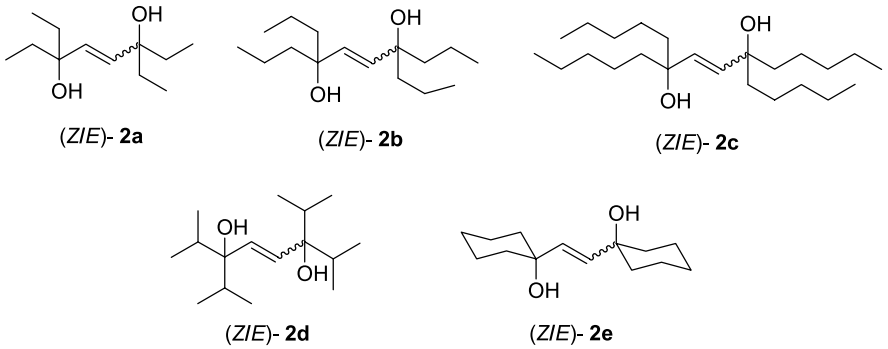


Chart 2.

Table 1. Preparation of compounds **2**

Entry	Starting material[a]	Electrophile R_2CO	Product[b]				
			No.	Conversion (%)	GC yield (%)[c]	Isolated yield (%)[d]	*Z*/*E* Ratio[e]
1	(*Z*)-**1**	Et_2CO	**2a**	>99	36 (55)	30	0.47/1
2	(*Z*)-**1**	$^nPr_2CO$	**2b**	>99	33 (—[f])	30	0.56/1
3	(*Z*)-**1**	$(n\text{-}C_5H_{11})_2CO$	**2c**	>99	36 (25)	35	0.76/1
4	(*Z*)-**1**	$^iPr_2CO$	**2d**	>99	25 (—[f])	15	0.10/1
5	(*Z*)-**1**	$(CH_2)_5CO$	**2e**	>99	30 (43)	20	0.67/1
6	(*E*)-**1**	Et_2CO	**2a**	>99	17 (48)	15	0.47/1
7	(*E*)-**1**	$(CH_2)_5CO$	**2e**	>99	32 (52)	18	0.67/1

[a] Purity of (*Z*)-**1**: *Z*/*E* ratio 96/4. Purity of (*E*)-**1**: *E*/*Z* ratio 89/11.
[b] All products **2** were >95% pure (GLC and/or 300 MHz ^{1}H NMR).
[c] In parenthesis estimated yield of the monocondensation alcohol **3**.
[d] Isolated yield of analytically pure compounds **2** after flash chromatography (neutral silica gel, hexane/ethyl acetate) based on the starting material **1**.
[e] Deduced from the crude reaction mixture by 300 MHz ^{1}H NMR.
[f] Not determined.

Due to the difficulty of assigning the stereochemistry of products **2** by spectroscopic means, we separated both diastereomers, looking for the possibility of performing a X-ray determination. That was the case for the major diastereomer (*E*)-**2e** (Fig. 1). Knowing the geometry of both (*Z*)- and (*E*)-**2**, we conclude that in all cases the olefinic protons in (*E*)-diastereomers appear at lower field than for the corresponding (*Z*)-ones.

Starting materials **1** were prepared from commercially available (*Z*)-1,2-dichloroethene by reaction with potassium phenylthiolate under ethanol reflux as a mixture of (*Z*/*E*)-diastereomers, which was separated by flash chromatography to yield both enriched (*Z*)- and (*E*)-**1**.[23]

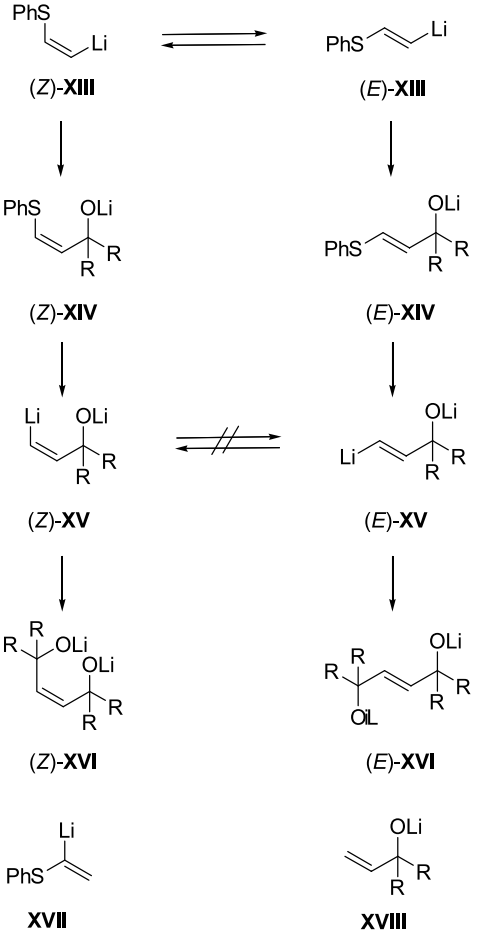
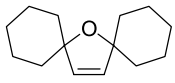


Chart 3.

Pure diols (*Z*)- and (*E*)-**2e** were treated separately under acidic conditions (H_3PO_4 85%) in order to study the corresponding possible dehydration, the results being different depending on the structure of the starting diol. Thus, as expected, compound (*Z*)-**2e** yielded the heterocycle **4e** in quantitative yield (>95%), while its (*E*)-isomer gave a mixture of olefinic compounds resulting from a dehydration process. This result suggests that no (*E*)→(*Z*) isomerization occurred under the assayed acidic reaction conditions.



4e

3. Conclusion

In conclusion, from the results described here, we propose that there is an equilibrium between both (*Z*)- and (*E*)-intermediates of type **XIII**, so the same ratio of (*Z*/*E*)-products **2** is obtained starting from differently enriched (*Z*/*E*)-mixtures of disulfides **1**. Even working with poor yields (due to the high instability of intermediates **XIII** and **XV**) the reaction allows the introduction of two electrophilic fragments at both carbon atoms of ethylene so, in this way, compounds **1** act as synthetic equivalents of the unknown ethene 1,2-dianion (see, for instance, intermediate **XII**). By-products **3** are not interesting from a synthetic point of view, because they can be easily prepared by addition of a vinyl

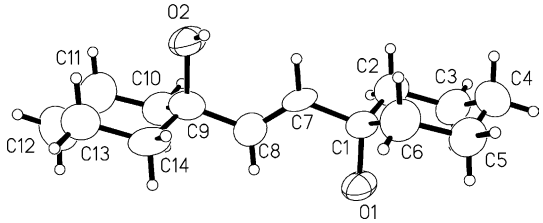


Figure 1.

metal (for example, commercially available vinylmagnesium bromide) to a ketone.

4. Experimental

4.1. General

For general information see Ref. 24. Lithium powder was prepared from commercially available lithium granules (99%, high sodium content, Aldrich) as it was already reported by us.[25] X-ray analysis was performed at the Technical Services of the University of Alicante, the corresponding details being given below.

4.2. Preparation of (*Z*)-and (*E*)-1,2-bis(phenylsulfanyl)-1-ethene [(*Z*)- and (*E*)-1][23]

(*Z*)-1,2-Dichloroethene (3 mL, 38.5 mmol) was added, with stirring, to a solution of potassium hydroxide (9.05 g, 137 mmol) and thiophenol (8.3 mL, 81 mmol) in ethanol (120 mL). The mixture was refluxed at 80 °C for 7 h, the solvent was then evaporated (15 Torr) and the resulting residue was diluted with water and extracted with ethyl acetate. The organic layer was dried over anhydrous $MgSO_4$ and evaporated (15 Torr) to give the desired mixture of (*Z*)- and (*E*)-diastereomers (80:20), which was separated by flash chromatography (neutral silica gel, hexane) to yield both enriched (*Z*) and (*E*)-**1**.

4.2.1. (*Z*)-1,2-Bis(phenylsulfanyl)-1-ethene [(*Z*)-1].[23] Yellow liquid. t_r=17.0 min; R_f (hexane)=0.2; ν (film) 3056, 3043, 928, 736, 687 cm^{-1}; δ_H 6.51 (2H, s, HC=CH), 7.21–7.42 (10H, m, ArH); δ_C 125.3, 126.9, 129.2, 129.4, 134.9; *m/z* 244 (M^+, 100%), 199 (10), 135 (67), 134 (54), 121 (11), 109 (28), 91 (33), 77 (11), 65 (13); HRMS: M^+, found 244.0370. $C_{14}H_{12}S_2$ requires 244.0380.

4.2.2. (*E*)-1,2- Bis(phenylsulfanyl)-1-ethene [(*E*)-1].[23] White solid. Mp 63 °C; t_r=17.5 min; R_f (hexane)=0.1; ν (KBr) 3061, 3059, 908, 733, 690 cm^{-1}; δ_H 6.49 (2H, s, HC=CH), 7.18–7.39 (10H, m, ArH); δ_C 124.8, 126.7, 129.0, 129.2, 135.0; *m/z* 244 (M^+, 100%), 199 (10), 135 (60), 134 (47), 109 (23), 91 (27), 65 (11); HRMS: M^+, found 244.0393. $C_{14}H_{12}S_2$ requires 244.0380.

4.3. DTBB-catalysed lithiation of (*Z*) and (*E*)-1,2-bis(phenylsulfanyl)ethene [(*Z*) and (*E*)-1] and in situ reaction with carbonyl compounds. Preparation of compounds 2

To a cooled green suspension of lithium (49 mg, 7 mmol) and DTBB (26 mg, 0.1 mmol) in THF (2 mL) at −78 °C was slowly added a solution of the corresponding electrophile (3 mmol) and (*Z*) or (*E*)-1,2-bis(phenylsulfanyl)ethene (244 mg, 1 mmol) in THF (3 mL). The resulting mixture was stirred for 3 h at the same temperature and then it was hydrolysed with water (5 mL) allowing the temperature to rise to 20 °C. The resulting mixture was extracted with ethyl acetate (3×10 mL). The organic layer was dried over anhydrous $MgSO_4$ and evaporated (15 Torr). The resulting residue was then purified by flash chromatography (neutral silica gel, hexane/ethyl acetate) to give the desired compounds. Solid products were recrystallized in hexane/diethyl ether. Yields are given in Table 1; physical, analytical spectroscopic data as well as literature references for the known compounds follow. Some by-products **3** (**3a**,**c**,**d**) were characterized by GLC-MS from the crude reaction mixture, the corresponding data (t_r and MS) as well as literature references also follow.

4.3.1. (*Z*)-3,6-Diethyl-4-octene-3,6-diol [(*Z*)-2a].[26] White solid. Mp 73 °C; t_r=11.1 min; R_f (hexane/ethyl acetate 8:2)=0.2; ν (KBr) 3364, 3053, 975, 736 cm^{-1}; δ_H 0.92 (12H, t, *J*=7.5 Hz, 4×CH_3), 1.60, 1.61 (8H, 2q, *J*=7.5 Hz, 4×CH_2), 5.28 (2H, s, HC=CH); δ_C 8.3 (CH_3), 34.4 (CH_2), 76.1 (COH), 135.1 (HC=CH); *m/z* 182 (M^+-H_2O, 2%), 171 (12), 154 (11), 153 (100), 57 (24); HRMS: $M^+-C_2H_5$, found 171.1389. $C_{10}H_{19}O_2$ requires 171.1385.

4.3.2. (*E*)-3,6-Diethyl-4-octene-3,6-diol [(*E*)-2a].[26] White solid. Mp 66 °C; t_r=10.9 min; R_f (hexane/ethyl acetate 8:2)=0.1; ν (KBr) 3603, 3467 (OH), 3010, 908, 734 cm^{-1}; δ_H 0.87 (12H, t, *J*=7.5 Hz, 4×CH_3), 1.55, 1.57 (8H, 2q, *J*=7.5 Hz, 4×CH_2), 5.56 (2H, s, HC=CH); δ_C 7.9 (CH_3), 33.4 (CH_2), 75.6 (COH), 133.7 (HC=CH); *m/z* 182 (M^+-H_2O, 2%), 172 (11), 171 (100), 153 (66), 135 (11), 125 (12), 107 (16), 97 (24), 93 (10), 85 (16), 83 (16), 81 (11), 69 (20), 57 (87), 55 (34); HRMS: M^+, found 171.1387. $C_{12}H_{24}O_2$ requires 171.1385.

4.3.3. (*Z*)-4,7-Dipropyl-5-decene-4,7-diol [(*Z*)-2b].[26] White solid. Mp 66–70 °C; t_r=13.4 min; R_f (hexane/ethyl acetate 8:2)=0.4; ν (KBr) 3384, 908, 735 cm^{-1}; δ_H 0.91 (12H, t, *J*=7.3 Hz, 4×CH_3), 1.26–1.56 (16H, m, 8×CH_2), 4.19 (2H, br s, 2×OH), 5.26 (2H, s, HC=CH); δ_C 14.5 (CH_3), 17.2 (CH_2CH_3), 44.8 (CH_2COH), 75.7 (COH), 135.0 (HC=CH); *m/z* 238 (M^+-H_2O, 1%), 196 (14), 195 (100), 71 (12); HRMS: $M^+-C_3H_7$, found 213.1843. $C_{13}H_{25}O_2$ requires 213.1855.

4.3.4. (*E*)-4,7-Dipropyl-5-decene-4,7-diol [(*E*)-2b].[26] White solid. Mp 57–62 °C; t_r=13.2 min; R_f (hexane/ethyl acetate 8:2)=0.3; ν (KBr) 3404, 3054, 975, 745 cm^{-1}; δ_H 0.90 (12H, t, *J*=7.3 Hz, 4×CH_3), 1.26–1.52 (16H, m, 8×CH_2), 5.58 (2H, s, HC=CH); δ_C 14.5 (CH_3), 16.8 (CH_2CH_3), 43.7 (CH_2COH), 75.2 (COH), 133.7 (HC=CH); *m/z* 238 (M^+-H_2O, 1%), 214 (14), 213 (100), 195 (37), 99 (13), 83 (15), 71 (50), 69 (22), 57 (11), 55 (12); HRMS: $M^+-C_3H_7$, found 213.1846. $C_{13}H_{25}O_2$ requires 213.1855

4.3.5. (*Z*)-6,9-Dipentyl-7-tetradecene-6,9-diol [(*Z*)-2c].[26] White solid. Mp 78 °C; t_r=17.6 min; R_f (hexane/ethyl acetate 8:2)=0.3; ν (KBr) 3383, 910, 740 cm^{-1}; δ_H 0.88 (12H, t, *J*=6.8 Hz, 4×CH_3), 1.23–1.33, 1.51–1.58 (32H, m, 16×CH_2), 5.26 (2H, s, HC=CH); δ_C 12.4 (CH_3), 21.0, 22.0, 30.7, 40.8 (CH_2), 74.1 (COH), 133.5 (HC=CH); *m/z* 350 (M^+-H_2O, 1%), 280 (21), 279 (100); HRMS: $M^+-C_5H_{11}$, found 297.2787. $C_{19}H_{37}O_2$ requires 297.2794.

4.3.6. (*E*)-6,9-Dipentyl-7-tetradecene-6,9-diol [(*E*)-2c].[26] White solid. Mp 70 °C; t_r=17.5 min; R_f (hexane/ethyl acetate 8:2)=0.2; ν (KBr) 3512, 3199, 908, 734 cm^{-1}; δ_H 0.88 (12H, t, *J*=6.6 Hz, 4×CH_3), 1.21–1.34, 1.43–1.59 (32H, m, 16×CH_2), 5.56 (2H, s, HC=CH); δ_C 14.0 (CH_3),

22.6, 23.3, 32.3, 41.5 (CH_2), 75.3 (COH), 133.8 (HC=CH); *m/z* 350 ($M^+ - H_2O$, 1%), 298 (21), 297 (100), 279 (27), 99 (15), 71 (17); HRMS: $M^+ - C_5H_{11}$, found 297.2787. $C_{19}H_{37}O_2$ requires 297.2794.

4.3.7. (*Z*)-3,6-Diisopropyl-2,7-dimethyl-4-octene-3,6-diol [(*Z*)-2d].[27] White solid. Mp 80 °C; $t_r = 13.4$ min; R_f (hexane/ethyl acetate 8:2) = 0.2; ν (KBr) 3554, 909, 738 cm^{-1}; δ_H 0.88, 0.92 (24H, 2d, $J = 6.7$ Hz, 8×CH_3), 1.90–1.98 (4H, m, 4×CH), 5.29 (2H, s, HC=CH); δ_C 16.9, 17.6 (CH_3), 33.7 (CH), 76.9, 80.2 (COH), 129.0 (HC=CH); *m/z* 238 ($M^+ - H_2O$, 1%), 214 (14), 213 (100), 195 (15), 127 (14), 109 (13), 97 (13), 71 (51), 69 (20); HRMS: $M^+ - C_3H_7$, found 213.1851. $C_{13}H_{25}O_2$ requires 213.1855.

4.3.8. (*E*)-3,6-Diisopropyl-2,7-dimethyl-4-octene-3,6-diol [(*E*)-2d].[27] White solid. Mp 62 °C. $t_r = 13.5$ min; R_f (hexane/ethyl acetate 8:2) = 0.1; ν (KBr) 3484, 918, 745 cm^{-1}; δ_H 0.86, 0.90 (24H, 2d, $J = 6.7$ Hz, 8×CH_3), 1.90–1.99 (4H, m, 4×CH), 5.51 (2H, s, HC=CH); δ_C 16.5, 17.7 (CH_3), 33.5 (CH), 77.2, 79.6 (COH), 132.0 (HC=CH); *m/z* 238 ($M^+ - H_2O$, 1%), 213 (16), 196 (14), 195 (100), 153 (29), 71 (21); HRMS: $M^+ - C_3H_7$, found 213.1846 $C_{13}H_{25}O_2$ requires 213.1855.

4.3.9. 1-[(*Z*)-2-(1-Hydroxycyclohexyl)-1-ethenyl]-1-cyclohexanol [(*Z*)-2e].[27] White solid. Mp 145 °C; t_r = 14.3 min; R_f (hexane/ethyl acetate 8:2) = 0.2; ν (KBr) 3603, 3467 (OH), 3010, 908, 734 cm^{-1}; δ_H 1.28–1.88 (20H, m, 10×CH_2), 3.88 (2H, br s, 2×OH), 5.40 (2H, s, HC=CH); δ_C 22.0, 25.4, 39.2 (CH_2), 72.0 (COH), 135.9 (HC=CH); *m/z* 224 (M^+, 12%), 206 (13), 164 (13), 163 (100), 149 (16), 145 (11), 135 (15), 107 (36), 95 (12), 91 (12), 81 (13), 79 (14), 67 (10), 55 (14); HRMS: M^+, found 224.1777. $C_{14}H_{24}O_2$ requires 224.1776.

4.3.10. 1-[(*E*)-2-(1-Hydroxycyclohexyl)-1-ethenyl]-1-cyclohexanol [(*E*)-2e].[27] White solid. Mp 117 °C; t_r = 14.2 min; R_f (hexane/ethyl acetate 8:2) = 0.1; ν (KBr) 3603, 3467 (OH), 3010, 908, 734 cm^{-1}; δ_H 1.26–1.67 (20H, m, 10×CH_2), 5.81 (2H, s, HC=CH); δ_C 22.1, 25.5, 38.1 (CH_2), 71.3 (COH), 135.1 (HC=CH); *m/z* 224 (M^+, 8%), 206 (20), 188 (17), 181 (62), 163 (27), 153 (13), 149 (11), 145 (35), 135 (18), 131 (16), 126 (13), 125 (100), 117 (10), 112 (36), 111 (27), 110 (14), 109 (13), 107 (26), 99 (21), 98 (14), 97 (28), 96 (25), 95 (24), 94 (13), 93 (20), 91 (23), 83 (23), 82 (14), 81 (40), 79 (29), 77 (14), 71 (11), 69 (17), 67 (27), 55 (47); HRMS: M^+, found 224.1790. $C_{14}H_{24}O_2$ requires 224.1776.

4.3.11. 3-Ethyl-1-penten-3-ol (3a).[28] $t_r = 4.5$ min; *m/z* 114 (M^+, 3%), 96 (10), 87 (16), 85 (100), 58 (27), 57 (10).

4.3.12. 3-Pentyl-1-octen-3-ol (3c). $t_r = 10.3$ min; *m/z* 198 (M^+, 1%), 128 (10), 127 (100), 67 (11), 57 (19), 55 (12).

4.3.13. 1-Vinylcyclohexanol (3e).[27] $t_r = 6.2$ min; *m/z* 126 (M^+, 7%), 111 (38), 98 (20), 97 (17), 84 (14), 83 (100), 79 (11), 70 (34), 55 (48).

4.4. Acidic treatment of (*Z*)-diol 2e

To a solution of the corresponding diol (0.1 mmol, 22 mg) in toluene (3 mL) was added H_3PO_4 85% (2 drops). The mixture was stirred for 2 h at room temperature, dried over anhydrous $MgSO_4$ and evaporated (1 Torr). The resulting residue was then purified by flash chromatography (neutral silica gel, hexane/ethyl acetate). Yield is given in the text and physical, analytical and spectroscopic data follow.

4.4.1. 7-Oxadispiro[5.1.5.2.]pentadec-14-ene (4e). Yellow liquid. $t_r = 11.1$ min; R_f (hexane/ethyl acetate 8:2) = 0.5; ν (film) 3025, 1651, 1075 cm^{-1}; δ_H 0.83–1.71 (20H, m, 10×CH_2), 5.86 (2H, s, HC=CH); δ_C 22.7, 23.6, 39.6 (CH_2), 88.3 (COH), 132.3 (HC=CH); *m/z* 206 (M^+, 21%), 164 (13), 163 (100), 135 (11), 107 (34), 94 (11); HRMS: M^+, found 206.1669. $C_{14}H_{22}O$ requires 206.1671.

4.5. X-ray analysis

Crystal data (deposited at the Cambridge Crystallographic Data Centre: CCDC 274485): $C_{14}H_{24}O_2$, $M = 224.33$; triclinic, $a = 9.7410(16)$ Å, $b = 19.424(3)$ Å, $c = 23.917(4)$ Å, $\alpha = 68.069°$, $\beta = 86.179°$, $\gamma = 87.858°$; $V = 6194.4(19)$ $Å^3$; space group $P(\bar{1})$; $Z = 12$; $D_c = 1.067$ Mg m^{-3}; $\lambda = 0.71073$ Å; $\mu = 0.069$ mm^{-1}; $F(000) = 1488$; $T = 297 \pm 1$ °C. Data collection was performed on a Bruker Smart CCD diffractometer in 'Servicios Técnicos de Investigación' of University of Alicante, based on three ω-scan runs (starting $\omega = -34°$) at values $\phi = 0°$, 120°, 240° with the detector at $2\theta = -32°$. An additional run of 100 frames, at $2\theta = -32°$, $\omega = -34°$ and $\phi = 0°$, was acquired to improve redundancy. For each of these runs, 606 frames were collected at 0.3° intervals and 30 s per frame. The diffraction frames were integrated using the program SAINT.[29] The structure was solved by direct methods[29] and refined to all 13242 unique F_o^2 by full matrix least squares.[30] All of the hydrogen atoms were placed at idealised positions and refined as rigid atoms. Final w$R_2 = 0.1588$ for all data and 878 parameters; $R1 = 0.0697$ for 3025 $F_o > 4\sigma(F_o)$.

Acknowledgements

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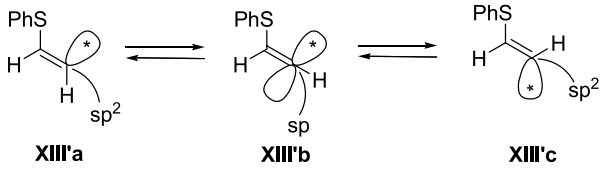

XIII′a **XIII′b** **XIII′c**

In addition, one referee suggested us that the former equilibrium could also take place before formation of the carbanions, through the corresponding radicals (*=·) initially generated; we thank the referee for suggesting us this possibility, which in fact can not be ruled out. On the other hand, as expected, the intermediate (*Z*)-**XIII** (ΔH_f= 68.98 Kcal/mol) is 6.59 Kcal/mol more stable than its diastereomer (*E*)-**XIII** (ΔH_f=75.57 Kcal/mol), from PM3 calculations (Hyperchem 7.5; Hypercube, Inc.).

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General synthesis of (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines via a copper(I)-catalyzed three-component reaction in water

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Abstract—A copper(I)-catalyzed three-component reaction to form (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines based on the Huisgen cycloaddition using amine, propargyl halide and azide in water was proposed. The process showed considerable synthetic advantages in terms of high atom economy, low environmental impact, atmospheric oxygen, wide substrate scope, mild reaction condition and good yields.

1. Introduction

1,2,3-Triazole derivatives have received much attention because of their wide range of applications[1] and biological activities such as anti-HIV,[2] antimicrobial agents[3] and β_3-adrenergic receptor agonist.[4] The most popular method for the construction of 1,2,3-triazoles frameworks is the 1,3-dipolar Huisgen cycloaddition reaction of azides with alkynes.[1a,5] However, the early Huisgen cycloaddition process required a strong electron-withdrawing substituent either on azide or on alkyne, and were often conducted at high temperature for a prolonged period of time, and usually led to the isolation of a mixture of 1,4-disubstituted- and 1,5-disubstituted-1,2,3-triazoles.[1e,5] Therefore, it is desirable to develop a new, convenient and regiocontrolled synthetic approach for the formation of triazoles. Recently, some important concepts and transition-metal catalysts to overcome the above drawbacks have been proposed.[6] Furthermore, triazoles have been utilized as a backbone of a bidentate phosphine ligand, and some new compounds have been synthesized.[7] These potent usefulness exhibited that the use of triazoles for organic synthetic purposes has been growing in scope and importance.

After extensively reviewed, we found both *N*-substituted and 4- or 5-substituted 1,2,3-trizoles had more potential application than simple 1,2,3-triazole derivatives.[4] Due to the limited number of commercially available alkynes and azides, the complex triazoles are usually synthesized in multi-step sequences. Multi-component reactions have been proven to be a very elegant and rapid way to access complex structures from simple building blocks. As a one-pot reaction, multi-component reactions generally afford good yields and are fundamentally different from two-component reactions in several aspects.[8] Over the past decade, various advanced sequential multi-component reactions have been developed in three- and four-component reactions involving Passerini-,[9] Ugi-,[10] and Mannich-type[11] reactions. In the case of Huisgen cycloaddition reaction, some more recent examples were reported using a one-pot procedure to prepare 1,2,3-triazole derivatives based on the three-component coupling reaction.[1e,12]

The increasing environmental consciousness of the chemical community has led to the search for more efficient and environmentally friendly methods for chemical syntheses.[13] Although it would be best not to use any solvent, frequently a solvent is required for a reaction because of various reasons. In such cases, the use of some solvents such as water is desirable.[14] In the last decade, there has been increasing recognition that organic reactions in water may offer advantages over those occurring in organic solvents.[15] The use of water as a solvent offers practical convenience as it alleviates the need to handle flammable, and reduce or eliminate environment damage caused by organic solvents. Water is the cheapest and safest

Keywords: Copper(I)-catalyzed; Three-component reaction; Water; Huisgen cycloaddition.
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solvent available, and frequently better selectivity is obtained in water. It also simplifies the tedious protection–deprotection sequence for molecules containing acidic protons, and increases the overall synthetic efficiency.[15] Then, there is a general agreement about the future of the use of water as a solvent.[16]

On the other hand, 5-aminomethyl-substituted 1,2,3-triazol-4-yl-*N*,*N*-dimethylmethaneamine hydrochloride analogues was reported to be a human neurokinin-1 receptor antagonist with a solubility in water, and the preparation of these analogues generally involved the prior reaction of amine and alkyne to form propargylamine, followed by other two-step transformations to product 1,2,3-triazole.[17] The most attractive access of propargylamines is the classical mannich reaction. However, the efficient preparation of propargylamines was hindered by rather harsh conditions, moderate yields and complex workup and purification procedures.[18] Therefore, it is desirable to develop a new, convenient and regiocontrolled synthetic approach for the formation of triazoles-4-yl-methanamine. On the other hand, (1-benzyl-, and 1-phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamines were, respectively, prepared from various starting materials using the 'click' chemistry approach.[6d,12c] These promoted us to initiate a corresponding study of three-component reaction. Herein, we wish to report an efficient and facile one-pot reaction of amines, propargyl halide and azides to generate (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamines in the presence of Cu(I) in water at room temperature (Scheme 1).

2. Results and discussion

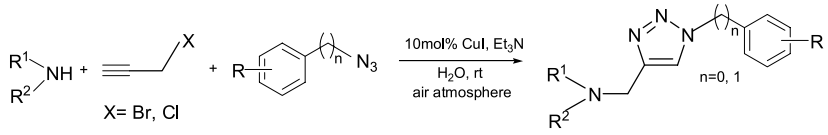
In preliminary experiments, we investigated the template reaction of diethylamine, propargyl bromide and benzyl azide using $CuSO_4 \cdot 5H_2O$–sodium ascorbate (Vc) system in a 2:1 mixture of water and *tert*-butyl alcohol (the 'click' chemistry condition),[6d] and the reaction only gave the corresponding compound **4b** in moderate yield (Table 1, entry 1). Encouraged by this positive result, an optimum reaction condition was explored using various solvents and catalysts. We were pleased to find Cu(I) could catalyze the three-component reaction in water in the presence of triethylamine without other co-solvent. Common Cu(I) salts, for example, CuCN, CuCl, CuBr, and CuI all gave good yields (entries 4–7). The reaction did not proceed in the presence of catalytic amount of copper powder. However, when the reaction was treated with stoichiometric copper powder (under 100 mol% amount of metal), a decent yield was obtained (entry 10). It was indicated that copper metal could also catalyze the three-component reaction, although it required a large amount of catalyst and extended reaction time, which was in good agreement with the previous results reported.[19] Furthermore, some Cu(II) salts, such as $CuSO_4$, $CuCl_2$, $Cu(OAc)_2$ in the absence of a reducing agent, were also evaluated, and negative results were observed. Other catalysts such as $ZnCl_2$, $InCl_3$, AgCl, AgI, and silver metal, were also investigated, which were not effective or non-active for the three-component reaction. However, a number of observations were worth highlighting, as they underscored the unusual reactivity aspects of the system. In other words, this was a very surprised process, which could effectively be catalyzed by either Cu(I) or copper metal. Finally, CuI was found to be the most effective in catalyzing the three-component reaction of amine, propargyl halide and azide (Table 1, entries 7–10).

Table 1. The effect of solvent and catalyst on three-component reaction[a]

Entry	Catalyst	Condition	Time (h)	Yield (%)
1	$CuSO_4$/Vc	H_2O–*t*-BuOH (1/1)	13	70
2	$CuSO_4$/Vc	H_2O	14	40
3	$CuSO_4$/Vc	H_2O–THF (1/1)	14	61
4	CuCl	H_2O	10	77
5	CuBr	H_2O	10	84
6	CuCN	H_2O	10	80
7	CuI	H_2O	10	88
8	CuI	H_2O–THF (1/1)	10	89
9	CuI	H_2O–DMF (1/1)	10	85
10	CuI	THF	10	86
11[b]	Cu	H_2O	24	54

[a] All reactions were performed with 2 mmol of Et_3N, 1.2 mmol of diethylamine, 2 mL of solvent, 1.2 mmol of propargyl bromide, 1.0 mmol of azide, and 10 mol% catalyst at room temperature, unless otherwise noted.
[b] Stoichiometric copper powder was used.

Under the optimized conditions, a number of substrates were investigated (Table 2). A variety of substituents, aromatic, benzyl, and aliphatic, were readily used in this transformation. Both electron-rich and -poor aromatic groups were tolerated in three-component reaction. Generally, the reaction was highly dependent on both electronic and steric effects. An evident steric effect was observed when we compared the yield of bulky diisopropylamine with that of dimethylamine (entries 1–3). On the whole, the better yields were obtained with cyclic amines in a short period of time (entries 4 and 6). Both aromatic azides bearing electron-withdrawing substituent Cl– and NO_2– group afforded the product in excellent yields (entries 12–15). Compared the propargyl bromide, the reaction of propargyl chloride, amines, and azide gave a slightly low yields (entries 5 and 11). Phenyl azide provided better results than electron-donating methylphenyl azide under the present reaction conditions (entries 16–18). The reaction was also tolerated with various functional groups. In addition to electron-rich and electron-poor C-aryl-substituted azides, benzyl azide, and even the less electrophilic phenoxyethyl azide could react to form the corresponding compounds in good yields, although the reaction time might be prolonged (entries 19–20). Moreover, this methodology could also be extended to the primary aliphatic amine (entry



Scheme 1.

Table 2. The reaction of amine, propargyl halide and azide catalyzed by Cu(I) in water[a]

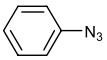
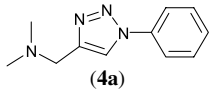
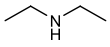
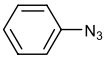
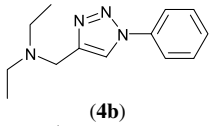
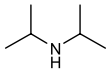
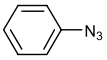
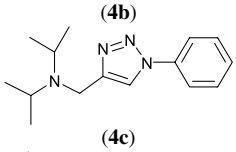
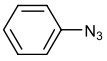
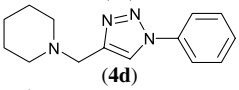
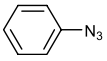
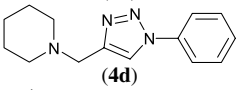
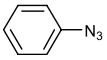
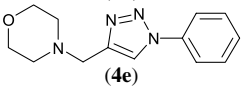
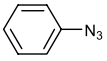
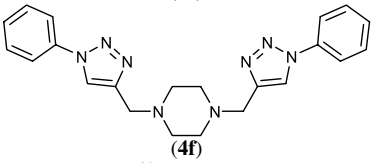
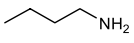
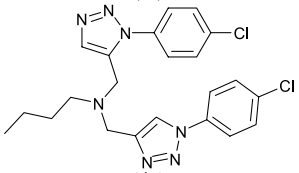
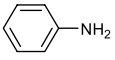
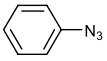
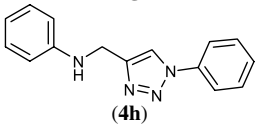
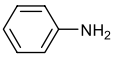
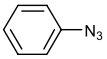
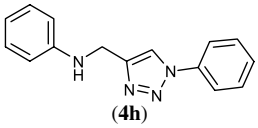
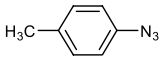
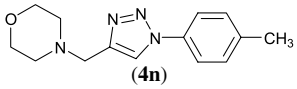
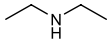
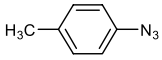
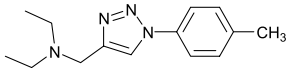
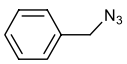
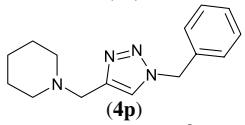
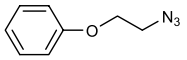
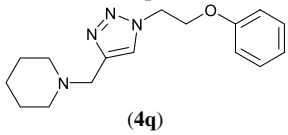
Entry	Propargyl halide	Amine	Azide	Time (h)/ medium	Product isolated	Yield (%)
1				8/water	 (**4a**)	92
2				10/water	 (**4b**)	88
3				14/water	 (**4c**)	75
4				7/water	 (**4d**)	95
5				12/water	 (**4d**)	89
6				7/water	 (**4e**)	93
7[b]				10/water	 (**4f**)	89
8[b]				14/water	 (**4g**)	86
9[c]				16/water	 (**4h**)	75
10[d]				16/water	 (**4h**)	78
11[c]				24/water	(**4h**)	70
12				7/water	(**4i**)	98
13				7/water	(**4j**)	95
14				10/water	(**4k**)	98
15				10/water	(**4l**)	96
16				9/water	(**4m**)	93

Table 2 (*continued*)

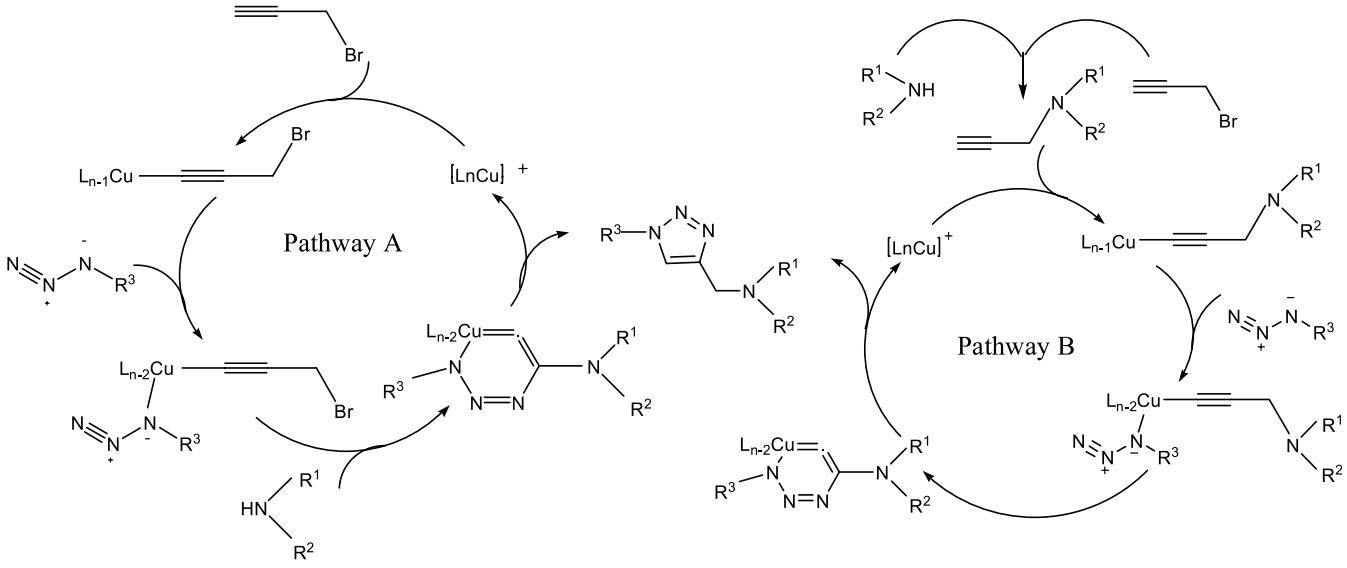
Entry	Propargyl halide	Amine	Azide	Time (h)/ medium	Product isolated	Yield (%)
17				10/water	 (**4n**)	90
18				13/water	 (**4o**)	83
19				16/water	 (**4p**)	94
20				16/water	 (**4q**)	91

[a] Typical procedure can be seen in 'Section 4', unless otherwise noted.
[b] Et_3N (3 mmol), 0.5 mmol of amine, 1.2 mmol of propargyl bromide and 1.2 mmol azide were used.
[c] Et_3N (2 mmol), 2 mmol of amine, 1 mmol of propargyl halide and 1 mmol azide were used.
[d] Et_3N (3 mmol), 0.5 mmol of amine, 2 mmol of propargyl bromide and 2 mmol azide were used; no disubstituted product was isolated.

8). Compared to secondary amines, the reaction of primary amines led to the disubstituted products in good yields when using an excess of Et_3N (3 equiv). For phenyl amine, only mono-substituted product was isolated even large excesses of propargyl bromide and phenyl azide were participated in the reaction (entries 9–11). It was presumed due to steric hindrance of bulk benzene ring. Diphenylamine, on the other hand, did not give the reaction even larger excess of base was used, presumably due to steric hindrance and/or weak nucleophilicity.

Herein, the effect of basicity was very vital in the three-component reaction. On the one hand, it could drive the rapid formation of propargyl amines and avoid self-coupling product of terminal alkynes. On the other hand, it was also known that copper(I) could readily inserts into terminal alkynes in the presence of base to promote the reaction.[20] Some inorganic and organic bases were investigated. Triethylamine showed better yields and no byproducts were observed. Moreover, it was known that, in the presence of a base and Cu(I) salts, terminal acetylenes could be converted to the corresponding alkynylides in water; if oxygen was not excluded, Cu(I)–acetylides could participate in oxidative Glaser coupling.[21] However, in our study, no coupling products were obtained, probably, six-membered copper(III) metallacycle was a preferable intermediate rather than alkynyl free radical one in Glaser coupling reaction (see below). We also observed that the three-component reaction in two-step gave higher yields in contrast to one-step procedure.[22] It was indicated that first the formation of propargylamines effectively suppressed the oxidative coupling reaction.

A tentative mechanism for the Cu(I)-catalyzed three-component reaction to form triazole derivatives was illustrated in Scheme 2, which may involve two possible



Scheme 2. Tentative mechanism for the three-component reaction of amine, propargyl bromide and azide.

pathway: A and B. For pathway B, in the first step, the reaction between propargyl bromide and a nucleophilic amine to form propargyl amine followed by the formation of copper(I) acetylide by displacing one of the H_2O ligands. The acetylide thus generated was reacted with azide to give the six-membered copper(III) metallacycle intermediate. After the ring contraction, a five-membered triazolyl-copper derivative was formed.[6d,19] Proteolysis of triazolyl-copper derivative released the triazole compound and regenerated the Cu(I) specie catalyst for further reactions. In further study, we prepared 1-phenyl-4-bromomethyl-1,2,3-triazole by a mixture of phenyl azide and propargyl bromide. Under the similar condition, the reactions of 1-phenyl-4-bromomethyl-1,2,3-triazole and several secondary amines were investigated, and expected products were obtained with lower yields. It was indicated that the early formation of 4-bromomethyl-1,2,3-triazole intermediates followed by the coupling of triazoles with amines to yield preferable compounds, was also an alternative mechanism (pathway A). Based on the above results, we proposed that pathway B was the preferable process. Herein, the formation of propargyl amine is a crucial factor for completion of the reaction in water because propargyl amine has a weak solubility in water, but the non-polar propargyl halide is not soluble in water.

3. Conclusions

In summary, we have demonstrated a new three-component protocol of amine, propargyl halide and azide in one-pot procedure for the synthesis of (1-substituted-1*H*-1,2,3-triazol-4-ylmethyl)-dialkylamine derivatives in the presence of copper(I) in water. The process showed the considerable synthetic advantages in terms of air, products diversity, mild reaction condition, simplicity of the reaction procedure, and good to excellent yields. The convenience with readily accessible starting materials (commercially available amines and propargyl halide) and simple experimental procedure as well as the simplicity of the reaction conditions (room temperature, water) can provide an access to a class of compounds that can serve as useful building blocks for synthesis. The rich array of functionality displayed by these products can provide opportunities for the creation of unique combinatorial libraries.

4. Experimental

4.1. General remarks

Column chromatography was carried out on silica gel. Melting points were measured using an electrothermal melting point apparatus, and uncorrected. The ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The ^1H chemical shifts were reported in ppm relative to tetramethylsilane, using the residual solvent signal as an internal reference and ^{13}C with $CDCl_3$ as internal standard. IR spectra were obtained using an FT IR spectrometer and only major peaks were reported in cm^{-1}. Mass spectra were recorded by the EI method or FAB method. All reagents were used directly as unless otherwise noted.

4.2. General procedure

The reaction was carried out in micro scale: a mixture of 2 mL of water, 2 mmol of Et_3N, 1.2 mmol of amine and 1.2 mmol of propargyl halide was stirred vigorously for 60 min at room temperature.[21] Then, 1.0 mmol of azide and 10 mol% of CuI were added into the mixture until complete consumption of the starting materials monitored by TLC.[17] The reaction mixture was diluted with 25 mL of water, cooled in ice, and extracted with CH_2Cl_2 (3×15 mL). The combined organic extracts were washed with brine, and dried ($MgSO_4$). After removal of the solvent under reduced pressure, the residue was purified on silica gel with petroleum–ethyl acetate (8:1–1:10).

4.3. Data of spectra

4.3.1. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-dimethylamine (4a). Solid, mp 75–77 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.71 (d, $J=8.4$ Hz, 2H), 7.49 (t, $J=7.2$, 8.4 Hz, 2H), 7.39 (t, $J=7.2$ Hz, 1H), 3.68 (s, 2H), 2.31 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.8, 137.0, 129.6, 128.5, 120.5, 120.3, 54.3, 45.1; IR (KBr, cm^{-1}) 2942, 2821, 2773, 1599, 1504, 1462, 1039; EI-MS *m*/*z* 202 (M^+), 202, 159, 130, 77; HRMS (EI) found $[M]^+=202.1208$, $C_{11}H_{14}N_4$ requires 202.1213.

4.3.2. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamine (4b). [12c]Sticky oil; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.75 (d, $J=8.4$ Hz, 2H), 7.52 (t, $J=6.9$, 8.4 Hz, 2H), 7.45–7.4 (m, 1H), 3.88 (s, 2H), 2.61 (q, $J=6.9$, 7.2, 7.5 Hz, 4H), 1.12 (t, $J=6.9$, 7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 137.1, 129.6, 128.5, 120.5, 120.3, 47.6, 46.8, 11.8; IR (KBr, cm^{-1}) 2970, 1599, 1504, 1465, 1041; EI-MS *m*/*z* 230 (M^+), 215, 159, 130, 77.

4.3.3. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-diisopropylamine (4c). Solid, mp 45–47 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.73 (d, $J=7.8$ Hz, 2H), 7.49 (t, $J=7.2$, 7.8 Hz, 2H), 7.42–7.38 (m, 1H), 3.83 (s, 2H), 3.09 (m, 2H), 1.04 (d, $J=6.6$ Hz, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 137.5, 129.9, 128.6, 120.6, 120.4, 49.1, 41.4, 21.0; IR (KBr, cm^{-1}) 2966, 1599, 1503, 1464, 1226, 1036; EI-MS *m*/*z* 258 (M^+), 243, 215, 159, 130, 100, 77; HRMS (EI) found $[M]^+=258.1840$, $C_{15}H_{22}N_4$ requires 202.1839.

4.3.4. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4d). Solid, mp 95–97 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.70 (d, $J=7.8$ Hz, 2H), 7.45 (t, $J=7.8$, 7.2 Hz, 2H), 7.41–7.38 (m, 1H), 3.70 (s, 2H), 2.47 (br s, 4H), 1.56 (m, 4H), 1.40 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 137.0, 129.6, 128.5, 120.6, 120.3, 54.3, 54.0, 25.8, 24.0; IR (KBr, cm^{-1}) 2934, 1599, 1504, 1465, 1231, 1042; EI-MS *m*/*z* 242 (M^+), 159, 130, 84, 77; HRMS (EI) found $[M]^+=242.1528$, $C_{14}H_{18}N_4$ requires 242.1526.

4.3.5. (1-Phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4e). Solid, mp 88–90 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.71 (d, $J=8.4$ Hz, 2H), 7.49 (t, $J=6.9$, 8.4 Hz, 2H), 7.42–7.37 (m, 1H), 3.72 (s, 2H), 3.70 (t, $J=7.8$, 6.9 Hz, 4H), 2.55 (t, $J=4.2$ Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 136.9, 129.6, 128.6, 120.7, 120.3, 66.8, 53.6, 53.4; IR (KBr, cm^{-1}) 2959, 2923, 2856,

2815, 1599, 1504, 1454, 1116; EI-MS *m/z* 244 (M^+), 226, 214, 201, 159, 130, 77; HRMS (EI) found $[M-N_2H]^+$ = 215.1179, $C_{13}H_{15}N_2O$ requires 215.1179.

4.3.6. 1,4-Bis-(1-phenyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperazine (4f). Solid, mp 158–160 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.12 (s, 2H), 7.71 (d, J=7.8 Hz, 4H), 7.50 (t, J=7.8, 7.2 Hz, 4H), 7.39 (t, J=7.2 Hz, 2H), 3.90 (s, 4H), 2.83 (br s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.1, 130.0, 129.1, 122.1, 120.9, 120.7, 52.9, 52.1; IR (KBr, cm^{-1}) 1598, 1503, 1461, 1045; FAB-MS *m/z* 401.3 $[M+1]^+$; HRMS (EI) found $[M]^+$ = 400.2117, $C_{22}H_{24}N_8$ requires 400.2118.

4.3.7. Bis-(1-[4-chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-butylamine (4g). Solid, mp 88–90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (s, 2H), 7.61 (m, 4H), 7.37 (m, 4H), 3.79 (s, 4H), 2.50 (t, J=7.2 Hz, 2H), 1.54 (m, 2H), 1.24 (m, 2H), 0.82 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 135.2, 134.0, 129.6, 126.3, 121.2, 121.0, 53.3, 47.4, 29.2, 20.2, 13.8; IR (KBr, cm^{-1}) 2956, 2930, 1501, 1226, 1096, 1043; FAB-MS *m/z* 456.2 $[M]^+$; HRMS (EI) found $[M]^+$ = 455.1389, $C_{22}H_{23}N_7Cl_2$ requires 455.1387.

4.3.8. (1-Phenyl)-1*H*-[1,2,3]triazol-4-ylmethyl)-phenylamine (4h). Solid, mp 138–140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.69 (d, J=8.1 Hz, 2H), 7.53–7.40 (m, 3H), 7.26–7.18 (m, 2H), 6.78–6.70 (m, 3H), 4.55 (s, 2H); 4.32 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.4, 147.0, 137.0, 129.7, 129.3, 128.7, 120.4, 119.8, 118.1, 113.1, 39.9; IR (KBr, cm^{-1}) 1598, 1462, 1320, 1105; EI-MS *m/z* 250 (M^+), 221, 130, 77; HRMS (EI) found $[M]^+$ = 250.1210, $C_{15}H_{14}N_4$ requires 250.1213.

4.3.9. (1-[4-Chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4i). Solid, mp 120–122 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.70 (d, J=8.7 Hz, 2H), 7.41 (d, J=8.7 Hz, 2H), 3.72 (s, 2H), 2.50 (br s, 4H), 1.60 (m, 4H), 1.45 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 135.5, 134.2, 129.8, 121.4, 120.7, 54.3, 53.9, 25.7, 23.9; IR (KBr, cm^{-1}) 2936, 1502, 1440, 1098, 1048; EI-MS *m/z* 276 (M^+), 247, 193, 84; HRMS (EI) found $[M]^+$ = 276.1136, $C_{14}H_{17}N_4Cl$ requires 276.1136.

4.3.10. (1-[4-Chloro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4j). Solid, mp 119–121 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.70 (d, J=8.7 Hz, 2H), 7.50 (d, J=8.7 Hz, 2H), 3.72–3.75 (m, 6H), 2.58 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.4, 135.7, 134.7, 130.1, 121.8, 121.0, 67.0, 53.8, 53.7; IR (KBr, cm^{-1}) 2925, 1502, 1115; EI-MS *m/z* 278 (M^+), 235, 193, 164; HRMS (EI) found $[M-N_2H]^+$ = 249.0786, $C_{13}H_{14}N_2ClO$ requires 249.0789.

4.3.11. (1-[4-Nitro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4k). Solid, mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, J=8.7 Hz, 2H), 8.09 (s, 1H), 8.00 (d, J=8.7 Hz, 2H), 3.75 (s, 2H), 2.51 (br s, 4H), 1.61 (m, 4H), 1.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.0, 146.8, 141.2, 125.5, 120.5, 120.2, 54.4, 53.9, 25.8, 24.0; IR (KBr, cm^{-1}) 2938, 1600, 1528, 1507, 1447, 1343, 1111, 1042, 909; EI-MS *m/z* 287 (M^+), 204, 129, 84; HRMS (EI) found $[M]^+$ = 287.1380, $C_{14}H_{17}N_5O_2$ requires 287.1377.

4.3.12. (1-[4-Nitro-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4l). Solid, mp 195–197 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J=8.7 Hz, 2H), 8.10 (s, 1H), 8.00 (d, J=8.7 Hz, 2H), 3.74–3.80 (m, 6H), 2.61 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.1, 145.9, 141.1, 125.5, 120.7, 120.3, 66.7, 53.5 (2C); IR (KBr, cm^{-1}) 1523, 1343, 1113, 856; EI-MS *m/z* 289 (M^+), 246, 204, 129, 86; HRMS (EI) found $[M-N_2H]^+$ = 260.1028, $C_{13}H_{14}N_3O_3$ requires 260.1030.

4.3.13. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4m). Solid, mp 109–111 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.58 (d, J=7.8 Hz, 2H), 7.27 (d, J=7.8 Hz, 1H), 3.68 (s, 2H), 2.46 (br s, 4H), 2.38 (s, 3H), 1.56 (br s, 4H), 1.41 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.3, 138.5, 134.7, 130.1, 120.7, 120.2, 54.2, 54.0, 25.7, 24.0, 21.0; IR (KBr, cm^{-1}) 2938, 1528, 1113; EI-MS *m/z* 256 (M^+), 173, 91, 84; HRMS (EI) found $[M]^+$ = 256.1684, $C_{15}H_{20}N_4$ requires 256.1682.

4.3.14. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-morpholine (4n). Solid, mp 102–103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.59 (d, J=8.1 Hz, 2H), 7.30 (d, J=8.1 Hz, 2H), 3.73 (s, 2H), 3.72 (t, J=4.5 Hz, 4H), 2.56 (br s, 4H), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 139.0, 135.0, 130.5, 121.0, 120.6, 67.1, 53.9, 53.7, 21.3; IR (KBr, cm^{-1}) 1521, 1449, 1113; EI-MS *m/z* 258 (M^+), 240, 228, 215, 173, 144, 91; HRMS (EI) found $[M-N_2H]^+$ = 229.1378, $C_{14}H_{17}N_2O$ requires 229.1335.

4.3.15. (1-[4-Methyl-phenyl]-1*H*-[1,2,3]triazol-4-ylmethyl)-diethylamine (4o). Oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.57 (d, J=8.1 Hz, 2H), 7.26 (d, J=8.1 Hz, 2H), 3.85 (s, 2H), 2.59 (q, 4H), 2.37 (s, 3H), 1.09 (t, J=7.2 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.6, 138.9, 135.1, 130.4, 121.0, 120.5, 47.9, 47.0, 21.3, 11.9; IR (KBr, cm^{-1}) 2970, 1520, 1459, 1226, 1042; EI-MS *m/z* 244 (M^+), 229, 215, 201, 187, 173, 144, 91, 72; HRMS (EI) found $[M]^+$ = 244.1678, $C_{14}H_{20}N_4$ requires 244.1682.

4.3.16. (1-Benzyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4p). Solid, mp 97–99 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.38–7.34 (m, 2H), 7.28 (m, 3H), 5.51 (s, 2H), 3.62 (s, 2H), 2.43 (br s, 4H), 1.58–1.53 (m, 4H), 1.43–1.41 (d, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 134.6, 129.0, 128.6, 128.0, 122.4, 54.2 (2C), 54.0, 25.7, 24.0; IR (KBr, cm^{-1}) 2931, 2771, 1445, 1306, 1050; EI-MS *m/z* 256 (M^+), 173, 91, 84; HRMS (EI) found $[M]^+$ = 256.1682, $C_{15}H_{20}N_4$ requires 256.1682.

4.3.17. (1-Phenoxyethyl-1*H*-[1,2,3]triazol-4-ylmethyl)-piperidine (4q). Solid, mp 103–104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.28 (t, J=8.4, 7.5 Hz, 2H), 6.97 (t, J=8.4, 7.5 Hz, 1H), 6.86 (d, J=9.0 Hz, 2H), 4.74 (t, J=4.8 Hz, 2H), 4.35 (t, J=4.8 Hz, 2H), 3.66 (s, 2H), 2.45 (br s, 4H), 1.62–1.54 (m, 4H), 1.45–1.41 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 144.6, 129.5, 123.8, 121.5, 114.4, 66.2, 54.1, 53.9, 49.6, 25.7, 24.0; IR (KBr, cm^{-1}) 2930, 2770, 1596, 1497, 1460, 1252, 1118, 1047; EI-MS *m/z* 286 (M^+), 203, 84; HRMS (EI) found $[M]^+$ = 286.1785, $C_{16}H_{22}N_4O$ requires 286.1788.

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22. The following procedure also was investigated: a simultaneous mixture (one-step procedure) of water, Et_3N, amines, propargyl bromide, azides, and CuI was stirred vigorously until consumption of the starting material. However, lower yields were obtained.

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Synthesis of multivalent neoglycoconjugates by 1,3 dipolar cycloaddition of nitrile oxides and alkynes and evaluation of their lectin-binding affinities

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Abstract—The synthesis of multivalent neoglycoconjugates by 1,3-dipolar cycloaddition of nitrile oxides and alkynes is reported. The nitrile oxides are generated in situ in the presence of alkynyl derivatives allowing the access to homo and hetero multivalent systems containing *O*- and *C*-linked glycosides and isoxazole bridges. The concanavalin A binding affinities of some of these neoglycoconjugates bearing mannose residues were evaluated by enzyme-linked lectin essay (ELLA).

1. Introduction

Multivalency[1] has been a central topic in biochemistry over the last decade since it became clear that is prevalent in biological systems governing many biological interactions. In particular, protein–carbohydrate interactions are intensively investigated, as they play a pivotal role in many complex biological events, including the cellular recognition in the processes of inflammation, immune response, tumour metastasis, and bacterial and viral infections.[2]

For those studies, synthetic multivalent ligands[3] have emerged as unique probes to take insights of the complex cell-surface-binding events as they can act as ligands that mimic endogenous multivalent arrays. The advantages of using such synthetic ligands are numerous. Thus, they can be used to dissect the contributions of various ligand features to a binding interaction that is naturally multivalent. On the other hand, physiological multivalent ligands are often too scarce, structurally heterogeneous, or complex to identify the relevant underlying molecular mechanisms. In addition, synthetic multivalent ligands can be generated such that the scaffold structure and the identity, number and spacing of binding elements can be varied systematically. As a consequence of the functional roles displayed by such molecules, the concept of multivalent design is now accepted as an effective strategy for designing ligands, inhibitors and drugs that influence biological systems potently and selectively.[4]

Carbohydrate containing multivalent systems have been developed by coupling saccharides in a multiple fashion to a variety of different carriers, giving rise to chemically well-defined homogeneous neoglycoconjugates that can be grouped into four main categories: glycoclusters, glycodendrimers, glycopolymers and glycoproteins with systematic varied shapes and carbohydrate densities.[3,5,6] In the case of glycoclusters and glycodendrimers, the formation of the link glycan-scaffold is usually performed in the later steps of the synthesis and have been carried out using a variety of strategies such as formation of thiourea[7] or amide bridges[7b,8] by reaction of amines with isothiocyanates or carboxylic acids, respectively, by use of glycosylation,[7b,8b,9] by nucleophilic substitution,[7e,8d,10] by the oxidative dimerization of propynyl glycopyranosides with palladium and cooper-catalyzed homo- and cross-coupling reactions,[11] by the Sonogashira-type cross coupling reaction of alkynyl glycosides,[12] and by photochemical addition of thiol to alkenes.[13]

In the search for new strategies for the covalent assembly of the different components of such multivalent structures, we[14a–c] and others[14d] have recently introduced the 1,3-dipolar cycloadditions of alkynes with azides and nitrile oxides as an efficient and highly versatile tool that has allowed the preparation of a variety of multivalent structures such as sugars heterodimers, glycoclusters, calix-sugars, multicalixarenes, and glycocyclodextrins. In

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the carbohydrate field inter- as well as intramolecular 1,3-dipolar cycloaddition has found previously application in the synthesis of a variety of compounds such as higher sugars,[15] C-disaccharides,[16] and aminocyclitols.[17]

The 1,3-dipolar cycloaddition is a highly useful reaction in which a dipolar compound containing at least one heteroatom reacts with a dipolarophile containing usually a double or triple bond generating a variety of structurally different heteroatom containing cycloadducts.[18] The cycloadduct from this reaction is typically a five-membered heterocyclic compound. In particular, nitrile oxides undergo efficient [3+2] cycloadditions with alkynes and alkenes to generate isoxazoles and 4,5-dihydroisoxazoles, respectively. Nitrile oxides are generally not isolable dipoles but are prepared in situ in the presence of a dipolarophile. The most common methods used for their preparation are the dehydrochlorination of hydroximoyl chlorides,[19] the oxidation of aldoximes[20] and the dehydration of primary nitroalkanes.[21] Cycloaddition of nitrile oxides to alkynes usually exhibit a high regio- and stereoselectivity, in contrast with the thermal cycloaddition of alkynes and azides, allowing the exclusive formation of the corresponding 3,5-disubstituted 1,2-oxazoles.

Continuing our efforts in the synthesis of multivalent neoglycoconjugates, we here report the synthesis of carbohydrate multivalent systems by 1,3-dipolar cycloaddition of nitrile oxides and alkynes as well as the biological evaluation of their binging affinities.[22]

2. Results and discussion

In order to develop a wide methodology for the construction of carbohydrate multivalent systems based in the 1,3-cycloaddition of nitrile oxides and alkynes, we decided to implement the three possible strategies depicted in Figure 1 by an adequate selection of mono and multivalent nitrile oxide and alkyne derivatives: (1) direct conjugation of nitrile oxide and alkyne sugars (strategy A), (2) grafting of alkyne sugars over a multivalent nitrile oxide scaffold (strategy B) and (3) grafting of nitrile oxide sugars over a multivalent alkyne scaffold (strategy C).

D-Glucose and D-mannose were the sugars selected to prepare easily accessible mono nitrile oxide and mono alkynyl derivatives. Thus, the propargyl glycosides **3** and **4** were obtained following already reported procedures[12a,23] starting from peracetylated-β-D-gluco- and α-D-mannopyranose, **1** and **2** respectively. These last compounds allowed also the preparation of the nitrile oxides derivatives **10** and **11** by exploiting the reactivity of the anomeric center. The reaction of **1** and **2** with 2-nitroethanol catalyzed by $BF_3 \cdot Et_2O$ gave the nitroethyl glycosides **5** and **6** in good yields with complete anomeric purity.[24] In order to also have access to multivalent neoglycoconjugates containing *C*-glycosides, the known nitro derivative **7**[25] was also prepared from D-mannose. For the synthesis of the corresponding nitrile oxide sugars, the dehydratation of compounds **5**–**7** was first essayed using the Mukaiyama procedure[21a] (phenylisocyanate and triethylamine under refluxing toluene). However, these conditions failed in the case of compounds **5** and **6** working only well in the case of the nitro derivative **7**. In order to circumvent this difficulty, the nitro derivatives **5** and **6** were transformed into the corresponding oximes **8** and **9**, by reaction with PhSH and $SnCl_2$,[26] which were now successfully converted into the corresponding nitrile oxides **10** and **11**, respectively, using the classical two-step oxidation procedure that implies halogenation with NCS and subsequent dehydrohalogenation with Et_3N (Scheme 1). All these nitrile oxide derivatives were prepared in situ in the presence of the appropriate alkyne (as described bellow) in order to obtain the desired isoxazoles.

In the present study, pentaerythritol was chosen as an adequate polyol to give access to multialkyne scaffolds. Thus, the tri and tetrapropargylated derivatives **13** and **14** were prepared by *O*-propargylation following the procedure

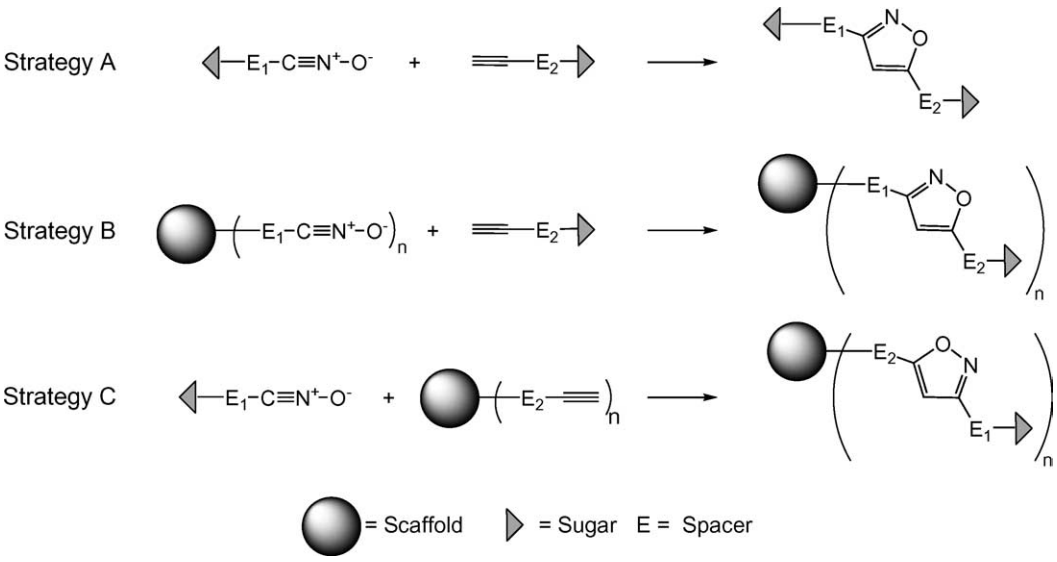
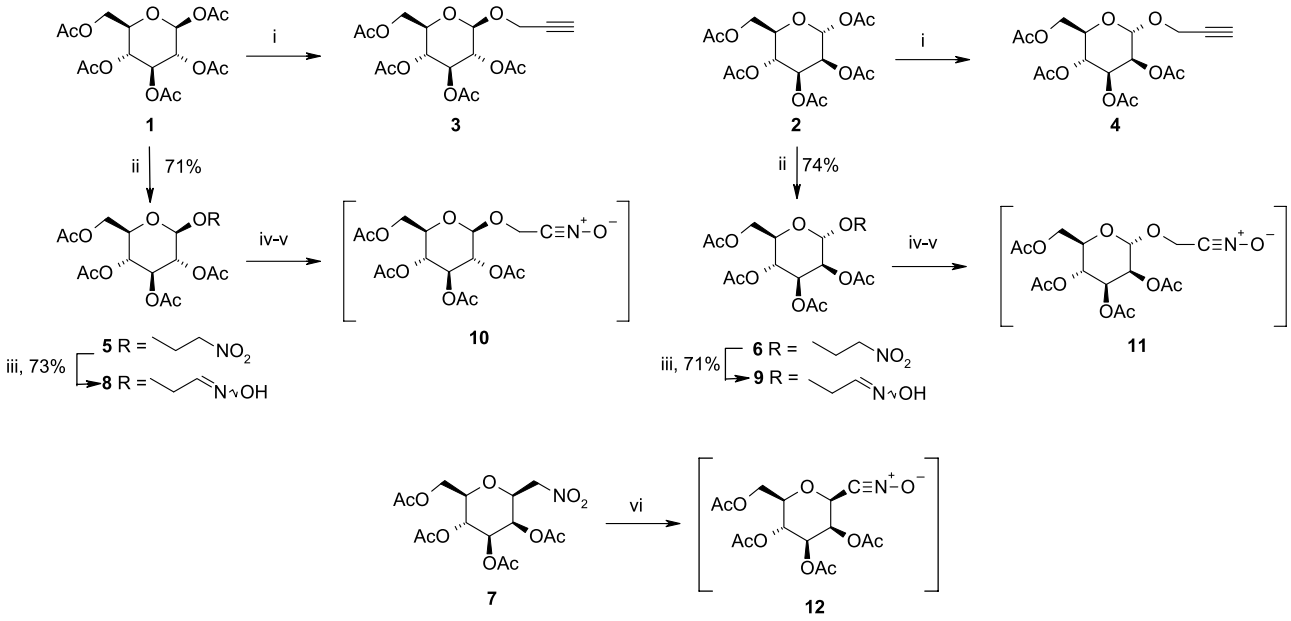
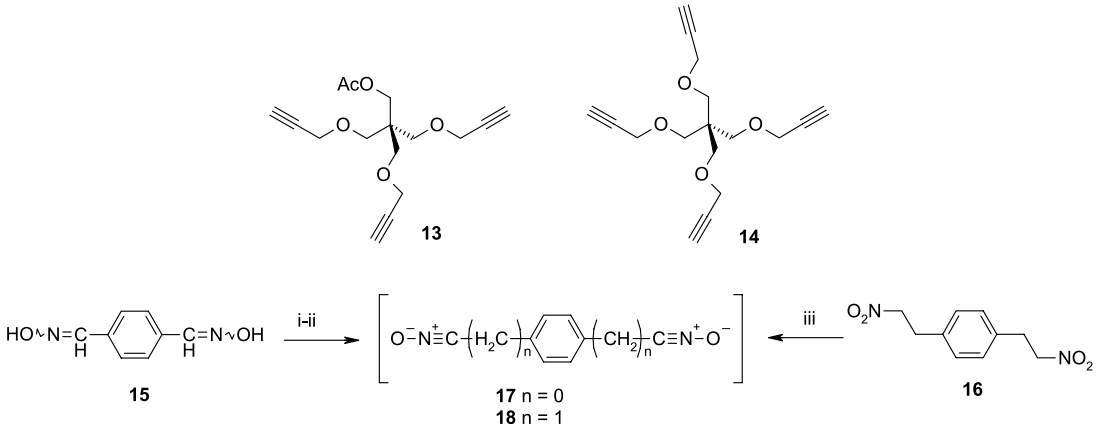


Figure 1. Strategies for the synthesis of multivalent carbohydrate systems by 1,3 cycloaddition of nitrile oxides and nitriles.



Scheme 1. Mono alkynes and nitrile oxides sugar derivatives: (i) Refs. 23 and 12a; (ii) $HOCH_2CH_2NO_2$, $BF_3 \cdot Et_2O$, CH_2Cl_2; (iii) $SnCl_2$, PhSH, Et_3N, CH_3CN; (iv) NCS, CH_2Cl_2; (v) Et_3N, toluene, reflux; (vi) PhNCO, Et_3N, toluene, reflux.



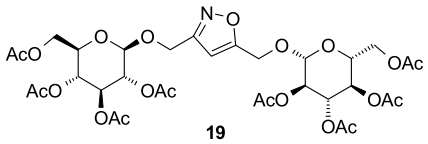
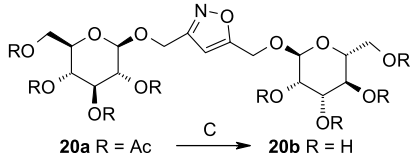
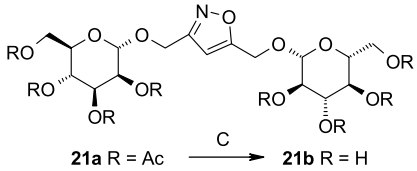
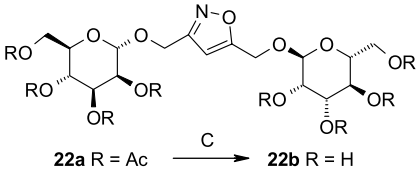
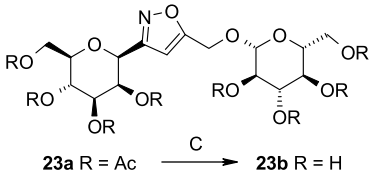
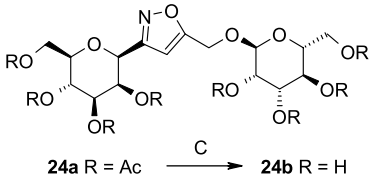
Scheme 2. Multivalent scaffolds: (i) NCS, DMF; (ii) Et_3N, toluene, reflux; (iii) PhNCO; Et_3N, toluene, reflux.

previously described by us for these compounds.[14a] On the other hand, the known oxime **15**[27] and the nitro derivative **16**[28] allowed the easy preparation of the dinitrile oxide benzene based scaffolds **17** and **18** using the procedures already mentioned for such compounds (halogenation–dehydrohalogenation for **15** and the Mukaiyama conditions for **16**, respectively) (Scheme 2).

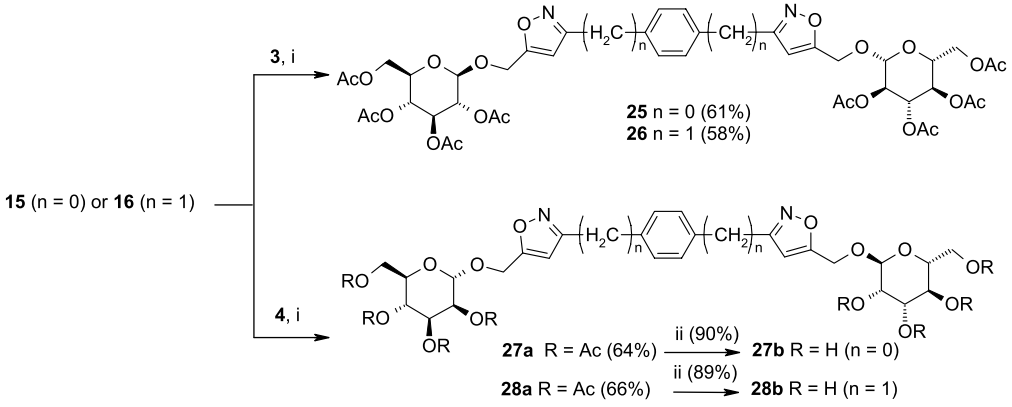
Once that the mono and divalent nitrile oxide precursor as well as the alkyne derivatives were obtained, we first carried out the conjugation of nitrile oxides prepared in situ with alkyne sugars to get the corresponding divalent neoglycoconjugates (strategy A, Fig. 1). By this way, **10** and **11** were reacted with **3** and **4** giving the homo divalent glycoconjugates **19** and **22a**, that bears two glucose and two mannose residues, respectively, and the hetero divalent glycoconjugates **20a** and **21a**, that contains glucose and mannose residues on the same molecule, in good yields. Similarly, the reaction of **12** with **3** and **4** allowed the synthesis of the *C*-glycoside containing neoglycoconjugates **23a** (hetero) and **24a** (homo) in high yield by direct mixture of the monovalent counterparts and use of the Mukaiyama conditions (Table 1). We next performed the synthesis of neoglyconjugates according with strategy B (Fig. 1): reaction of multivalent nitrile oxide scaffolds with monovalent alkyne sugar derivatives. Thus, the nitrile oxides **17** was first obtained from the nitro compound **15** and then directly reacted with the alkynes **3** and **4** in refluxing toluene yielding the rigid divalent glycoconjugates **25** and **27a**. Analogously, the divalent systems **26** and **28a** were prepared by direct mixture of the nitro compound **16** and the alkynes **3** and **4** that under the Mukaiyama conditions allowed the generation of the nitrile oxide **18** and their in situ conjugation with the alkynes (Scheme 3).

Finally, the tri and tetravalent alkyne derivatives of pentaerythrytol **13** and **14** allowed the implementation of strategy C: reaction of multivalent alkyne scaffolds with monovalent nitrile sugar derivatives. These compounds in the reaction with the nitro alkyne **7** under the Mukaiyama

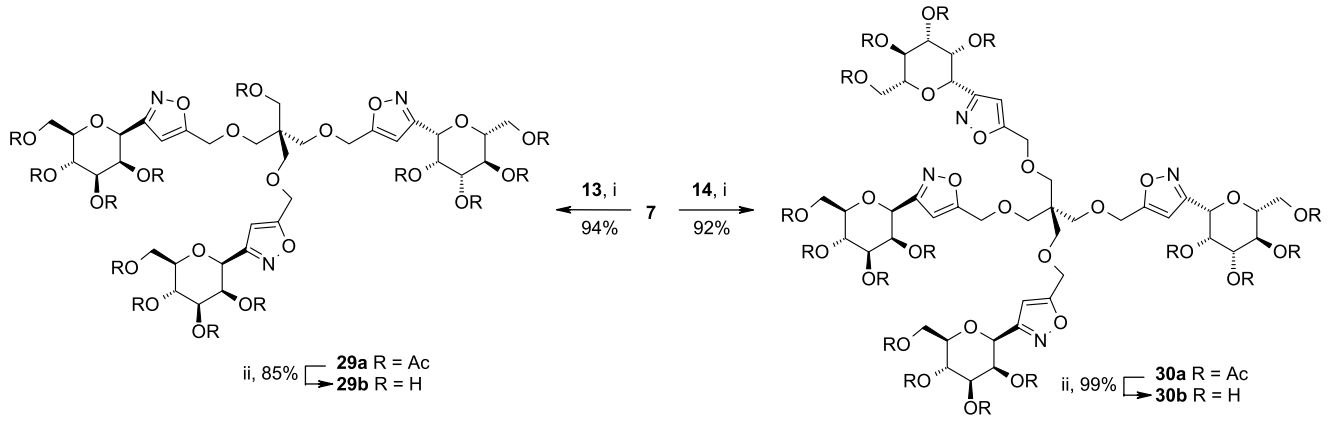
Table 1. Synthesis of divalent neoglycoconjugates by 1,3-dipolar cycloaddition of nitrile oxide sugars and alkynyl sugars

No.	Nitrile oxide sugar precursor	Alkyne sugar	Conditions	Divalent neoglycoconjugate	Yield
1	**8**	**3**	A	 **19**	59%
2	**8**	**4**	A	 **20a** R = Ac → (C) **20b** R = H	61% for **20a**, 100% for **20b**
3	**9**	**3**	A	 **21a** R = Ac → (C) **21b** R = H	58% for **21a**, 100% for **21b**
4	**9**	**4**	A	 **22a** R = Ac → (C) **22b** R = H	65% for **22a**, 99% for **22b**
5	**7**	**3**	B	 **23a** R = Ac → (C) **23b** R = H	77% for **23a**, 100% for **23b**
6	**7**	**4**	B	 **24a** R = Ac → (C) **24b** R = H	80% for **24a**, 87% for **24b**

Conditions: A: (i) **8** or **9**, NCS, CH_2Cl_2, rt; (ii) **3** or **4**, Et_3N, toluene, reflux. (B) PhNCO, Et_3N, toluene, reflux. (C) NaMeO, MeOH.



Scheme 3. Divalent glycoconjugates from divalent nitrile oxides: (i) for **15**: (a) NCS, DMF; (b) Et_3N, toluene, reflux; for **16**: PhNCO, Et_3N, toluene, reflux; (ii) NaMeO, MeOH.



Scheme 4. Multivalent glycoconjugates from multivalent alkynes: (i) PhNCO, Et_3N, toluene, reflux; (ii) NaMeO, MeOH.

Table 2. ELLA data for binding inhibition of HRP-labeled Con A by multivalent mannoside neoglycoconjugates

Parameter	Compound						
	Me–O–Man	**22b**	**24b**	**27b**	**28b**	**29b**	**30b**
IC_{50} (mM)	0.89	0.29	0.76	0.067	0.26	>4[a]	0.96
Re. potency	1	3.07	1.17	13.3	3.42		0.93
Rel potency[b]	1	1.54		6.65	1.71		0.24

[a] The binding inhibition for this compound at 4 mM is 38.1%.
[b] Per mannopyranosyl residue relative to methyl α-D-mannopyranoside.

conditions led to the tri and tetravalent mannose-containing glycoconjugates **29a** and **30a** in excellent yields (92 and 94%, respectively) (Scheme 4).

In all the thermal 1,3-cycloaddition performed in the present study, the 3,5-disubsituted isoxazol derivatives were exclusively obtained regardless the nature of the nitrile oxide and the alkynes used.[29]

The new glycoconjugates obtained having at least one mannose moiety (**20a**–**24a** and **27a**–**30a**) were de-*O*-acetylated to obtain the corresponding hydroxylated derivatives (**20b**–**24b** and **27b**–**30b**) (see Schemes 2 and 3 and Table 1). The biological essays were performed in the homo neoglycoconjugates **22b**, **23b** and **27**–**30b** to evaluate the relative binding inhibitory properties against peroxidase-labeled Concavalin A (Con A) lectin. These multivalent systems were used to inhibit the lectin binding to *Saccharomices cerevisiae* mannan that was used as coating material in competitive solid-phase microtiter plate assays. Triplicate results were obtained for the construction of the inhibition curves. The results expressed as the IC_{50} values and compared with the low-affinity inhibitor methyl α-D-mannopyranoside (see Table 2) indicated a Con A affinity enhancement for the multivalent α-D-mannosides (**22b**, **27b** and **28b**) relative to methyl α-D-mannopyranoside (1.54–6.65 fold per hapten). For these *O*-glycosides the higher value of IC_{50} for compound **27b** in relation with the more flexible compounds **22b** and **28b** could be interpreted on the basis of the rigidity of the systems and/or to the secondary interactions with the *p*-xylene ring. However, for these last two compounds the length of the connecting spacer between the mannose residues seems to be not a determinant factor on the affinity as deduced for their IC_{50} similar values. On the other hand, the results found for the *C*-mannoside containing neoglycoconjugates (**29b** and **30b**) indicate that those compounds are also recognized by Con A. To the best of our knowledge this is the first reported case in which β-*C*-mannoside multivalent systems show an affinity binding for a lectin.[30] Although the inhibitory properties are lower that the related *O*-glycosides, this is a valuable finding since carbon-linked glycosides are stable to

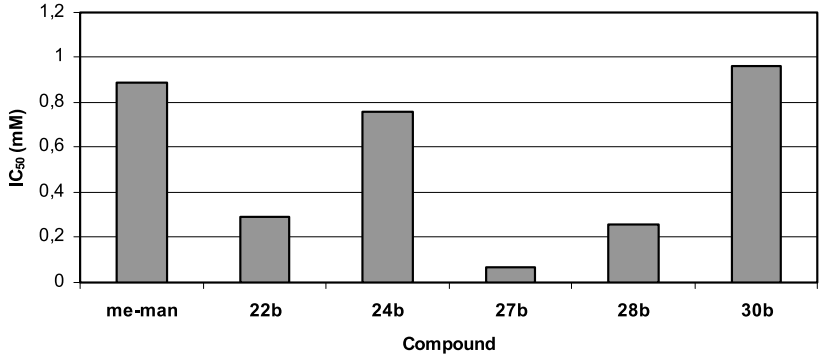


Figure 2. IC_{50} values.

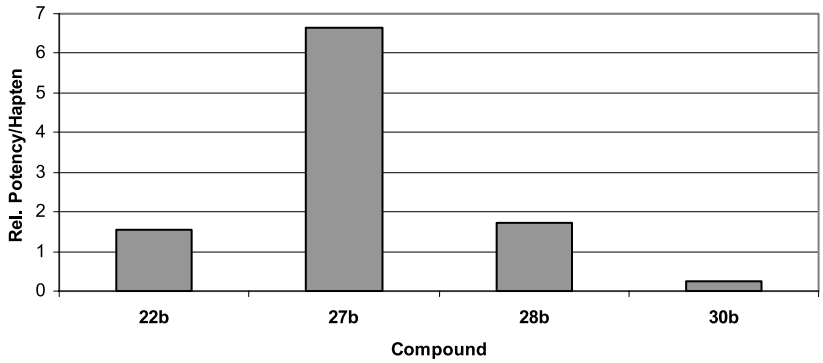


Figure 3. Relative potency per hapten.

enzymatic hydrolysis and could therefore be use in the development of potent inhibitors. In addition, it should be mentioned that those compounds show an important multivalent effect as deduced from the compared IC_{50} values of **29b** and **30b** (Figs. 2 and 3).

3. Conclusions

In conclusion, we have demonstrated that the 1,3-cycloaddition of nitrile oxide and alkynes is an adequate methodology for the construction of synthetic multivalent carbohydrates allowing the assembly of such compounds from complementary functionalizated building blocks. The implementation of this methodology has allowed the synthesis of a variety of divalent and multivalent homo and hetero neoglycoconjugates containing *O*- and *C*-linked glycosides. The binding affinities of the more representative examples of the new mannose containing neoglycoconjugates with Con A were evaluated allowing the postulation of some significant conclusions of the influence of the structure in the inhibitory properties.

4. Experimental

4.1. General

TLC was performed on Merck Silica Gel 60 F_{254} aluminium sheets. Reagents used for developing plates include ceric sulphate (1% w/v) and ammonium sulphate (2.5% w/v) in 10% (v/v) aqueous sulphuric acid, iodine, ethanolic sulfuric acid (10% v/v) and by UV light when applicable. Flash column chromatography was performed on Silica Gel Merck (230–400 mesh, ASTM). Optical rotations were recorded on a Perkin-Elmer 141 polarimeter at rt. IR spectra were recorded on a Satellite Mattson FTIR. ^{1}H and ^{13}C NMR spectra were recorded at rt on a Bruker (300–400 MHz) spectrometer. Chemical shifts are given in ppm and referenced to internal $CDCl_3$. *J* values are given in Hz. Assignments were based on COSY, HMQC, NOESY and DEPT. FAB mass spectra were recorded on a Fissons VG Autospec-Q spectrometer, using *m*-nitrobenzyl alcohol or thioglycerol as matrix. Matrix-assisted laser desorption/ionization and time-of-flight mass spectrometry (MALDI-TOF MS) were recorded on a Bruker Daltonics (AUTOFLEX) spectrometer using DGB as matrix.

4.2. Synthesis of the nitro derivatives 5 and 6

To a cold solution (0 °C) of **1** or **2** (2 g, 5.13 mmol) in dry CH_2Cl_2 (50 mL) and 2-nitroethanol (2 mL, 28 mmol) was added dropwise $BF_3{\cdot}Et_2O$ (1 mL, 7.7 mmol). The solution was kept at rt for 16 h. The reaction mixture was washed with $NaHCO_3$ aqueous saturated solution (3×50 mL) and water (50 mL). The organic phase was dried (Na_2SO_4) and evaporated to yield a crude that was purified by column chromatography (ether/hexane 5:1).

4.2.1. Synthesis of 2-nitroethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (5). Isolated as a solid in 71% yield: mp 118–120 °C (lit. 114–115 °C)[24]; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.21 (t, 1H, J=9.5 Hz, H-3), 5.06 (t, 1H, J=9.7 Hz, H-4), 4.95 (dd, 1H, J=9.5, 8.2 Hz, H-2), 4.61 (d, 1H, J=7.9 Hz, H-1), 4.65–4.50 (m, 2H, CH_2NO_2), 4.35–4.10 (m, 4H, H-6,6′, CH_2O), 3.77 (ddd, 1H, J=9.9, 4.4, 2.4 Hz, H-5), 2.09, 2.02, 2.02, 2.00 (4s, 12H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 169.8, 169.2, 169.1 (CO), 100.8 (C-1), 74.6 (CH_2NO_2), 72.2 (C-3), 71.7 (C-5), 70.5 (C-2), 68.0 (C-4), 65.2 (C-6), 61.5 (CH_2O), 20.4, 20.3, 20.1 (*Me*CO).

4.2.2. Synthesis of 2-nitroethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (6). Isolated as a solid in 74% yield: mp 73–75 °C; $[\alpha]_D$ +41 (*c* 1, chloroform); IR (KBr) 1747, 1557, 1371, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.28 (t, 1H, J=9.6 Hz, H-4), 5.24 (d, 1H, J=3.0 Hz, H-2), 5.22 (dd, 1H, J=9.6, 3.0 Hz, H-3), 4.88 (s, 1H, H-1), 4.66 (ddd, 1H, J=14.4, 7.2, 3.3 Hz, CH_2NO_2), 4.59 (ddd, 1H, J=14.4, 5.5, 3.5 Hz, CH_2NO_2), 4.33 (ddd, 1H, J=15.5, 7.3, 3.3 Hz, CH_2O), 4.28 (dd, 1H, J=12.4, 5.4 Hz, H-6), 4.15 (dd, 1H, J=12.3, 2.4 Hz, H-6), 4.01 (ddd, 1H, J=11.5, 5.4, 3.5 Hz, CH_2O), 3.96 (ddd, 1H, J=10.8, 5.3, 2.3 Hz, H-5), 2.16, 2.12, 2.05, 1.99 (4s, 12H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 169.9, 169.8 (CO), 98.0 (C-1), 74.1 (CH_2NO_2), 69.3, 69.1, 68.8, 65.8 (C-2,3,4,5), 63.7 (CH_2O), 62.3 (C-6), 20.8, 20.7, 20.7, 20.6 (*Me*CO); HRMS (*m*/*z*) (FAB+) calcd for $C_{16}H_{23}NO_{12}Na$ 444.1118; found 444.1116.

4.3. Synthesis of the oxyme derivatives 8 and 9

A solution of **6** or **8** (0.5 g, 1.19 mmol) in acetonitrile (8 mL) was added to a mixture of $SnCl_2$ (0.339 g, 1.78 mmol), PhSH (0.56 mL, 5.3 mmol) and Et_3N (0.8 mL, 5.7 mmol) in acetonitrile (12 mL). The reaction

mixture was kept at rt for 2.5 h. Evaporation of the solvents was followed by column chromatography of the resulting crude.

4.3.1. Synthesis of 2-hydroxymoylethyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (8). Column chromatography (EtOAc/hexane 2:3) gave **8** (0.351 g, 73%) as a syrup: the compound showed $[\alpha]_D$, IR and ^{1}H NMR data in complete concordance with those reported[31] ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.3, 170.2, 169.7, 169.5, 169.5, 147.6, 101.0, 100.0, 73.3, 72.0, 72.0, 71.2, 71.2, 69.9, 68.6, 68.4, 67.3, 66.2, 66.1, 62.0, 61.9, 20.7, 20.7, 20.6.

4.3.2. Synthesis of 2-hydroxymoylethyl 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranoside (9). Column chromatography (ether) gave **9** (0.343 g, 71%) as a syrup IR (KBr) 3415, 1748, 1371, 1228, 1086, 1049 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.60 (br s, 0.4H), 8.38 (br s, 0.6H), 7.52 (t, 0.6H, J=5.8 Hz), 6.94 (t, 0.4H, J=3.5 Hz), 5.40–5.25 (m, 3H), 4.89 (s, 0.6H), 4.87 (s, 0.4H), 4.56 (dd, 0.4H, J=16.0, 3.7 Hz), 4.43 (dd, 0.4H, J=15.9, 3.6 Hz), 4.32–3.96 (m, 4.2H), 2.17, 2.16, 2.12, 2.11, 2.05, 2.01, 1.99 (6s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 170.0, 169.8, 149.1, 146.9, 97.8, 97.4, 69.4, 68.9, 66.1, 65.0, 62.5, 61.9, 20.9, 20.7; HRMS (*m*/*z*) (FAB+) calcd for $C_{16}H_{23}NO_{11}Na$ 428.1169; found 428.1164.

4.4. Synthesis of the divalent neoglycoconjugates 19, 20a–22a

To a solution of the oxyme (**8** or **9**) (0.4 mmol) in CH_2Cl_2 (3 mL) was added *N*-chlorosuccinimide (0.5 mmol). The solution was kept at rt for 16 h. After this time the solvent was removed and the crude was dissolved in toluene (10 mL). The solution was now added to a mixture of the alkyne (**3** or **4**) (1.8 mmol) and Et_3N (1.8 mmol) in toluene (10 mL). The reaction mixture was refluxed for 24 h. Evaporation was followed by column chromatography (EtOAc/hexane 1:1→3:1).

4.4.1. 3,5-Bis(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl) isoxazole (19). Obtained as a syrup in 59% yield: $[\alpha]_D$ −23 (*c* 1, chloroform); IR (film) 2924, 1754, 1368, 1222, 1040 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.27 (s, 1H), 5.22 (t, 1H, J=9.3 Hz), 5.20 (t, 1H, J=9.4 Hz), 5.10 (t, 1H, J=9.7 Hz), 5.09 (t, 1H, J=9.6 Hz), 5.02 (dd, 1H, J=9.6, 7.9 Hz), 5.01 (dd, 1H, J=9.5, 7.8 Hz), 4.90 (d, 1H, J=13.5 Hz), 4.86 (d, 1H, J=12.7 Hz), 4.76 (d, 1H, J=13.0 Hz), 4.75 (d, 1H, J=13.9 Hz), 4.63 (d, 1H, J=7.8 Hz), 4.59 (d, 1H, J=7.9 Hz), 4.27 (dd, 1H, J=12.4, 1.8 Hz), 4.25 (dd, 1H, J=12.3, 2.0 Hz), 4.14 (dd, 1H, J=12.4, 2.4 Hz), 4.12 (dd, 1H, J=12.4, 2.4 Hz), 3.8–3.7 (m, 2H), 2.11, 2.10, 2.04, 2.03, 2.01 (5s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.7, 170.2, 169.4, 169.3, 125.6, 100.0, 72.8, 72.7, 72.2, 72.1, 71.2, 71.1, 68.4, 62.4, 61.9, 61.6, 20.8, 20.7; HRMS (*m*/*z*) (FAB+) calcd for $C_{33}H_{43}NO_{21}Na$ 812.2225; found 812.2225.

4.4.2. 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-oxymethyl)-5-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl) isoxazole (20a). Obtained as a syrup in 61% yield: $[\alpha]_D$ +11, $[\alpha]_{436}$ +21 (*c* 1, chloroform); IR (film) 1751, 1370, 1224, 1045 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.34 (s, 1H), 5.35–5.25 (m, 3H), 5.20 (t, 1H, J=9.4 Hz), 5.08 (t, 1H, J=9.7 Hz), 5.02 (t, 1H, J=8.5 Hz), 4.93 (s, 1H), 4.90–4.65 (m, 4H), 4.61 (d, 1H, J=7.9 Hz), 4.30–4.05 (m, 4H), 4.05–3.95 (m, 1H), 3.72 (ddd, 1H, J=9.7, 4.7, 2.4 Hz), 2.14, 2.10, 2.08, 2.03, 2.02, 2.01, 1.97, 1.97 (8s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.4, 167.9, 160.8, 103.3, 99.8, 97.4, 72.7, 72.1 71.1, 69.3, 69.2, 68.8, 68.3, 65.9, 62.3, 61.8, 60.1, 20.8, 20.8, 20.6, 20.5; HRMS (*m*/*z*) (MALDITOF) calcd for $C_{33}H_{43}NO_{21}Na$ 812.2225; found 812.233.

4.4.3. 3-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl) isoxazole (21a). Obtained as a syrup in 58% yield: $[\alpha]_D$ +16, $[\alpha]_{436}$ +30 (*c* 1, chloroform); IR (film) 1751, 1370, 1225 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.37 (s, 1H, H-4 isoxazole), 5.37–58 (m, 2H, H-3,4 Man), 5.24 (m, 1H, H-2 Man), 5.23 (t, 1H, J=9.4 Hz, H-3 Glu), 5.11 (t, 1H, J=9.6 Hz, H-4 Glu), 5.05 (dd, 1H, J=9.4, 7.8 Hz, H-2 Glu), 4.92 (d, 1H, J=1.7 Hz, H-1 Man), 4.91 (d, 1H, J=12.5 Hz, CH_2O), 4.80 (d, 1H, J=14.0 Hz, CH_2O), 4.78 (d, 1H, J=12.7 Hz, CH_2O), 4.67 (d, 1H, J=8.0 Hz, H-1 Glu), 4.66 (d, 1H, J=12.5 Hz, CH_2O), 4.29 (dd, 1H, J=12.3, 5.1 Hz, H-6 Man), 6.28 (dd, 1H, J=12.3, 4.1 Hz, H-6 Glu), 4.17 (dd, 1H, J=11.8, 2.3 Hz, H-6′ Glu), 4.12 (dd, 1H, J=12.3, 2.5 Hz, H-6′ Man), 4.03 (ddd, 1H, J=9.6, 5.4, 2.3 Hz, H-5 Man), 3.76 (ddd, 1H, J=9.9, 4.6, 2.3 Hz, H-5 Glu), 2.16, 2.12, 2.11, 2.06, 2.05, 2.03, 2.00 (7s, 24H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 170.2, 170.1, 169.89, 169.7, 169.4, 168.8 (CO), 160.1 (C-3 isoxazole), 103.0 (C-4 isoxazole), 99.7 (C-1 Glu), 97.1 (C-1 Man) 72.6 (C-2 Man), 72.1 (C-5 Glu), 71.0 (C-2 Glu), 69.4 (C-3 Glu), 69.0 (C-5 Man), 68.8, 66.0 (C-3,4 Man), 68.2 (C-4 Glu), 62.4, 61.8. (C-6 Glu, C-6 Man), 61.4, 60.8 (CH_2O), 20.8, 20.7, 20.7, 20.6 (*Me*CO); HRMS (*m*/*z*) (MALDITOF) calcd for $C_{33}H_{43}NO_{21}Na$ 812.2225; found 812.2240.

4.4.4. 3,5-Bis(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)isoxazole (22a). Obtained as a solid in 65% yield: mp 120–121 °C; $[\alpha]_D$ +66 (*c* 1, chloroform); IR (KBr) 1752, 1376, 1221 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.42 (s, 1H), 5.40–5.25 (m, 6H), 4.97 (d, 1H, J=1.0 Hz), 4.95 (d, 1H, J=1.2 Hz), 4.82–4.65 (m, 4H), 4.29 (dd, 2H, J=12.3, 5.2 Hz), 4.12 (dd, 1H, J=12.2, 2.4 Hz), 4.11 (dd, 1H, J=12.2, 2.4 Hz), 4.04 (ddd, 2H, J=10.0, 5.3, 2.6 Hz), 2.16, 2.12, 2.05, 1.99 (4s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.8, 169.7, 168.1, 160.1, 103.4, 97.3, 97.1, 69.2, 69.1, 69.0, 68.9, 68.8, 68.8, 65.9, 65.8, 62.3, 62.2, 60.7, 60.0, 20.7, 20.6, 20.6; HRMS (*m*/*z*) (FAB+) calcd for $C_{33}H_{43}NO_{21}Na$ 812.2225; found 812.2227.

4.5. Synthesis of the divalent neoglycoconjugates 23–24a

A solution of the alkyne (**3** or **4**) (0.2 mmol), **7** (1.2 equiv), PhNCO (1.2 equiv) and Et_3N (0.1 mL) in toluene (15 mL) was refluxed for 60 h. Evaporation gave a crude that was purified by column chromatography (EtOAc/hexane 2:1).

4.5.1. 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl) isoxazole (23a). Isolated as a syrup in 77% yield: $[\alpha]_D$ −43

(*c* 1, chloroform); IR (film) 1749, 1369, 1225, 1054 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.32 (s, 1H, H-5 isoxazole), 5.67 (d, 1H, $J=1.8$ Hz, H-2 Man), 5.33 (t, 1H, $J=9.9$ Hz, H-4 Man), 5.25–5.15 (m, 2H, H-3 Man, H-3 Glu), 5.10 (t, 1H, $J=9.6$ Hz, H-4 Glu), 5.03 (t, 1H, $J=8.7$ Hz, H-2 Glu), 4.94 (s, 1H, H-1 Man), 4.90 (d, 1H, $J=14.0$ Hz, CH_2O), 4.72 (d, 1H, $J=13.9$ Hz, CH_2O), 4.61 (d, 1H, $J=7.8$ Hz, H-1 Glu), 4.35–4.05 (m, 4H, H-6,6′ Man, H-6,6′ Glu), 4.9–4.8 (m, 1H, H-5 Man), 4.8–4.7 (m, 1H, H-5 Glu), 2.11, 2.10, 2.08, 2.08, 2.03, 2.03, 2.01, 2.00 (8s, 24H, Ac); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.7, 168.4, 160.4 (CO), 102.5 (C-5 isoxazole), 100.0 (C-1 Glu), 76.9 (C-5 Man), 72.5 (C-3 Glu), 72.5 (C-1 Man), 72.1 (C-5 Glu), 71.8 (C-3 Man), 71.0 (C-2 Glu), 69.5 (C-2 Man), 68.2 (C-4 Glu), 65.7 (C-4 Man), 62.7 (C-6 Man), 61.7 (C-6 Glu), 61.6 (CH_2O), 20.8, 20.7, 20.7 (*Me*CO); HRMS (*m*/*z*) (FAB+) calcd for $C_{32}H_{41}NO_{20}Na$ 782.2120; found 782.2113.

4.5.2. 3-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)-5-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl) isoxazole (24a). Isolated as a syrup in 80% yield: $[\alpha]_D$ +10, $[\alpha]_{436}$ +20 (*c* 1, chloroform); IR (film) 1751, 1372, 1226, 1051 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.39 (s, 1H), 5.68 (d, 1H, $J=3.0$ Hz), 5.34 (t, 1H, $J=9.9$ Hz), 5.35–5.27 (m, 3H), 5.22 (dd, 1H, $J=10.0$, 3.1 Hz), 4.94 (br s, 1H), 4.92 (br s, 1H), 4.76 (d, 1H, $J=13.4$ Hz), 4.66 (d, 1H, $J=13.4$ Hz), 4.34–4.27 (m, 2H), 4.21 (dd, 1H, $J=12.3$, 1.7 Hz), 4.11 (dd, 1H, $J=12.4$, 1.9 Hz), 4.03 (m, 1H), 3.84 (m, 1H), 2.14, 2.10, 2.10, 2.06, 2.06, 2.03, 1.98, 1.98 (8s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 167.8, 160.5, 103.0, 97.3, 77.0, 72.5, 71.8, 69.5, 69.2, 68.8, 65.9, 65.8, 62.8, 62.3, 60.0, 20.8, 20.7; HRMS (*m*/*z*) (FAB+) calcd for $C_{32}H_{41}NO_{20}Na$ 782.2120; found 782.2118.

4.6. Synthesis of the divalent neoglycoconjugates 25 and 27a

To a solution of the oxyme **15** (0.25 mmol) in DMF (2 mL) was added *N*-chlorosuccinimide (0.6 mmol). The solution was kept at rt for 16 h. After this time the solvent was removed and the crude was dissolved in toluene (10 mL). The solution was now added to a mixture of the alkyne (**3** or **4**) (1.0 mmol) and Et_3N (2.0 mmol) in toluene (10 mL). The reaction mixture was refluxed for 48 h. Evaporation was followed by column chromatography (EtOAc/hexane 1:1→3:1).

4.6.1. 1,4-Di-[5′-(2″,3″,4″,6″-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)-isoxazole-3′-yl]benzene (27a). Obtained as a syrup in 64%: $[\alpha]_D$ +67 (*c* 1, chloroform); IR (film) 1748, 1371, 1226 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 4H), 6.70 (s, 2H), 5.50–5.25 (m, 6H), 5.01 (br s, 2H), 4.86 (d, 2H, $J=13.6$ Hz), 4.78 (d, 2H, $J=13.6$ Hz), 4.32 (dd, 2H, $J=12.2$, 5.1 Hz), 4.20–4.0 (m, 4H), 2.17, 2.12, 2.06, 2.01 (4s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 169.9, 169.7, 168.3, 161.9, 130.3, 127.5, 101.9, 97.5, 69.3, 68.9, 62.3, 60.3, 20.8, 20.7, 20.7, 20.6; HRMS (*m*/*z*) (FAB+) calcd for $C_{42}H_{48}N_2O_{22}Na$ 955.2596; found 955.2591.

4.6.2. 1,4-Di-[5′-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)-isoxazole-3′-yl]benzene (25). Obtained as a solid in 61%: mp 170–172 °C; $[\alpha]_D$ −40 (*c* 1, chloroform); IR (film) 1754, 1368, 1223, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.94 (s, 4H), 6.66 (s, 2H), 5.27 (t, 2H, $J=9.3$ Hz), 5.16 (t, 2H, $J=9.4$ Hz), 5.11 (t, 2H, $J=8.6$ Hz), 5.00 (d, 2H, $J=13.9$ Hz), 4.87 (d, 2H, $J=13.9$ Hz), 4.73 (d, 2H, $J=7.8$ Hz), 4.33 (dd, 2H, $J=12.3$, 4.6 Hz), 4.21 (d, 2H, $J=12.2$ Hz), 3.80 (m, 2H), 2.13, 2.08, 2.07, 2.04 (4s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 170.2, 169.4, 168.8, 161.8, 130.4, 127.4, 101.6, 100.1, 72.7, 72.2, 71.1, 68.3, 61.8, 61.8, 20.7, 20.6; HRMS (*m*/*z*) (FAB+) calcd for $C_{42}H_{48}N_2O_{22}Na$ 955.2596; found 955.2589.

4.7. Synthesis of the divalent neoglycoconjugates 26 and 28a

A solution of the alkyne (**3** or **4**) (2.2 mmol), the nitro derivative **16** (1.0 mmol), PhNCO (4.0 mmol) and Et_3N (0.4 mL) in toluene (50 mL) was refluxed for 60 h in the presence of 4 Å molecular sieves. Evaporation gave a crude that was purified by column chromatography (EtOAc/hexane 2:1→3:1).

4.7.1. 1,4-Di-[5′-(2″,3″,4″,6″-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)-isoxazole-3′-yl-methyl] benzene (28a). Isolated as a syrup in 66%: $[\alpha]_D$ +55 (*c* 1, chloroform); IR (film) 3501, 1761, 1612, 1515, 1433, 1373, 1239, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (s, 4H), 6.07 (s, 2H), 5.30, 5.26, 5.24 (3m, 6H), 4.90 (br s, 2H), 4.69 (d, 2H, $J=8.2$ Hz), 4.61 (d, 2H, $J=8.2$ Hz), 4.25 (dd, 2H, $J=12.2$, 5.0 Hz), 4.03 (dd, 2H, $J=12.2$, 2.1 Hz), 3.98 (m, 2H), 3.97 (s, 4H), 2.13, 2.08, 2.02, 1.97 (4s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.4, 169.7, 169.5, 167.3, 162.9, 135.5, 129.1, 103.8, 97.4, 69.1, 68.9, 68.7, 65.8, 62.1, 60.1, 31.8, 20.7, 20.6, 20.5; HRMS (*m*/*z*) (FAB+) calcd for $C_{44}H_{52}N_2O_{22}Na$ 983.2909; found 983.2908.

4.7.2. 1,4-Di-[5′-(2″,3″,4″,6″-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)-isoxazole-3′-yl-methyl] benzene (26). Isolated as a syrup in 58% yield: $[\alpha]_D$ −27 (*c* 1, chloroform); IR (film) 1755, 1368, 1224, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.17 (s, 4H), 5.99 (s, 2H), 5.17 (t, 2H, $J=9.4$ Hz), 5.06 (t, 2H, $J=9.6$ Hz), 4.98 (t, 2H, $J=9.1$ Hz), 4.80 (d, 2H, $J=13.9$ Hz), 4.67 (d, 2H, $J=13.9$ Hz), 4.58 (d, 2H, $J=7.7$ Hz), 4.23 (dd, 2H, $J=12.5$, 3.6 Hz), 4.10 (d, 2H, $J=12.2$ Hz), 3.95 (s, 4H), 3.69 (m, 2H), 2.05, 2.00, 1.98, 1.93 (4s, 24H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 168.0, 162.9, 135.8, 129.2, 103.4, 100.0, 72.6, 72.1, 71.0, 68.2, 61.8, 61.7, 32.0, 20.7, 20.6; HRMS (*m*/*z*) (FAB+) calcd for $C_{44}H_{52}N_2O_{22}Na$ 983.2909; found 983.2905.

4.8. Synthesis of the multivalent neoglycoconjugates 29–30a

A solution of the alkyne (**13** or **14**) (0.2 mmol), **7** (2 equiv per alkyne function), PhNCO (2 equiv per alkyne function) and Et_3N (0.1 mL) in toluene (15 mL) was refluxed for 60 h. Evaporation gave a crude that was purified by column chromatography.

4.8.1. 1,1′-C-[[2-[(Acetyloxy)methyl]-2-[[[3-(2,3,4,6-tetra-*O*-acetyl-β-D-mannoyranosyl)-5-isoxazolyl]methoxy]methyl]-1,3-propanediyl]bis(oxymethylene-5,3-isoxazolediyl)]bis[1,5-anhydro-2,2′,3,3′,4,4′,6,6′-octaacetate-(1*S*,1′*S*)D-mannitol] (29a). Column chromatography

(EtOAc/hexane 1:1→3:1) of the crude gave 29a (94%) as a syrup: $[\alpha]_D$ −28 (*c* 1, chloroform); IR (film) 1748, 1370, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.30 (s, 3H), 5.68 (d, 3H, *J*=2.9 Hz), 5.34 (t, 3H, *J*=9.9 Hz), 5.25 (dd, 3H, *J*=10.0, 3.3 Hz), 4.98 (br s, 3H), 4.51 (s, 6H), 4.31 (dd, 3H, *J*=12.4, 5.6 Hz), 4.20 (dd, 3H, *J*=12.2, 2.1 Hz), 4.08 (d, 1H, *J*=11.0 Hz), 4.05 (d, 1H, *J*=11.1 Hz), 3.86 (ddd, 3H, *J*=9.9, 5.6, 2.1 Hz), 3.46 (br s, 6H), 2.08, 2.08, 2.05, 2.00, 1.99 (5s, 39H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.8, 169.8, 169.3, 160.3, 102.2, 76.7, 72.6, 71.9, 69.5, 69.2, 65.8, 64.0, 62.8, 44.4, 20.8, 20.7, 20.6; HRMS (*m/z*) (MALDITOF) calcd for $C_{61}H_{77}N_3O_{35}Na$ 1434.4235; found 1434.2508.

4.8.2. 1,1′-C-[[2,2-Bis[[[3-(2,3,4,6-tetra-*O*-acetyl-β-D-mannopyranosyl)-5-isoxazolyl]methoxy]methyl]-1,3-propanediyl]bis(oxymethylene-5,3-isoxazolediyl)]bis-[1,5-anhydro-2,2′,3,3′,4,4′,6,6′-octaacetate-(1*S*,1′*S*)-Dmannitol] (30a). Column chromatography (EtOAc/ hexane 1:1→4:1) of the crude gave 30a (92%) as a syrup: $[\alpha]_D$ −16.5 (*c* 1, chloroform); IR (film) 1750, 1639, 1369, 1227 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.31 (s, 4H), 5.70 (s, 4H), 5.35 (t, 4H, *J*=9.8 Hz), 5.27 (dd, 4H, *J*=10.0, 3.1 Hz), 5.03 (s, 4H), 4.50 (s, 8H), 4.32 (dd, 4H, *J*=12.4, 5.5 Hz), 4.20 (br d, 4H, *J*=12.2 Hz), 3.89 (m, 4H), 3.44 (br s, 8H), 2.09, 2.09, 2.04, 1.99 (4s, 48H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.0, 169.8, 169.2, 160.3, 102.3, 76.8, 72.6, 71.9, 69.5, 69.1, 65.9, 64.0, 62.8, 20.8, 20.8, 20.7; HRMS (*m/z*) (FAB+) calcd for $C_{77}H_{96}N_4O_{44}Na$ 1803.5295; found 1803.5300.

4.9. Preparation of the hydroxylated derivatives

Standard Zemplen de-O-acetylation with NaMeO/MeOH of the acetylated derivatives **20**–**24a** and **27**–**30a** (0.2 mmol) was followed by evaporation of the solvent gave and purification by column chromatography. The obtained solution was lyophilized to yield the corresponding hydroxylated derivatives

4.9.1. 3-(β-D-Glucopyranosyloxymethyl)-5-(α-D-mannopyranosyloxymethyl) isoxazole (20b). Column chromatography (EtOAc/MeOH 1:1) and lyophilization gave **20b** (100%) as a foam solid: $[\alpha]_D$ +18, $[\alpha]_{436}$ +29 (*c* 0.36, water); IR (film) 3404, 2926, 1638, 1421, 1133, 1077 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.63 (s, 1H), 4.25 (d, 1H, *J*=7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 161.3, 103.7, 102.4, 99.4, 77.0, 76.6, 74.5, 73.3, 70.8, 70.0, 70.0, 66.8, 61.2, 61.2, 61.1, 58.2; HRMS (*m/z*) (FAB+) calcd for $C_{17}H_{27}NO_{13}Na$ 476.1380; found 476.1379.

4.9.2. 3-(α-D-Mannopyranosyloxymethyl)-5-(β-D-glucopyranosyloxymethyl) isoxazole (21b). Column chromatography (EtOAc/MeOH 2:1→1:1) and lyophilization gave **21b** (100%) as a foam solid: $[\alpha]_D$ +21 (*c* 0.36, H_2O); IR (film) 3411, 2928, 1638, 1133, 1078 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.58 (s, 1H), 4.26 (d, 1H, *J*=7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.3, 160.9, 103.3, 102.3, 99.4, 77.1, 76.6, 74.5, 73.3, 70.8, 70.1, 66.9, 61.2, 61.1, 60.5, 59.0; HRMS (*m/z*) (FAB+) calcd for $C_{17}H_{27}NO_{13}Na$ 476.1380; found 476.1387.

4.9.3. 3,5-Bis(α-D-mannopyranosyloxymethyl) isoxazole (22b).[32] Column chromatography (EtOAc/MeOH 2:1→1:1) and lyophilization gave **22b** (99%) as a foam solid: $[\alpha]_D$ +80 (*c* 1, water); IR (KBr) 3410, 2932, 1134, 1060 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.54 (s, 1H); ^{13}C NMR(75 MHz, DMSO-d_6): δ 169.0, 161.0, 103.3, 99.4, 74.4, 70.8, 70.0, 70.0, 66.9, 66.8, 61.2, 61.1, 59.0, 58.2.

4.9.4. 3-(β-D-Mannopyranosyl)-5-(β-D-glucopyranosyloxymethyl) isoxazole (23b). Column chromatography (EtOAc/MeOH 1:1) and lyophilization gave **23b** (100%) as a foam solid: $[\alpha]_D$ −11, $[\alpha]_{436}$ −13 (*c* 0.34, water); IR (film) 3385, 2923, 1439, 1075 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.56 (s, 1H), 4.87 (d, 1H, *J*=13.4 Hz), 4.69 (d, 1H, *J*=13.4 Hz), 4.62 (s, 1H), 4.27 (d, 1H, *J*=7.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 129.1, 128.4, 125.5, 104.3, 102.4, 81.8, 77.2, 76.9, 74.6, 73.6, 73.4, 71.6, 70.3, 67.1, 61.7, 61.4, 60.6; HRMS (*m/z*) (FAB+) calcd for $C_{16}H_{25}NO_{12}Na$ 446.1274; found 446.1276.

4.9.5. 3-(β-D-Mannopyranosyl)-5-(α-D-mannopyranosyloxymethyl) isoxazole (24b). Column chromatography (EtOAc/MeOH 2:1→1:1) and lyophilization gave **24b** (87%) as a foam solid: $[\alpha]_D$ +50 (*c* 1, water); IR (film) 3412, 2928, 1638, 1095, 1061 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.53 (s, 1H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 163.1, 104.0, 99.1, 81.6, 74.3, 74.2, 73.0, 71.3, 70.8, 69.9, 66.8, 66.8, 61.4, 61.1, 58.0; HRMS (*m/z*) (FAB+) calcd for $C_{16}H_{25}NO_{12}Na$ 446.1274; found 446.1276.

4.9.6. 1,4-Di-[5′-(α-D-mannopyranosyloxymethyl)-isoxazole-3′-yl]benzene (27b).[32] Column chromatography (EtOAc/MeOH 2:1) and lyophilization gave **27b** (90%) as a foam solid: $[\alpha]_D$ +121 (*c* 0.25, water); IR (film) 3394, 2932, 1426, 1134, 1060 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 8.03 (s, 4H), 7.18 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 169.9, 161.2, 130.0, 127.3, 102.0, 99.6, 74.5, 70.8, 70.0, 66.9, 61.2, 58.5.

4.9.7. 1,4-Di-[5′-(α-D-mannopyranosyloxymethyl)-isoxazole-3′-yl-methyl] benzene (28b). Column chromatography (EtOAc/MeOH 2:1) and lyophilization gave **28b** (89%) as a solid: mp 88–90 °C; $[\alpha]_D$ +70 (*c* 0.5, water); IR (KBr) 3392, 2929, 1611, 1423, 1133, 1060 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 7.23 (s, 4H), 6.34 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.6, 162.7, 135.7, 128.9, 103.5, 99.3, 74.3, 70.7, 69.9, 66.7, 61.0, 58.2, 30.9; HRMS (*m/z*) (FAB+) calcd for $C_{28}H_{36}N_2O_{14}Na$ 647.2064; found 647.2070.

4.9.8. 1,1′-C-[[2-[Hydroxymethyl]-2-[[[3-(β-D-mannopyranosyl)-5-isoxazolyl]methoxy]methyl]-1,3-propanediyl]bis(oxymethylene-5,3-isoxazolediyl)]bis[1,5-anhydro-(1*S*,1′*S*)-D-mannitol] (29b).[32] Column chromatography (acetonitrile/H_2O 9:1) and lyophilization gave **29b** (85%) as a foam solid: $[\alpha]_D$ +56 (*c* 1, water); IR (film) 3420, 2927, 2884, 1096 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.51 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.0, 162.9, 103.6, 81.6, 74.2, 73.0, 71.2, 69.4, 66.8, 63.4, 61.4, 45.4.

4.9.9. 1,1′-C-[[2,2-Bis[[[3-(β-D-mannopyranosyl)-5-isoxazolyl]methoxy]methyl]-1,3-propanediyl]bis(oxymethylene-5,3-isoxazolediyl)]bis[1,5-anhydro-(1*S*,1′*S*)-D-mannitol] (30b). Column chromatography (acetonitrile/H_2O 3:1) and lyophilization gave **30b** (99%) as a foam solid: $[\alpha]_D$ +22, $[\alpha]_{436}$ +60 (*c* 0.5, water); IR (film) 3347, 2921, 1434, 1095 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) (selected signals): δ 6.50 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 163.2, 103.9, 81.7, 74.4, 73.4, 71.5, 69.3, 67.1, 63.6, 61.7, 45.4; HRMS (*m*/*z*) (MALDITOF) calcd for $C_{48}H_{70}N_4O_{28}Na$ 1131.360; found 1131.399.

4.10. Enzyme-linked lectin assay (ELLA)

ELLA assays were carried out as previously described.[33] Experiments were carried out using a Metertech Σ960 instrument. Microtitration plates were coated with *S. cerevisiae* mannan at 100 μL/well of a solution of 10 μg/mL in 10 mM phosphate buffer (PBS, pH 7.4) for 2 h at 37 °C. The wells were then washed twice with 10 mM phosphate buffer containing 1% (v/v) Tween 20 (PBST) and once with PBS. This washing procedure was repeated after each incubation period. Wells were then blocked with 300 μL/well of BSA/PBS (1% w/v) for 2 h at 37 °C. Each inhibitor was added in serial dilutions (60 μL/well) of the glycoconjugates **22b**, **24b** and **27b–30b** or methyl α-D-mannopyranoside in PBS (pH 6.8, containing 0.1 mM Ca^{2+} and 0.1 mM Mn^{2+}) and the peroxidase-labeled Con A (60 μL/well of a solution of 50 μg/mL in PBS, pH 6.8, containing 0.1 mM Ca^{2+} and 0.1 mM Mn^{2+}) was added. The mixtures of glycoclusters or methyl α-D-mannopyranoside and the peroxidase-labeled lectin (100 μL/well) were added and the plates were incubated for 2 h at 37 °C. After that, 50μL/well of a solution of *o*-phenylenediamine dihydrochloride (20 mg/50 mL) in citrate–phosphate buffer (pH 5.0 with 0.4% H_2O_2) was added. The plates were incubated for 30 min at 37 °C. The reactions were stopped by addition of aqueous H_2SO_4 (50 μL/well, 1.25 M) and the absorbance measured at 492 nm.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.057.

Supporting information available: ^1H NMR spectra for compounds **20b–24b** and **27b–30b**.

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Automated batch scale-up of microwave-promoted Suzuki and Heck coupling reactions in water using ultra-low metal catalyst concentrations

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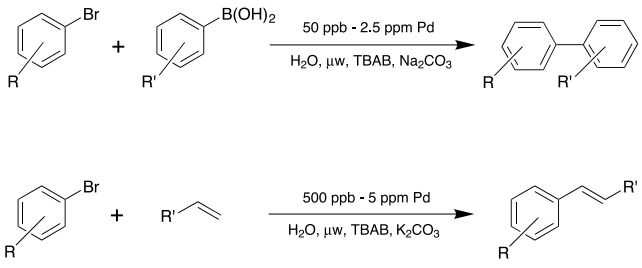
Abstract—Representative Suzuki and Heck couplings in water using ultra-low catalyst concentrations have been scaled-up using an automated batch stop-flow microwave apparatus. Our scale-up methodology shows proof of concept and is easy, fast and cheap to run.

1. Introduction

Microwave-promoted synthesis is an area of increasing interest in both academic and industrial laboratories. It was not until 1986 that the first reports of microwave-heating in organic synthesis appeared in the literature.[1,2] The work was performed using a domestic microwave. Since these publications, much has changed in terms of the apparatus available for microwave-promoted synthesis and the technique has found a valuable place in the synthetic chemist's toolbox. This is evidenced by the large number of papers and reviews currently appearing in the literature.[3–5] As well as being energy efficient, microwaves can also enhance the rate of reactions and in many cases improve product yields. Also, as the field matures, people are finding that they can perform chemistry using microwave heating that can not be achieved using 'conventional' heating methods, this opening up new avenues for synthesis.

Our research in the area of microwave-promoted chemistry recently led to the discovery that it is possible to perform Suzuki[6] and Heck[7] couplings in water using ultra-low quantities of palladium catalyst (Scheme 1). Water is an excellent solvent for microwave-promoted synthesis. Although it has a dielectric loss factor which puts it into the category of only a medium absorber, even in the absence of any additives it heats up rapidly upon microwave irradiation. Using a sealed vessel it is possible to heat water to well above its boiling point. Water also offers practical advantages over organic solvents.[8] Our reactions were performed using a scientific microwave apparatus, working on a 1 mmol scale in a 10 mL sealed glass vessel. The reactions are run using between 50 ppb and 5 ppm palladium, and are complete in between 5 and 20 min depending on the coupling and the substrate used. This therefore offers an easy, fast and efficient route to biaryl- and alkene-functionalised products. Lengthy metal extraction steps for product purification are not required because such small quantities of metal catalyst are used.[9] Indeed, in many cases the metal could be left in the product. Since both the Suzuki[10] and Heck[11] couplings are used on a regular basis in the chemical industry for the preparation of, for example, pharmaceuticals, natural products and advanced materials, we were keen to address issues of scale-up to prepare gram instead of milligram of product. The results from our laboratory are presented here.



Scheme 1. Suzuki and Heck couplings in water.

Keywords: Microwave; Water; Suzuki.
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2. Results and discussion

Scale-up of microwave-promoted reactions has been an issue of considerable interest over the last few years. Although chemists are discovering that microwave chemistry has the advantage of greatly reducing reaction times and improving product yields when run on small scales, translation of methodologies to larger scale apparatus can be problematic. There are two possible scale-up options. The first is to use a continuous flow microwave cell,[12] this technology being used successfully for a number of different reactions.[13–15] Included in this list is a Suzuki coupling.[16] The authors use 20 mol% $PdCl_2(PPh_3)_2$ as the catalyst, ethanol as the solvent and triethylamine as a base. The Suzuki reaction has also been used to demonstrate the applicability of a microreactor and a flow-capillary reactor, both developed for use in conjunction with microwave heating.[17,18,19] A circulating fluidized-bed reactor has also been developed for microwave-promoted catalysis and used for the decomposition of trichloroethylene but not for fine-chemicals synthesis.[20] The drawbacks of a continuous flow microwave apparatus are that it can be difficult to process solids, highly viscous liquids or heterogeneous reaction mixtures. Also, adaptation of conditions from simple small scale reactions to the continuous flow cell could end up being time consuming.

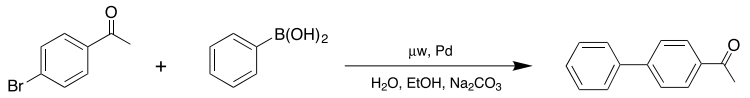
The other option is to use a batch-type process. This could either involve using one large vessel or parallel batch reactors. For a microwave operating at the typical frequency of 2.45 GHz, microwave penetration is generally in the order of cm, depending on the dielectric properties of the reaction medium. This therefore limits the size of a large batch reactor. Success has been found using one large batch reactor,[21–23] and also using the parallel approach. The latter has recently been applied successfully by Kappe and co-workers to the scale-up of reactions such as the Biginelli dihydropyrimidine synthesis, the Diels–Alder cycloaddition as well as a Heck coupling.[24] and by Alcázar and co-workers to alkylation reactions.[25] In both reports, translation of reaction conditions developed on commercially available single-mode to a multimode reactor for the scale-up proved not to be a problem. The disadvantage, however, of these batch reactors are that the individual reaction vessels need to be filled with reagents and loaded into the microwave cavity manually.

We decided to focus our attention on the CEM Voyager microwave system. This combines the advantages of a batch reactor with those of a continuous flow reactor. It is a single-mode apparatus with one, 80 mL vessel in the microwave cavity. The reaction mixture is pumped into and out of the vessel by a peristaltic pump, these functions, as well as running the reaction, being controlled using a computer. This gives a high degree of automation to the process. The reaction mixture can be introduced into the microwave vessel from two separate feed lines. After the reaction is complete, the reaction vessel can be vented to remove an overpressure and then the contents of the reactor pumped into a collection vessel. Since only one reaction vessel is used, the time taken to cool the reaction mixture down to room temperature at the end of the run are significantly shorter than those reported for the parallel batch reactors using multimode apparatus (20–30 min). If necessary, the reactor can then be cleaned with solvent before the next run.

Our first objective was to test the scalability of our coupling protocols in moving to the larger 80 mL reaction vessel from the smaller 10 mL reaction vessels in which we had performed all our original work. This work was performed with the same microwave apparatus as that used for the smaller scale experiments, the only difference being the size of vessel used and the temperature measurement device (fiber-optic probe directly placed into the reaction mixture by way of an immersion well as opposed to an external IR sensor located outside the reaction vessel). Starting with the Suzuki reaction we focused on the coupling of 4-bromoacetophenone with phenylboronic acid. Optimisation data are shown in Table 1. Our coupling protocols developed earlier involved either the use of tetrabutylammonium bromide (TBAB) as a phase-transfer agent in conjunction with water as the only solvent or else a 1:1 water/ethanol mixture as the reaction medium (no TBAB). The mixture is stirred throughout the reaction. For scale-up purposes we felt that the water/ethanol solvent system would be more useful so we focused on this. On the 1 mmol scale in the 10 mL reaction vessels, our optimum reaction conditions were 1.3 equiv boronic acid, 1 equiv aryl halide, 3.7 equiv Na_2CO_3, 250 ppb palladium[†] and 1 mL each of water and ethanol. The reaction mixture was heated to 150 °C and held at this temperature for 5 min before cooling back to room temperature. With 4-bromoacetophenone we obtained a 99% product yield (Table 1, entry 1). Repeating this reaction on a 10 mmol scale keeping the ratios of reagents and reaction conditions the same, but using 10 mL each of water and ethanol gave a 96% yield of the desired product (Table 1, entry 2). This shows the direct scalability of the chemistry from the small to the large reaction vessels. Our attention turned to how we would be able to pump the reaction mixture into the vessel in the stop-flow apparatus. The best method was to introduce the aryl halide, boronic acid and palladium dissolved in ethanol and the base dissolved in water. Both of these mixtures were homogeneous and we envisioned could easily be pumped. We could have moved directly to the Voyager stop-flow apparatus with these conditions. However, we decided to study the effects on product yield of reducing the palladium concentration, the quantity of base in the reaction and the stoichiometric ratio of the boronic acid and aryl halide to 1:1. Reducing the quantity of base used from 3.7 to 1 equiv has little effect on product yield (Table 1, entries 3 and 4). Reduction of the palladium concentration from 250 to 50 ppb also has negligible effect on the product yield (Table 1, entries 5 and 6). A stoichiometric ratio of boronic acid and aryl halide of 1:1 gives a comparable yield to the original ratio of 1.3:1 (Table 1, entry 7). We also investigated the effects of adding a small volume of organic solvent to the reaction mixture, this being necessary when using the Voyager in order to clean the lines between the peristaltic pump and the reaction vessel thus avoiding contamination. Addition of 4 mL ethyl acetate to the reaction mixture has little effect on product yield (Table 1,

[†] When working in water, a major problem can be precipitation of palladium from a stock solution, particularly when working with a salt such as palladium acetate. This is however, avoided by using an acid stabilized stock solution. We therefore used a commercially available 1000 ppm palladium solution stabilized with 20% HCl as our catalyst source. This was diluted accordingly to give solutions of the desired concentrations. For low concentrations, a couple of drops of HCl were added to avoid precipitation of the palladium from solution. In addition, the solutions were prepared freshly each day from the 1000 ppm stock.

Table 1. Optimisation of conditions for the scale-up of microwave-promoted Suzuki coupling reactions in water[a]

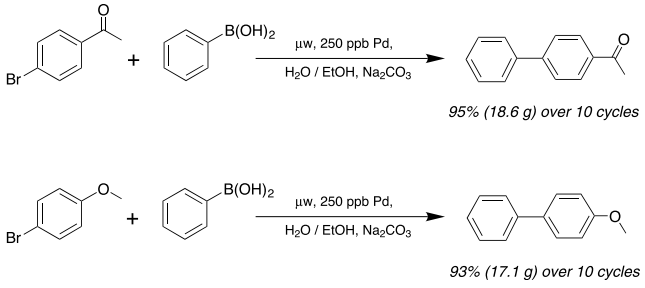


Entry	Aryl halide/ mmol	Boronic acid/ mmol	Na_2CO_3/mmol	H_2O/mL	EtOH/mL	Pd/ppb	Biaryl yield/%
1	1	1.3	3.7	1	1	250	99
2	10	13	37	10	10	250	96
3	10	13	20	10	10	250	98
4	10	13	10	10	10	250	99
5	10	13	10	10	10	100	99
6	10	13	10	10	10	50	99
7	10	10	10	10	10	50	96
8[b]	10	10	10	10	10	250	91
9[c]	10	10	10	10	10	50	75
10[c]	10	10	10	10	10	250	99
11[d]	10	10	10	10	10	50	45
12[d]	10	10	10	10	10	250	91

[a] Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to 150 °C where it was then held for 5 min.
[b] Run using an additional 4 mL ethyl acetate as solvent.
[c] Using 4-bromotoluene as the aryl halide substrate.
[d] Using 4-bromoanisole as the aryl halide substrate.

entry 8). We next screened 4-bromotoluene (Table 1, entries 9 and 10) and 4-bromoanisole (Table 1, entries 11 and 12) as substrates in the reaction using the 80 mL reaction vessel. We found that the optimum catalyst concentration was 250 ppb, this reflecting our previously published observations using the 10 mL vessel.

In moving to the Voyager, we set the apparatus firstly to run one cycle of a 10 mmol reaction using 1 equiv aryl halide, 1 equiv boronic acid, 1 equiv Na_2CO_3 and a 250 ppb palladium concentration. Using 4-bromoacetophenone and phenylboronic acid as test substrates, we found that the pumping of the reagents into the reaction vessel was easy, the reaction was run and was successful but pumping the product out of the vessel at the end was initially problematic. This was because the biaryl product solidifies below 90 °C and blocks the exit tube. This problem was easily overcome by programming an additional step into the protocol. After the reaction mixture has cooled to 110 °C, the excess pressure in the reaction vessel is vented and 15 mL ethyl acetate added to dissolve the biaryl product. The entire mixture is then pumped into the collection vessel. This makes for easy removal of the product and also removes the need for an additional cleaning step at the end of the protocol. We then ran 10 cycles of a 10 mmol reaction using 4-bromoacetophenone and 4-bromoanisole as aryl halide substrates (Scheme 2). Monitoring the product yield



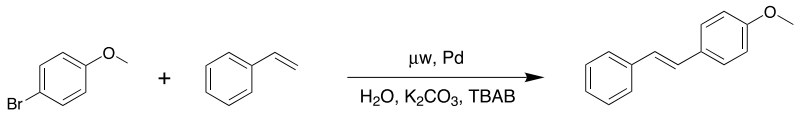
Scheme 2.

of the first four reaction mixtures showed that batch-to-batch consistency was excellent, variations of 2% being observed. The overall reaction yield from the combination of all ten product mixtures was 95% (18.6 g) with 4-bromoacetophenone and 93% (17.1 g) with 4-bromoanisole. Each cycle took approximately 15 min; 2 min to load the reaction vessel, 11 min for the reaction (3 min to reach temperature, 5 min to run reaction at 150 °C, 3 min for cool-down to 110 °C) and 2 min to pump the product out. Since the reaction is run in aqueous medium and only 250 ppb palladium is used, product isolation is easy and there is no need for a dedicated palladium removal step.

We next, turned our attention to the Heck reaction. For optimisation of reaction conditions, we focused on the coupling of 4-bromoanisole with styrene. Optimisation data are shown in Table 2. On the 1 mmol scale in the 10 mL reaction vessels, our optimum reaction conditions were 1 equiv aryl halide, 2 equiv styrene, 3.7 equiv K_2CO_3, 1 equiv TBAB, 1–5 ppm palladium and 2 mL water. The reaction mixture was heated to 170 °C and held at this temperature for 10 min before cooling back to room temperature. We found that increasing the quantity of palladium added does not improve product yields significantly once above a level of 2 ppm (Table 2, entries 1–3). Important to note is that the reaction mixture is NOT stirred since this gives higher product yields.[‡] Repeating this reaction on a 10 mmol scale keeping the ratios of reagents and reaction conditions the same, but using 5 ppm Pd and 20 mL water gave a 76% yield of the desired product (Table 2, entry 4). This is only slightly lower

[‡] As discussed in our initial report, we attribute the effects of stirring to problems associated with competitive decomposition of the starting aryl halide and styrene during the course of the reaction. In the absence of stirring, the reaction mixture forms two distinct phases; a lower aqueous layer containing the base and an upper organic layer containing the organic substrates. We believe that one of the key roles of the water is simply to dissolve the base and that the coupling reaction takes place either at the aqueous/organic interface or else the palladium migrates to the organic phase where it could feasibly be stabilized as a cluster or lower order species by the TBAB. When the reaction mixture is stirred the aryl halide is more exposed to the basic aqueous medium and this could accelerate the competitive decomposition process.

Table 2. Optimisation of conditions for the scale-up of microwave-promoted Heck coupling reaction in water[a]



Entry	Aryl halide/mmol	Styrene/mmol	K_2CO_3/mmol	TBAB/mmol	H_2O/mL	Co-solvent	Pd/ppm	Stilbene yield/%
1	1	2	3.7	1	2	None	10	90
2	1	2	3.7	1	2	None	2.5	83
3	1	2	3.7	1	2	None	1	59
4	10	20	37	10	20	None	5	76
5	10	20	37	2.5	20	None	5	32
6	10	12	37	10	20	None	5	64
7	10	20	20	10	20	None	5	53
8	10	20	37	10	17.5	Ethanol, 2.5 mL	5	65
9	10	20	37	10	17.5	nmp, 2.5 mL	5	27
10	10	20	37	10	17.5	dmf, 2.5 mL	5	66
11[b]	10	20	37	10	17.5	dmf, 2.5 mL	5	91
12[b]	10	20	37	10	15	dmf, 5 mL	5	80
13[b]	10	20	37	10	17.5	dmf, 3.5 mL	5	74
14[b,c]	10	20	37	10	17.5	dmf, 2.5 mL	5	74
15[c,d]	10	20	37	10	17.5	dmf, 2.5 mL	5	67
16[b,e]	10	20	37	10	17.5	dmf, 2.5 mL	5	79
17[d,e]	10	20	37	10	17.5	dmf, 2.5 mL	5	92

[a] Initial microwave irradiation of 120 W was used, the temperature being ramped from rt to 170 °C where it was then held for 10 min.
[b] Ramped from rt to 170 °C where it was then held for 20 min.
[c] Using 4-bromotoluene as the aryl halide substrate.
[d] Ramped from rt to 170 °C where it was then held for 15 min.
[e] Using 4-bromoacetophenone as the aryl halide substrate.

than in the case of the 1 mmol reaction but, rather than increase the palladium concentration, we decided to stay at this level.

Again we could have moved directly to the Voyager stop-flow apparatus with these conditions without further optimisation but we wanted to investigate the effects of reducing the quantity of TBAB, styrene or base used in the reaction. We found that product yields dropped as a result in all cases (Table 2, entries 5–7). We also needed to develop a methodology that would allow us to pump the reaction mixture into the vessel in the stop-flow apparatus. We wanted to dissolve the organic substrates into a suitable solvent for pumping and screened ethanol, nmp and dmf as possible candidates for this role. We prepared different stock solutions and, pouring these into the 80 mL vessel, ran the reaction (Table 2, entries 8–10). The use of any of the three solvents resulted in lower product yields than using neat water but dmf was the least deleterious. Building in this, we found that simply extending the reaction time to 20 min using water/dmf as the reaction mixture led to a 91% product yield (Table 2, entry 11). The relative ratio of water to dmf was found to be important (Table 2, entry 12). The optimum ratio was found to be 7:1 water to dmf. We also ran the reaction using an additional 1 mL of dmf, this being necessary when using the Voyager for purposes of flushing the lines (Table 2, entry 13). This has a slightly deleterious effect on the product yield.[§] Whilst it is clear that using less dmf overall would be ideal, we found that the solubility of solid substrates in smaller volumes than 4 mmol/mL begins to cause a problem when pumping reagents into the stop-flow vessel thus we decided to take forward our conditions of 2.5 mL dmf for introduction of the reagents followed by 1 mL dmf for cleaning. We screened 4-bromotoluene (Table 2, entries 14 and 15) and 4-bromoacetophenone (Table 1, entries 16 and 17) as substrates in the reaction using the 80 mL reaction vessel. We found that shorter reaction times can be employed when using these substrates. Indeed, with 4-bromoacetophenone, a reaction time of 20 min gives a lower yield than a reaction time of 10 min. We attribute this to competitive decomposition of the stilbene product in the hot basic aqueous medium.

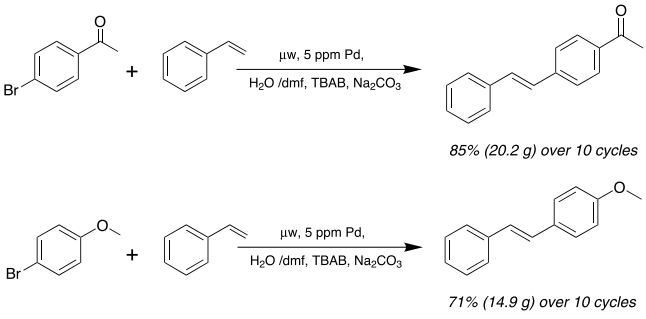
Moving to the Voyager, again we set the apparatus firstly to run one cycle of a 10 mmol reaction using 4-bromoanisole and styrene as test substrates. Pumping of the reagents into the reaction vessel was easy, the reaction was run and, after the reaction mixture had cooled to 110 °C, the excess pressure in the reaction vessel was vented and 15 mL dmf added to dissolve the product. The entire mixture was then pumped into the collection vessel and the product isolated. An 73% yield was obtained. We then ran ten cycles of a 10 mmol reaction. The overall reaction yield from the combination of all ten product mixtures was 71% (14.9 g). Each cycle took approximately 26 min (3 min to reach temperature, 20 min to run reaction at 150 °C, 3 min for cool-down to 110 °C). We then repeated the procedure using 4-bromoacetophenone. Since our previous optimisation experiments with this substrate showed that a reaction time of only 15 min rather than 20 min was needed so this was applied when using the Voyager. From the ten cycles of 10 mmol, we obtained a 85% (20.2 g) yield.

3. Conclusion

We have shown that Suzuki and Heck couplings in water

[§] Using ethyl acetate in the wash step as in the Suzuki reaction was not possible in the case of the Heck couplings because, if this is added, very high pressures are developed during the course of the reaction. Thus, for safety, dmf was used and the resultant drop in product yield accepted.

using ultra-low catalyst loadings and microwave heating can be easily scaled up from the 1 to 10 mmol scale and adapted to the automated stop-flow Voyager apparatus. It would be possible to take conditions directly from small scale experiments and transfer them to the Voyager with few, if any, modifications, particularly in the case of the Suzuki coupling. Since microwave reactions can be performed so rapidly, we decided to take some time to re-optimise the reaction conditions so as to minimise the quantities of additives, reduce the stoichiometric excesses of reagents where possible and also improve product yields. The additional optimisation experiments for both couplings took us very little time to complete. Our results from the Voyager compare favourably with Suzuki[26] and Heck[27] coupling protocols that have been scaled up using conventional heating and reported in the literature. Although not at this stage at a kg level, our methodology shows proof of concept and is easy, fast and cheap to run. The capital cost of one or more Voyager systems is less than that of a large batch reactor and the associated reagent/product transport and heating apparatus for use with conventional heating. Also, and very importantly, due to the relatively small volumes of each reaction cycle and the protection measures built in to the microwave apparatus, the reaction is very safe to run. Work is currently underway to increase the scale of the reaction as well as investigate the scope for scale-up of other microwave-promoted methodologies developed in our laboratory (Scheme 3).



Scheme 3.

4. Experimental

4.1. General methods

All materials were obtained from commercial suppliers and used without further purification. The palladium stock solution used was elemental Pd in 20% HCl. Concentration 1000 mg/mL. Baker cat. no. 5772-04. Ultra-pure water, purified to a specific resistance of >16 mΩ cm was used for the optimisation experiments. Standard distilled water was used for the automated stop-flow batch reactions. All reactions were carried out in air. ^{1}H and ^{13}C NMR spectra were recorded at 293 K on a 300 MHz spectrometer.

4.2. Description of the microwave apparatus

Microwave reactions were conducted using a commercially available monomode microwave unit (CEM Discover). The machine consists of a continuous focused microwave power delivery system with operator selectable power output from 0 to 300 W. Optimisation reactions were performed in a thick-walled glass vessel (capacity 80 mL, maximum working volume 50 mL) sealed with a septum with ports for pressure and temperature measurement devices. The pressure is controlled by a load cell connected directly to the vessel. The pressure limit was set to 300 psi for all reactions, beyond, which the apparatus shuts down. This upper limit was never reached in any of the runs but is set as a safety measure. The temperature of the contents of the vessel was monitored using a calibrated fiber-optic probe inserted into the reaction vessel by means of a sapphire immersion well. The contents of the vessel are stirred, when required, by means of a rotating magnetic plate located below the floor of the microwave cavity and a Teflon-coated magnetic stir bar in the vessel. Temperature, pressure and power profiles were monitored using commercially available software provided by the microwave manufacturer. For the automated stop-flow batch reactions, the CEM Voyager apparatus was used. The basic running of the microwave steps remains the same as with the Discover; the reactions being performed in the same thick-walled glass vessel, the pressure being controlled by a load cell connected directly to the vessel and the temperature monitored using a fiber-optic probe. Two additional ports allow for introduction of the reagents into the reaction vessel via a PFA tube of 1.6 mm ID and venting of the vessel at the end of the reaction via another PFA tube. At the end of the reaction, the product is pumped out using the same PFA tube as that used for introduction of the reagents. Movement of material in and out of the vessel is by way of a peristaltic pump and an automated valve mechanism.

4.3. Representative example of a Suzuki coupling using the 80 mL vessel for optimisation: reaction between 4-bromoacetophenone and phenylboronic acid

In an 80 mL glass vessel was placed 4-bromoacetophenone (1.99 g, 10.0 mmol), phenylboronic acid (1.22 g, 10.0 mmol), Na_2CO_3 (1.06 g, 10 mmol), palladium stock solution and ethanol (10 mL). Water was added to give a total solvent volume of 20 mL. The vessel was sealed and placed into the microwave cavity. Initial microwave irradiation of 300 W was used, the temperature being ramped from rt to the desired temperature of 150 °C. Once this was reached, taking around 3 min, the reaction mixture was held at this temperature for a further 5 min. After allowing the mixture to cool to room temperature, the reaction vessel was opened and the contents poured into a separating funnel. Water (100 mL) and ethyl acetate (100 mL) were added and the organic material extracted and removed. After further extraction of the aqueous layer with ethyl acetate, combining the organic washings and drying them over $MgSO_4$, the ethyl acetate was removed in vacuo leaving the crude product, which was characterised by comparison of NMR data with that in the literature.

4.4. Representative example of a Heck coupling using the 80 mL vessel for optimisation: reaction between 4-bromoanisole and styrene

In an 80 mL glass vessel was placed 4-bromoanisole (1.87 g, 1.25 mL, 10.0 mmol), styrene (2.08 g, 2.30 mL, 20.0 mmol), K_2CO_3 (5.11 g, 37 mmol), tetrabutylammonium bromide

(3.22 g, 10.0 mmol), palladium stock solution and organic solvent (if used). Water was added to give a total solvent volume of 20 mL. The vessel was sealed and placed into the microwave cavity. Initial microwave irradiation of 120 W was used, the temperature being ramped from rt to the desired temperature of 170 °C. Once this was reached, taking around 5 min, the reaction mixture was held at this temperature for 20 min. After allowing the mixture to cool to room temperature, the product was isolated and purified using the same procedure as in the Suzuki reaction and was characterised by comparison of NMR data with that in the literature.

4.5. Representative example of a Suzuki coupling using the automated stop-flow apparatus: reaction between 4-bromoacetophenone and phenylboronic acid

Two stock solutions were prepared, one containing sodium carbonate (10.6 g, 100 mmol) in 100 mL water, the other containing 4-bromoacetophenone (19.9 g, 100 mmol), phenylboronic acid (12.2 g, 100 mmol) and palladium stock solution in ethanol (total volume 100 mL). The apparatus was programmed to run a series of operations sequentially. Firstly, 10 mL of each of the stock solutions was introduced into the reaction vessel, washing the transfer tubes with 2 mL ethyl acetate between addition of the first and second solutions and again after introduction of the second. Next in a heating step, an initial microwave irradiation of 300 W was used, the temperature being ramped from rt to the desired temperature of 150 °C. Once this was reached (around 3 min), the reaction mixture was held at this temperature for 5 min. Thirdly, in a cooling step, the reaction mixture was cooled to 110 °C using forced air passing around the glass reaction vessel and then any remaining overpressure vented. Next, 30 mL ethyl acetate was added via the reagent inlet tube and then the whole contents of the vessel pumped out into a collection container. A further 10 mL ethyl acetate was pumped into the vessel to dissolve any remaining organic material and then this pumped into the collection container. This was the end of the procedure. The whole add, heat, remove process was then repeated a further nine times to give a total of 10 cycles of 10 mmol reactions. Each product mixture could be collected individually and the product conversion monitored or all pooled into one collection container. The product was isolated and purified using the same procedure as in case of the 10 mmol optimisation reactions.

4.6. Representative example of a Heck coupling using the automated stop-flow apparatus: reaction between 4-bromoanisole and styrene

Two stock solutions were prepared, one containing sodium carbonate (51.1 g, 370 mmol) and tetrabutylammonium bromide (32.2 g, 100 mmol) in 175 mL water, the other containing 4-bromoanisole (18.7 g, 12.5 mL, 100 mmol), styrene (20.8 g, 23.0 mL, 200 mmol) and palladium stock solution in dmf (total volume 25 mL). The apparatus was again programmed to run a series of operations sequentially. Aliquots of the stock solutions were added; 17.5 mL of the water stock solution and 2.5 mL of the dmf stock solution with washing of the transfer tubes with 0.5 mL dmf between addition of the first and second solutions and again after introduction of the second. The addition steps were performed with the stir module turned on. Next in a heating step in which the stirring was turned OFF, an initial microwave irradiation of 120 W was used to ramp the temperature from rt to the desired temperature of 170 °C. Once this was reached (around 5 min), the reaction mixture was held at this temperature for 20 min. As with the Suzuki reaction, the mixture was cooled to 110 °C, solvent added (in this case dmf), the stirring turned ON, the product mixture stirred and then pumped into the collection container, further solvent pumped into the reaction vessel and then this also transferred to the collection vessel. The whole add, heat, remove process was then repeated a further nine times to give a total of ten cycles of 10 mmol reactions, the product being isolated and purified using the same procedure as in case of the 10 mmol optimisation reactions.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2005.07.063

Spectral data for the coupling products and schematics of and information on the CEM Voyager system.

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Catalytic processes for the functionalisation and desymmetrisation of malononitrile derivatives

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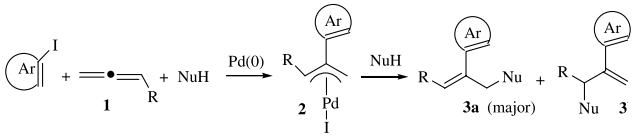
Abstract—Palladium catalysed 3-component cascades are described involving aryl/heteroaryl iodides, allene and benzyl malononitrile. Catalytic monohydration and monoamination of malononitriles to the corresponding monoamides and monoamidines are also described together with several examples of mono-oxazoline formation.

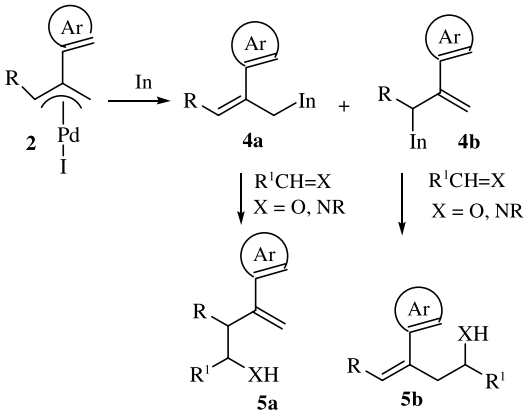
1. Introduction

π-Allylpalladium (II) complexes are important intermediates in a plethora of catalytic reactions including allylic substitutions,[1] allylic oxidation[2] and 1,4-oxidation of conjugated dienes.[3] These reactions all involve nucleophlic attack of carbon or heteroatomic nucleophiles on the π-allyl moiety. Heteroatom nucleophiles, including RCO_2H,[4] H_2O,[5] ROH[6] and amines[7] (primary and secondary), have proved particularly valuable in complex molecule synthesis. Carbon nucleophiles include malonates,[8] malononitriles,[9] and ketones.[10] We and others have been involved in generating π-allylpalladium (II) intermediates via aryl/heteroaryl iodides and allenes in the presence of palladium(0)[11–15] (Scheme 1).



Scheme 1.

In the Pd(0) catalysed reactions of allene **1** with aryl/heteroaryl iodides, carbopalladation of allene with ArPdI takes place to give π-allylpalladium (II) intermediate **2**, which reacts with nucleophiles mainly or exclusively at the less substituted terminus to give **3a/3b** (Scheme 1). Acyl and hydropalladation of allenes are additional versatile routes to π-allylpalladium species, which have been imaginatively exploited in harness with nucleophilic attack.[16–18] We have also demonstrated how the normal electrophilic reactivity of π-allylpalladium **2** generated from aryl/heteroaryl iodides and allenes can be reversed by reductive transmetallation with indium powder. The resultant umpolung allylindium species **4a/4b** subsequently add to electrophilic C=X (X=O, NR) derivatives affording homoallylic alcohols/amines **5a/5b** (Scheme 2).[19]



Scheme 2.

Keywords: 3-Component cascade; Palladium catalysis; Hydration; Amidines; Oxazolines.
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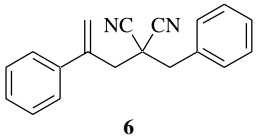
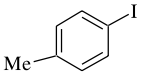
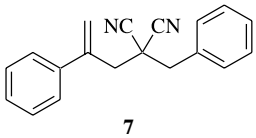
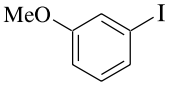
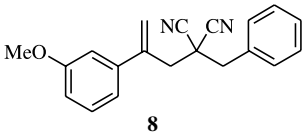
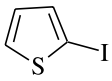
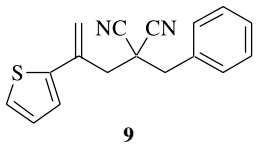
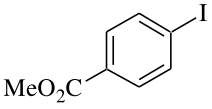
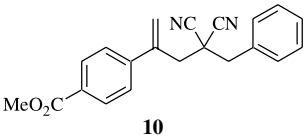
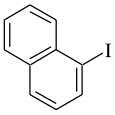
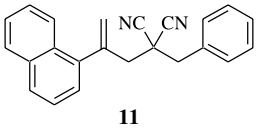
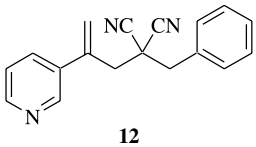
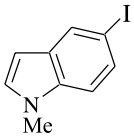
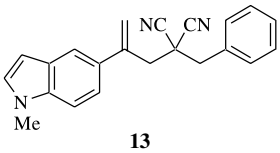
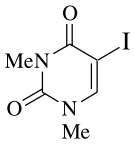
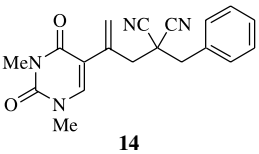
In this paper, we report the palladium catalysed 3-component cascade synthesis of 2-benzyl aryl/heteroaryl allyl malononitriles utlising benzyl malononitrile as the pro-nucleophile (Scheme 1) and the subsequent selective desymmetrisation of malononitrile derivatives by catalytic monohydration, and monoamination.

1.1. 3-Component cascades

Iodobenzene (1.5 mmol) reacted with allene (1 bar), benzyl malononitrile (1 mmol), $Pd(OAc)_2$ (5 mol%), triphenylphosphine (10 mol%) and Cs_2CO_3 (2 mol equiv) in THF (10 ml) at 90 °C for 14 h to afford **6** in 85% yield (Table 1, entry 1). Electron rich, electron poor, and neutral aryl iodides were successfully employed in the cascade process affording **6–11** in 60–73% yield (Table 1, entries 2–6). However, 3-iodopyridine, 1-methyl-5-iodoindole and 5-iodo-1,3-dimethyluracil resulted in moderate yields of **12–14** (Table 1, entries 7–9). We further optimized reaction conditions using 3-iodopyridine as the model compound. Decreasing the reaction temperature to 70 °C afforded **12** in 67% yield whilst changing the base to K_2CO_3 afforded a

Table 1. Palladium catalysed 3-component cascades[a]

Entry	Ar–I	Product	Yield (%)[b]	
			Cs_2CO_3	K_2CO_3
1		 **6**	85	87
2		 **7**	73	78
3		 **8**	66	80
4		 **9**	66	80
5		 **10**	66	83
6		 **11**	60	75
7		 **12**	44	80[c]
8		 **13**	59	70[c]
9		 **14**	40	85[c]

[a] All the reactions were carried out in THF at 100 °C for 14 h in a Schlenk tube using $Pd(OAc)_2$ (10 mol%), PPh_3 (20 mol%), base (2 mol equiv), allene (1 bar), aryl iodide (1.5 mmol) and benzyl malononitrile (1 mmol).
[b] Isolated yield.
[c] 70 °C, 14 h.

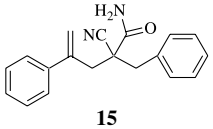
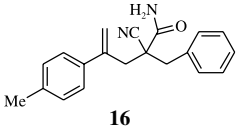
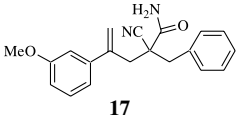
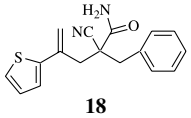
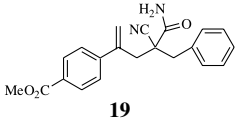
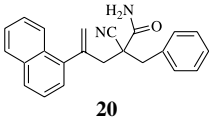
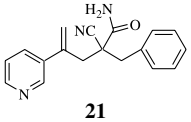
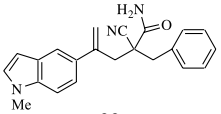
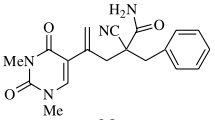
Table 2. Optimisation of monohydration of malononitriles

Entry	Catalyst	Solvent	Temperature (°C)	Time (h)	Conversion (%)
1	KF–Al_2O_3[a]	*t*-BuoH	83	1	100
2	KF–Al_2O_3[a]	THF	83	20	28
3	KF–Al_2O_3[a]	Toluene	83	20	<10
4	Pt-complex[b]	THF	100	14	62
5	Pt-complex[b]	Toluene	100	14	<10

[a] 40% w/w of KF–Al_2O_3 (0.76 mmol of KI/1 mmol of substrate).
[b] Pt-complex 0.4 mol%.

further increase in yield to 80% (Table 1, entry 7). We next, applied these optimized conditions (K_2CO_3 at 70 °C) to 5-iodo-1,3-dimethyluracil and 1-methyl-5-iodoindole affording **13** (70%) and **14** (85%) in excellent yield. These results prompted an extensive comparison between Cs_2CO_3 and K_2CO_3 (Table 1). In all cases, K_2CO_3 was found to be

Table 3. Monohydration of malononitrile using KF–Al_2O_3 in *t*-BuOH[a]

Entry	Substrate	Product	Time (h)	Yield (%)[b] (Conversion %)[c]
1	**6**	 **15**	1	65 (100)
2	**7**	 **16**	1	58 (100)
3	**8**	 **17**	1 0.75 0.30[d]	33 (100) 50 (100) 70 (100)
4	**9**	 **18**	1	57 (100)
5	**10**	 **19**	1	61 (21)
6	**11**	 **20**	1	75 (100)
7	**12**	 **21**	1	71 (100)
8	**13**	 **22**	1	61 (100)
9	**14**	 **23**	3 2[d]	42 (50) 83 (100)

[a] 40% w/w of KF–Al_2O_3 (0.76 mmol of KF/1 mmol of substrate) *t*-BuOH, reflux.
[b] Isolated yield.
[c] % Conversion from ^{1}H NMR of crude product.
[d] Reaction carried out at 90 °C in a Schlenk tube.

better than Cs_2CO_3. One possible explanation is that in THF, K_2CO_3 produces a more active Pd(0) polycarbonate species[20] $[Pd(0)(CO_3)_n]^{2n-}[2nK^+]$ analogous to the effect of Cl^- ions from $R_4N^+Cl^-$.[21]

1.2. Catalytic monohydration of malononitriles

Initially, we explored the monohydration of **6** to the monoamide mononitrile **15** using either KF–Al_2O_3 or $Pt(H)(Me_2POH)(Me_2PO)_2H$ (Pt-complex) as catalysts in different solvents (Table 2).[22,23] The best conversion of **6** to **15** was achieved when using KF–Al_2O_3 and *t*-BuOH at reflux temperature (Table 2, entry 1).

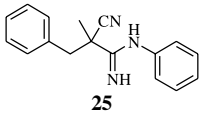
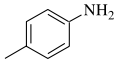
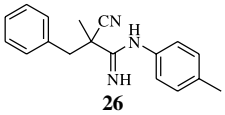
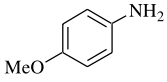
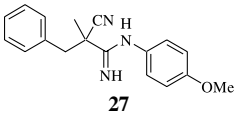
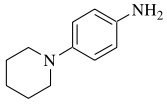
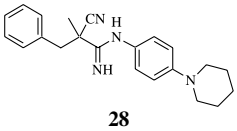
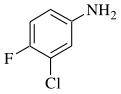
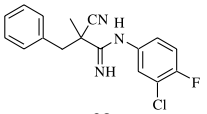
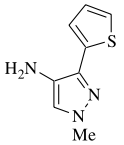
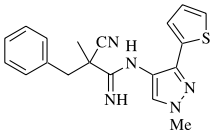
The platinum catalyst in THF 100 °C afforded only 62% conversion to **15** (Table 2, entry 4). The success of the KF–Al_2O_3/*t*-BuOH system prompted investigation of the monohydration of all the malononitrile derivatives under these conditions (Table 3). In general yields of monohydrated products were moderate to good (57–75%). Substrate **8** gave a low yield (Table 3, entry 3) under the standard conditions. Closer study showed the product to be unstable and successive reduction of the reaction time led to the desired product in 70% yield after 30 min (Table 3, entry 3). In the case of **10** and **14** incomplete conversion occurred (Table 3, entries 5 and 9). We further optimized the reaction conditions for **14** and found that carrying out the reaction in a Schlenk tube at 90 °C for 2 h gave full conversion and an 83% yield of **23** (Table 3, entry 9).

We briefly studied a sequential palladium catalysed allenylation–hydration reaction using a 3-component cascade involving 3-iodopyridine (1.5 mol), allene (1 bar) and benzyl malononitrile (1 mol), K_2CO_3 (2 mol equiv), in the presence of a catalyst system comprising $Pd(OAc)_2$ (10 mol%) and PPh_3 (20 mol%) in *t*-BuOH at 70 °C for 14 h, followed by filtration of the reaction mixture and subsequent addition of 40% w/w of KF–Al_2O_3 (0.76 mmol of KF) and continued heating at 80 °C for a further hour to afford **21** in 48% yield.

1.3. Catalytic monoamination of malononitriles

Amidines are important class of biologically active compounds. They have been utilized inter alia for the treatment of infectious diseases,[24] myocardial infraction, stroke, deep vein thrombosis,[25–28] cancer[29] and Alzheimer's disease.[30] This prompted us to investigate catalytic monoamination of malononitriles. Initially, we explored the monoamination reaction using $AlMe_3$ as the catalyst[31] and benzylmethyl malononitrile **24** as the substrate. Thus, **24** (1 mmol), aniline (1 mmol) and $AlMe_3$ (1.2 mmol) in

Table 4. Monoamination of malononitrile derivatives[a]

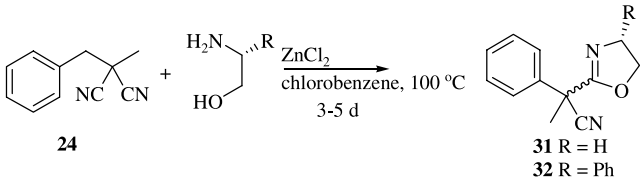
Entry	Amine	Amidine	Yield[b] (%) (Conversion%)[c]
1		 **25**	63 (100)
2		 **26**	72 (100)
3		 **27**	78 (100)
4		 **28**	47 (100) 70 (100)[d]
5		 **29**	45 (72)[e]
6		 **30**	63 (70)[e]

[a] All reactions were carried out in toluene (5 ml) at 80 °C using AlMe, (1.2 mmol), primary amine (1.2 mmol) and substrate **24** (1 mmol).
[b] Isolated yield.
[c] Conversion from ^1H NMR.
[d] 80 °C, 7 h.
[e] 100 °C , 5 h.

toluene (5 ml) at 80 °C over 17 h afforded **25** in 63% yield. Other catalysts such as $FeCl_3$, $CuCl_2$, $PdCl_2$, $RuCl_3$, $CoCl_2$ and $AlCl_3$ failed to give any product under essentially the same reaction conditions. We incorporated a variety of substitutents into aniline producing the corresponding amidines in moderate to good yield (Table 4, entries 2–4). 4-Piperidinyl aniline under the standard conditions (toluene, 80 °C, 17 h) afforded **28** in 47% yield. The NMR spectrum of the crude reaction mixture indicated the reaction had proceeded to 100% conversion. However, decreasing the reaction time to 7 h resulted in a 70% yield of **28** (Table 4, entry 4). In a number of cases (Table 4, entries 5 and 6) incomplete conversion and moderate yields were obtained at 80 °C over 17 h. Increasing the reaction temperature to 100 °C, and decreasing the reaction time to 5 h. This improved the yield but not the conversion. (Table 4, entries 5 and 6).

1.4. Catalytic monofunctionalisation of malononitriles to oxazolines

Appropriately functionalized chiral oxazolines have been utilised as chiral ligands in many transition metal catalysed reactions including Cu catalysed asymmetric conjugate addition,[32] palladium catalysed Heck reactions[33] and allylic substitution reactions.[34] This prompted a brief look at desymmetrisation of malononitrile derivatives via oxazoline formation (Scheme 3). Initially, we explored the reaction of benzyl methyl malononitrile **24** using $ZnCl_2$ as the catalyst and ethanolamine as the amino alcohol. Thus, **24** (1 mmol), ethanolamine (1.3 mmol) and $ZnCl_2$ (0.5 mmol) in chlorobenzene at 100 °C over 5 days afforded **31** in 50% yield based on 30% conversion (Scheme 3). We thought introducing a substitutent into the ethanolamine chain might favour the cyclisation step due to a buttressing effect Thus, **24** (1 mmol), (*R*)-(2)-amino-2-phenylethanol (1.3 mmol) and $ZnCl_2$ (0.5 mmol) in chlorobenzene at 100 °C over 3 days afforded **32**, as a separable 1:1 mixture of chiral diastereoisomers (Scheme 3), in 75% yield based on 80% conversion.



Scheme 3.

The diastereomers **32a** and **32b** were separated by flash chromatography and their absolute stereochemistries established by X-ray crystallography (Figs. 1 and 2).

In conclusion, we have developed a palladium catalysed 3-component cascades involving aryl/heteroaryl iodides, allenes and benzyl malononitrile resulting in the formation of 2 new C–C bonds. Catalytic selective desymmetrisation of malononitrile derivatives via monohydration, monoamination and oxazoline formation opens up a wide range of further synthetic possibilities.

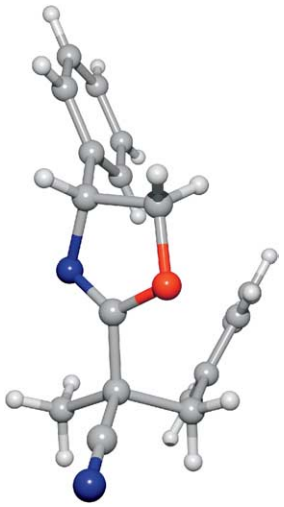


Figure 1. 32a.

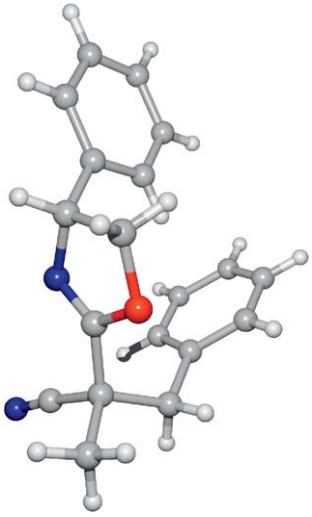


Figure 2. 32b.

2. Experimental

Melting points were determined on a Reichert hot-stage apparatus and are uncorrected. Mass spectral data were obtained from a VG Autospec instrument operating at 70 eV (EI and FAB) or ZD 2000 electrospray instrument (ES). Accurate molecular masses were obtained from the EPSRC Swansea Mass Spectroscopy service using perfluorotributylamine or polyethylenimine as an internal standard. Microanalyses were obtained using a Carbo Erba MOD11016 instrument. IR spectra were determined on a Nicolet Magna FT-IR 560 spectrometer. The IR samples were prepared as thin films by evaporation of a solution of the compound in DCM onto a germanium plate. Nuclear magnetic resonance spectra were recorded on Bruker DPX250, DPX300 and DPX500 instruments operating at 250, 300 and 500 MHz, respectively. Solvents were dried according to established methods, unless purchased dry from Aldrich in sure-seal bottles. Palladium acetate was supplied by Johnson Matthey and used as received. The term ether refers to diethyl ether and the term petrol refers to the 40–60 °C boiling point fraction of petroleum ether.

2.1. General procedure for 3-component cascade reactions

Benzyl malononitrile (1 mmol), aryl iodide (1.5 mmol), palladium acetate (10 mol%), triphenylphosphine (20 mol%) and potassium carbonate (2 mmol) were mixed in dry THF (10 ml) in a Schlenk tube. The mixture was degassed, using two freeze, pump, thaw cycles before addition of allene (1 bar) and then heated at 90 °C for 14 h with stirring, cooled to room temperature and any excess pressure vented from the Schlenk tube. The reaction mixture was filtered, the solids rinsed with dichloromethane and the filtrate concentrated in vacuo. The crude product was purified by flash column chromatography.

2.1.1. 2-Benzyl-2-(2′-phenylallyl)-malononitrile (6). Prepared from benzyl malononitrile (0.156 g, 1 mmol), iodobenzene (0.306 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 1:4 v/v ether/petroleum ether afforded the product (0.236 g, 87%) as colourless plates, mp 81–83 °C; R_f 0.42 (1:1 v/v ether/petroleum ether); (Found: C, 83.65; H, 6.05; N, 10.55. $C_{19}H_{16}N_2$ requires: C, 83.80; H, 5.90; N, 10.30%); IR 3085, 3052, 2932, 2248, 1496, 1436 and 913 cm^{-1}; δ (^{1}H, 250 MHz) 7.40–7.29 (m, 10H, ArH), 5.62 and 5.50 (2×s, 2×1H, CH_2=), 3.18 (s, 2H, CH_2Ph), 3.13 (s, 2H, CH_2C=); δ (^{13}C) 141.47 (Cq), 140.09 (Cq), 132.42 (Cq), 130.69 (2×CH), 129.36 (2×CH), 129.23 (2×CH), 129.18 (CH), 129.05 (CH), 127.04 (2×CH), 120.94 (CH_2), 115.18 (2×CN), 44.05 (CH_2), 42.91 (CH_2) and 39.79 (CH); *m/z* (EI) (%); 272 (M^+, 14), 118 (67), 91 (100).

2.1.2. Benzyl [2-(4′-methylphenyl)prop-2-enyl]-malononitrile (7). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 4-iodotoluene (0.327 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 1:4 v/v ether/petroleum ether afforded the product (0.223 g, 78%) as a colourless oil; R_f 0.45 (1:1 v/v ether/petroleum ether); (Found: C, 83.65; H, 6.50; N, 9.75. $C_{20}H_{18}N_2$ requires: C, 83.85; H, 6.30; N, 9.80%); IR (film) 3383, 2248, 914 and 825 cm^{-1}; δ (^{1}H, 250 MHz) 7.41–7.34 (m, 5H, ArH), 7.30 and 7.17 (2×d, 2×2H, J=8.0 Hz, ArH), 5.60 and 5.44 (2×s, 2×1H, CH_2=C), 3.16 (s, 2H, CH_2Ph), 3.12 (s, 2H, CH_2C=) and 2.35 (s, 3H, Me); δ (^{13}C) 141.21 (Cq), 138.95 (Cq), 137.15 (Cq), 132.48 (Cq), 130.68 (2×CH), 129.86 (2×CH), 129.34 (2×CH), 129.20 (CH), 126.84 (2×CH), 120.19 (CH_2), 115.23 (2×CN), 44.01 (CH_2), 42.86 (CH_2), 39.86 (Cq) and 21.60 (Me); *m/z* (ES) (%); 309 (M^++Na, 100), 290 (25).

2.1.3. 2-Benzyl-2-[2-(3′-methoxyphenyl)-allyl]-malononitrile (8). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 3-iodoanisole (0.18 ml, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 1:1 v/v ether/petroleum ether afforded the product (0.241 g, 80%) as colourless plates, mp 62–63 °C; R_f 0.40 (1:1 v/v ether/petroleum ether); (Found: C, 79.20; H, 6.10; N, 9.20. $C_{20}H_{18}N_2O$ requires: C, 79.40; H, 6.00; N, 9.30%); IR 3375, 2961, 2248, 1576; δ (^{1}H, 250 MHz) 7.40–7.31 (m, 5H, ArH), 7.30 (s, 1H, ArH), 6.98–6.85 (m, 3H, ArH), 5.62 and 5.48 (2×s, 2×1H, CH_2=C), 3.79 (s, 3H, Me), 3.14 (s, 2H, CH_2C=) and 3.10 (s, 2H, CH_2Ph); δ (^{13}C) 160.22 (Cq), 141.60 (Cq), 141.32 (Cq), 132.49 (Cq), 130.71 (2×CH), 130.22 (CH), 129.36 (2×CH), 129.23 (2×CH), 121.01 (CH_2), 119.44 (CH), 115.22 (2×CN), 114.15 (CH), 113.11 (CH), 55.74 (Me), 43.94 (CH_2), 42.85 (CH_2) and 39.87 (Cq); *m/z* (ES) (%); 325 (M^++Na, 100).

2.1.4. 2-Benzyl-2-(2′-thiophen-2-yl-allyl)-malononitrile (9). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 2-iodothiophene (0.15 ml, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 1:9 v/v ether/petroleum ether afforded the product (0.219 g, 79%) as colourless prisms, mp 97–98 °C; R_f 0.40 (1:1 v/v ether/petroleum ether); (Found: C, 73.40; H, 5.00; N, 10.20; S, 11.45. $C_{17}H_{14}N_2S$ requires: C, 73.35; H, 5.05; N, 10.10; S, 11.50%); IR 3032, 2248; 1455, 1436, 1093, 902 and 851 δ (^{1}H, 250 MHz) 7.40 (br s, 5H, ArH), 7.25 (dd, 1H, J=1.1, 3.6 Hz, ArH), 7.05 (dd, 1H, J=1.1, 3.6 Hz, ArH), 7.00 (dd, 1H, J=3.6, 5.0 Hz, ArH), 5.77 and 5.42 (2×s, 2×1H, CH_2=C), 3.23 (s, 2H, CH_2Ph) and 3.14 (s, 2H, CH_2C=C); δ (^{13}C) 142.55 (Cq), 133.42 (Cq), 132.27 (Cq), 130.72 (2×CH), 129.41 (2×CH), 129.31 (CH), 128.11 (CH), 126.24 (CH), 125.15 (CH), 118.68 (Cq), 115.21 (2×CN), 44.06 (CH_2), 42.67 (CH_2) and 39.85 (Cq); *m/z* (EI) (%); 278 (M^+, 22), 124 (81), 109 (32), 91 (100).

2.1.5. 4-(3,3-Dicyano-1-methylene-4-phenyl-butyl)-benzoic acid methyl ester (10). Prepared from benzyl malononitrile (0.156 g, 1 mmol), methyl 4-iodobenzoate (0.393 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 3:7 v/v ether/petroleum ether afforded the product (0.273 g, 83%) as colourless prisms, mp 97–98 °C; R_f 0.25 (1:1 v/v ether/petroleum ether); (Found: C, 76.15; H, 5.60; N, 8.40; $C_{21}H_{18}N_2O_2$ requires: C, 76.30; H, 5.50; N, 8.50%); IR 3033, 2952, 2248, 2210, 1718, 1280 and 1120; δ (^{1}H, 250 MHz) 8.04 and 7.47 (2×dt, 2×2H, J=1.9, 8.5 Hz, ArH), 7.42–7.32 (m, 5H, ArH), 5.71 and 5.60 (2×s, 2×1H, CH_2=C), 3.18 (s, 2H, CH_2C=), 3.16 (s, 2H, CH_2-Ph) and 2.92 (s, 3H, Me); δ (^{13}C) 144.45 (Cq), 141.23 (Cq), 132.67 (Cq), 130.64 (2×CH), 130.48 (2×CH), 129.41 (CH), 129.33 (2×CH), 127.00 (2×CH), 122.63 (CH_2), 115.21 (2×CN), 52.60 (Me), 44.17 (CH_2), 42.57 (CH_2) and 39.67 (Cq); *m/z* (ES) (%); 348 (M^++H_2O, 100), 331 (M^++H, 10), 299 (72).

2.1.6. 2-Benzyl-2-(2′-naphthalene-1-yl-allyl)-malononitrile (11). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 1-iodonaphthalene (0.381 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) by the general procedure. Flash column chromatography eluting with 1:9 v/v ether/petroleum ether afforded the product (0.241 g, 75%) as colourless prisms, mp 122–124 °C; R_f 0.5 (1:1 v/v ether/petroleum ether); (Found: C, 85.50; H, 5.75; N, 8.70; $C_{23}H_{18}N_2$ requires: C, 85.65; H, 5.60; N, 8.70%); IR (film) 3061, 3035, 2248, 2213, 1497 1456, 1088 and 926 cm^{-1}; δ (^{1}H, 250 MHz) 8.01–7.98 (m, 1H, naphthyl), 7.91–7.84 (m, 2H, naphthyl),

7.56–7.51 (m, 2H, naphthyl), 7.49–7.45 (m, 2H, naphthyl), 7.34–7.31 (m, 3×1H, ArH), 7.25–7.21 (m, 2×1H, ArH), 5.84 and 5.60 (2×d, 2×1H, J=0.5 Hz, CH_2=C), 3.24 (s, 2H, CH_2C=C) and 3.07 (s, 2H, CH_2Ph); δ (^{13}C) 140.88 (Cq), 138.63 (Cq), 134.28 (Cq), 130.63 (2×CH), 129.28 (CH), 129.25 (2×CH), 129.17 (CH), 127.01 (CH), 126.75 (CH), 126.49 (CH), 125.70 (CH), 125.23 (CH), 123.91 (CH), 115.10 (2×CN), 45.40 (CH_2), 43.92 (CH_2) and 39.64 (Cq); *m/z* (ES) (%); 340 ($M^+ + H_2O$, 100), 323 ($M^+ + H$, 93).

2.1.7. Benzyl-(2-pyridin-3-ylprop-2-enyl)-malononitrile (12). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 3-iodopyridine (0.307 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) heated at 70 °C by the general procedure. Flash column chromatography eluting with ether afforded the product (0.218 g, 80%) as colourless prisms, mp 122–124 °C; R_f 0.2 (ether); (Found: C, 79.15; H, 5.45; N, 15.60; $C_{18}H_{15}N_3$ requires: C, 79.10; H, 5.50; N, 15.40%); IR (film) 3033, 2248, 1497, 1455, 1023 and 931 cm^{-1}; δ (^1H, 250 MHz) 8.67 (d, 1H, J=2.0 Hz, ArH), 8.59 (dd, 1H, J=1.3, 4.8 Hz, ArH), 7.70 (dt, 1H, J=2.0, 7.9 Hz, ArH), 7.42–7.32 (m, 6H, ArH), 5.69 and 5.62 (2×s, 2×1H, CH_2=C), 3.21 (s, 2H, CH_2Ph) and 3.16 (s, 2H, CH_2C=C); δ (^{13}C) 150.16 (CH), 148.08 (CH), 138.56 (Cq), 135.59 (Cq), 134.42 (CH), 131.98 (Cq), 130.66 (2×CH), 129.45 (2×CH), 129.39 (CH), 123.83 (CH), 122.74 (CH), 114.98 (2×CN), 44.25 (CH_2), 42.51 (CH_2) and 39.48 (Cq); *m/z* (ES) (%); 274 ($M^+ + H$, 86).

2.1.8. 2-Benzyl-2-[2′-(1-methyl-1*H*-indol-5-yl)-allyl]-malononitrile (13). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 1-methyl-5-iodoindole (0.385 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) and heated at 70 °C by the general procedure. Flash column chromatography eluting with 1:4 v/v ether/petroleum ether afforded the product (0.227 g, 70%) as colourless plates, mp 123–125 °C; R_f 0.3 (1:4 v/v ether/petroleum ether); (Found: C, 81.05; H, 6.05; N, 13.00; $C_{22}H_{19}N_3$ requires: C, 81.20; H, 5.90; N, 12.90%); IR 3385, 3033, 2941, 2247, 2217, 1490,1246, 1082 and 886 cm^{-1}; δ (^1H, 250 MHz) 7.65 (s, 1H, ArH), 7.35–7.25 (m, 7H, 7×ArH), 7.05 (d, 1H, J=3.3 Hz, ArH), 6.49 (dd, 1H, J=0.5, 3.3 Hz, ArH), 5.60 and 5.44 (2×s, 2×1H, CH_2=C), 3.78 (s, 3H, Me), 3.27 (s, 2H, CH_2C=C) and 3.08 (s, 2H, CH_2Ph); δ (^{13}C) 141.87 (Cq), 138.56 (Cq), 132.30 (Cq), 132.30 (Cq), 131.17 (Cq), 130.24 (2×CH), 129.76 (CH), 128.83 (2×CH), 128.65 (CH), 128.56 (CH), 120.51 (CH), 119.03 (CH), 118.96 (CH_2), 114.97 (2×CN), 109.44 (CH), 101.42 (CH), 43.41 (CH_2), 43.17 (CH_2), 39.66 (Cq), and 32.93 (Me); *m/z* (ES) (%); 326 ($M^+ + H$, 100).

2.1.9. 2-Benzyl-2-[2′-(1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl)-allyl]-malononitrile (14). Prepared from benzyl malononitrile (0.156 g, 1 mmol), 5-iodo-1,3-dimethyluracil (0.399 g, 1.5 mmol), allene (1 bar) and potassium carbonate (0.276 g, 2 mmol) in dry THF (10 ml) at 70 °C by the general procedure. Flash column chromatography eluting with ether afforded the product (0.283 g, 85%) as colourless plates, mp 162–163 °C; R_f 0.3 (ether); (Found: C, 68.15; H, 5.50; N, 16.90; $C_{19}H_{18}N_4O_2$ requires: C, 68.25; H, 5.40; N, 16.80%); IR 3357, 3065, 2248, 1701, 1650, 1455 and 918 cm^{-1}; δ (^1H, 250 MHz) 7.40–7.37 (br s, 5H, ArH), 7.28 (s, 1H, ArH), 5.36 and 5.33 (2×s, 2×1H, CH_2=C), 3.44 and 3.35 (2×s, 2×3H, 2×Me), 3.27 (s, 2H, CH_2C=C) and 3.23 (s, 2H, CH_2Ph); δ (^{13}C) 162.81 (C=O), 151.77 (C=O), 141.77 (CH), 137.12 (Cq), 132.20 (Cq), 130.68 (2×CH), 129.37 (2×CH), 129.26 (CH), 122.40 (CH_2), 115.36 (2×CN), 113.37 (Cq), 44.31 (CH_2), 41.80 (CH_2), 39.71 (Cq), 37.60 (Me) and 28.44 (Me); *m/z* (ES) (%); 357 (M^+ + Na, 98), 335 (15).

2.2. General procedure for monohydration of malononitrile derivatives

A mixture of the malononitrile derivative (1 mmol) and 40% w/w KF–Al_2O_3 containing 15% of water (0.130 g) in *t*-BuOH (10 ml) was heated at reflux temperature for 1 h with efficient stirring (crossed magnetic stirring bar). The reaction mixture was filtered, the solids rinsed with dichloromethane and the filtrate concentrated in vacuo. The crude product was purified by flash column chromatography.

2.2.1. 2-Benzyl-2-cyano-4-phenyl-pent-4-enamide (15). Prepared from 2-benzyl-2-(2′-phenylallyl)-malononitrile (0.272 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:4 v/v ether/petroleum ether afforded the product (0.182 g, 63%) as colourless plates, mp 97–98 °C; R_f 0.2 (1:1 v/v ether/petroleum ether); (Found: C, 78.35; H, 6.40; N, 9.95; $C_{19}H_{18}N_2O$ requires: C, 78.60; H, 6.25; N, 9.65%); IR (film) 3373, 2236, 1684 and 1652 cm^{-1}; δ (^1H, 250 MHz) 7.42–7.26 (m, 10H, ArH), 5.81 and 5.24 (2×br s, 2×1H, NH_2), 5.46 and 5.35 (2×d, 2×1H, J=0.8 Hz, CH_2=C), 3.33 and 3.00 (AB quartet, J=13.3 Hz, CH_2C=C), 3.24 and 2.94 (AB quartet, J=13.3 Hz, CH_2Ph); δ (^{13}C) 169.10 (C=O), 143.48 (Cq), 140.81 (Cq), 134.67 (Cq), 130.57 (2×CH), 128.94 (2×CH), 128.77 (2×CH), 128.50 (CH), 128.21 (CH), 127.20 (2×CH), 120.33 (CN), 119.31 (CH_2), 52.01 (Cq), 43.49 (CH_2) and 42.27 (CH_2); *m/z* (ES) (%); 313 (M^+ + Na, 10).

2.2.2. 2-Benzyl-2-cyano-4-(4′-methylphenyl)pent-4-enamide (16). Prepared from benzyl [2-(4′-methylphenyl)-prop-2-enyl] malononitrile (0.286 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:4 v/v ethyl acetate /petroleum ether afforded the product (0.176 g, 58%) as colourless prisms, mp 112–113 °C; R_f 0.32 (1:4 v/v ethyl acetate /petroleum ether); (Found: C, 78.65; H, 6.70; N, 9.20; $C_{20}H_{20}N_2O$ requires: C, 78.90; H, 6.60; N, 9.20%); IR 3462, 3334, 2238, 1695, 1605 and 825 cm^{-1}; δ (^1H, 250 MHz) 7.41–7.27 (m, 10H, ArH), 5.83 and 5.35 (2×br s, 2×1H, NH_2), 5.43 and 5.30 (2×d, 2×1H, J=1.0 Hz, CH_2=C), 3.29 and 2.98 (AB quartet, J=14.0 Hz, CH_2C=C), 3.23 and 2.94 (AB quartet, J=13.3 Hz, CH_2Ph) and 2.33 (s, 3H, Me); δ (^{13}C) 168.95 (C=O), 143.25 (Cq), 138.33 (Cq), 136.34 (Cq), 134.70 (Cq), 130.56 (2×CH), 129.45 (2×CH), 128.91 (2×CH), 128.17 (CH), 127.01 (2×CH), 121.05 (Cq), 118.56 (CN), 52.06 (Cq), 43.47 (CH_2), 42.26 (CH_2) and 21.55 (Me); *m/z* (ES) (%); 305 ($M^+ + H$, 47).

2.2.3. 2-Benzyl-2-cyano-4-(3′-methoxylphenyl)pent-4-enamide (17). A solution of 2-benzyl-2-[2-(3′-methoxyphenyl)-allyl]-malononitrile (0.302 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) was heated at 90 °C in a sealed Schlenk tube for 20 min. Flash column chromatography eluting with 1:4 v/v ethyl acetate/ petroleum ether afforded the product (0.224 g, 70%) as a colourless oil, R_f 0.2 (3:7 v/v ethyl acetate/ petroleum ether); (Found: C, 74.80; H, 6.15; N, 8.90; $C_{20}H_{20}N_2O_2$ requires: C, 75.00; H, 6.30; N, 8.75%); IR 3346, 3335, 3186, 2236, 1691, 1599 and 1576 cm^{-1}; δ (^{1}H, 250 MHz) 7.30–7.20 (m, 6H, ArH), 7.00 (dd, 1H, J=0.9, 8.0 Hz, ArH), 6.92 (dd, 1H, J=0.9, 2.4 Hz, ArH), 6.83 (dd, 1H, J=2.4, 8.0 Hz, ArH), 5.85 and 5.48 (2×br s, 2×1H, NH_2), 5.48 and 5.34 (2×d, 2×1H, J=0.5 Hz, CH_2=C), 3.80 (s, 3H, Me), 3.29 (dd, 1H, J=0.5, 14.2 Hz, *H*CHC=C), 2.98 (d, 1H, J=14.2 Hz, *H*CHC=C) and 3.22 and 2.93 (AB quartet, J=13.3 Hz, CH_2Ph); δ (^{13}C) 169.06 (C=O), 159.84 (Cq), 143.30 (Cq), 142.23 (Cq), 134.66 (Cq), 130.57 (2×CH), 129.78 (CH), 128.94 (2×CH), 128.21 (CH), 120.31 (CN), 119.69 (CH), 119.41 (CH_2), 113.76 (CH), 113.07 (CH), 55.66 (Me), 52.03 (Cq), 43.46 (CH_2) and 42.24 (CH_2); *m/z* (ES) (%); 321 (M^++H, 100), 105 (28).

2.2.4. 2-Benzyl-2-cyano-4-thien-2-ylpent-4-enamide (18). Prepared from 2-benzyl-2-(2′-thiophen-2-yl-allyl)-malononitrile (0.278 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:1 v/v diethyl ether/ petroleum ether afforded the product (0.169 g, 57%) as colourless prisms, mp 139–140 °C; R_f 0.2 (1:1 v/v diethyl ether/petroleum ether); (Found: C, 68.60; H, 5.50; N, 9.45; S, 10.75; $C_{17}H_{16}N_2OS$ requires: C, 68.90; H, 5.40; N, 9.45; S, 10.80%); IR 3462, 3335, 2238, 1688, 1604, 1455 and 1378 cm^{-1}; δ (^{1}H, 250 MHz) 7.33–7.31 (m, 5H, ArH), 7.20 (dd, 1H, J=0.9, 5.0 Hz, ArH), 7.07 (dd, 1H, J=0.9, 3.5 Hz, ArH), 6.97 (dd, 1H, J=3.5, 5.0 Hz, ArH), 5.97 and 5.46 (2×br s, 2×1H, NH_2), 5.64 and 5.26 (AB quartet, CH_2=C, J=1.5 Hz), 3.31 and 3.01 (AB quartet, CH_2Ph, J=13 Hz) and 3.25 and 2.96 (AB quartet, CH_2C=C, J=14 Hz); δ (^{13}C) 166.50 (C=O), 141.88 (Cq), 133.74 (Cq), 132.15 (Cq), 128.23 (2×CH), 126.60 (2×CH), 125.89 (CH), 123.19 (CH), 122.56 (CH), 1118.03 (CN), 114.87 (CH_2), 49.75 (Cq), 41.02 (CH_2) and 39.57 (CH_2); *m/z* (ES) (%); 297 (M^++H, 71), 105 (100).

2.2.5. Methyl 4-[1-(3-amino-2-benzyl-2-cyano-3-oxopropyl)vinyl] benzoate (19). Prepared from methyl 4-(3,3-dicyano-1-methylene-4-phenyl-butyl)-benzoate (0.330 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) was heated in a sealed Schlenk tube under argon at 90 °C for 4 h. Flash column chromatography eluting with 1:9 v/v ethyl acetate/dichloromethane afforded the product (0.057 g, 69% yield, 24% conversion) as colourless prisms, mp 123–124 °C; R_f 0.2 (1:1 v/v ethyl acetate/ dichloromethane); (Found: C, 72.20; H, 5.85; N, 8.20; $C_{21}H_{20}N_2O_3$ requires: C, 72.40; H, 5.80; N, 8.05%); IR 3463, 3335, 3031, 2952, 2238, 1717, 1685, 1280 and 1120 cm^{-1}; δ (^{1}H, 250 MHz) 8.00 and 7.47 (2×dt, 2×2×CH, J=8.0, 18.2 Hz, ArH), 7.33–7.24 (m, 5H, ArH), 5.81 and 5.20 (2×br s, 2×1H, NH_2), 5.56 and 5.45 (2×s, 2×1H, CH_2=C), 3.91 (s, 3H, Me), 3.36 and 2.98 (AB quartet, J=14.0 Hz, CH_2C=C), 3.24 and 2.95 (AB quartet, J=13.3 Hz, CH_2Ph); δ (^{13}C) 168.13 (C=O), 166.75 (Cq), 144.81 (Cq), 142.36 (Cq), 133.99 (Cq), 130.12 (2×CH), 129.69 (2×CH), 128.59 (2×CH), 127.90 (CH), 126.78 (2×CH), 120.67 (CH_2), 119.81 (CN), 52.14 (Me), 51.57 (Cq), 43.24 (CH_2) and 41.58 (CH_2); *m/z* (ES) 349 (M^++H, 82), 105 (100).

2.2.6. 2-Benzyl-2-cyano-4-(1-naphthyl)pent-4-enamide (20). Prepared from 2-benzyl-2-(2′-naphthalene-1-yl-allyl)-malononitrile (0.322 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:1 v/v ether/ petroleum ether afforded the product (0.255 g, 75%) as colourless prism, mp 185–186 °C; R_f 0.2 (1:1 v/v ether/ petroleum ether); (Found: C, 80.90; H, 6.05; N, 8.30; $C_{23}H_{20}N_2O$ requires: C, 81.15; H, 5.90; N, 8.20%); IR 3459, 3335, 2237 and 1694 cm^{-1}; δ (^{1}H, 250 MHz) 8.09 (d, 1H, J=7.1 Hz, ArH), 7.87–7.76 (m, 2×1H, ArH), 7.55–7.47 (m, 2×1H, ArH), 7.42 (d, 2×1H, J=5.0 Hz, ArH), 7.28–7.25 (m, 3H, ArH), 7.21–7.17 (m, 2×1H, ArH), 5.74 and 5.23 (2×br s, 2×1H, NH_2), 5.71 and 5.44 (2×s, 2×1H, CH_2=C), 3.46 and 3.05 (AB quartet, J=14.0 Hz, CH_2C=C), 3.13 and 2.90 (AB quartet, J=13.3 Hz, CH_2Ph); δ (^{13}C) 168.62 (C=O), 142.68 (Cq), 139.57 (Cq), 134.45 (Cq), 134.14 (Cq), 131.45 (Cq), 130.48 (2×CH), 128.97 (CH), 128.90 (2×CH), 128.63 (CH), 128.20 (CH), 126.60 (CH), 126.43 (CH), 126.25 (CH), 125.77 (CH), 125.48 (CH), 121.96 (CH_2), 120.37 (CN), 51.60 (Cq), 45.00 (CH_2) and 43.72 (CH_2); *m/z* (ES) (%); 341 (M^++H, 85), 115 (28), 105 (67).

2.2.7. 2-Benzyl-2-cyano-4-pyridin-3-ylpent-4-enamide (21). Prepared from benzyl (2-pyridin-3-ylprop-2-enyl)-malononitrile (0.273 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:9 v/v methanol/dichloromethane afforded the product (0.208 g, 71%) as colourless prisms, mp 130–131 °C; R_f 0.4 (1:9 v/v methanol/ dichloromethane); (Found: C, 74.15; H, 5.80; N, 14.30; $C_{18}H_{17}N_3O$ requires: C, 74.20; H, 5.90; N, 14.40%); IR 3367, 2238, 1685, 1496, 1455, 1029 and 918 cm^{-1}; δ (^{1}H, 250 MHz) 8.64 and 8.52 (2×br s, 2×1H, ArH), 7.69 (d, 1H, J=8.0 Hz, ArH), 7.33–7.23 (m, 6H, ArH), 5.92 and 5.54 (2×br s, 2×1H, NH_2), 5.52 and 5.46 (2×s, 2×1H, CH_2=C), 3.36 and 2.92 (AB quartet, J=14.0 Hz, CH_2C=C), 3.26 and 2.97 (AB quartet, J=13.3 Hz, CH_2Ph); δ (^{13}C) 168.54 (C=O), 149.55 (CH), 148.39 (CH), 140.46 (Cq), 134.9 (CH), 134.31 (Cq), 130.52 (2×CH), 129.02 (2×CH), 128.34 (CH), 121.17 (CH_2), 120.19 (CN), 51.86 (Cq), 43.74 (CH_2) and 41.99 (CH_2); *m/z* (ES) (%); 292 (M^++H, 100).

2.2.8. 2-Benzyl-2-cyano-4-(1-methyl-1*H*-indol-5-yl)pent-4-enamide (22). Prepared from 2-benzyl-2-[2-(1-methyl-1*H*-indol-5-yl)-allyl]-malononitrile (0.325 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure. Flash column chromatography eluting with 1:9 v/v ethyl acetate/dichloromethane afforded the product (0.209 g, 61%) as colourless plates, mp 170–171 °C; R_f 0.3 (1:9 v/v ethyl acetate/dichloromethane); (Found: C, 76.65; H, 6.05; N, 11.95; $C_{22}H_{21}N_3O$ requires: C, 76.90; H, 6.15; N, 12.20%); IR 3435, 2230, 2109, 1679, 1640 cm^{-1}; δ (^{1}H, 250 MHz) 7.66 (s, 1H, ArH), 7.31–7.23 (br s, 7H,

ArH), 7.03 (d, 1H, $J=3.0$ Hz, ArH), 6.46 (d, 1H, $J=3.0$ Hz, ArH), 5.77 and 5.21 (2×br s, 2×1H, NH_2), 5.45 and 5.30 (2×d, 2×1H, $J=1.2$ Hz, CH_2=C), 3.77 (s, 3H, Me), 3.37 and 3.08 (AB quartet, $J=14.0$ Hz, CH_2C=C), 3.22 and 2.93 (AB quartet, CH_2Ph, $J=13.2$ Hz,); δ (^{13}C) 168.68 (C=O), 144.01 (Cq), 136.60 (Cq), 134.48 (Cq), 131.75 (Cq), 130.19 (2×CH), 129.43 (CH), 128.45 (2×CH), 128.36 (CH), 127.67 (Cq), 120.86 (CH), 120.07 (CN), 119.28 (CH), 117.37 (CH_2), 108.96 (CH), 101.39 (CH), 51.87 (Cq), 43.01 (CH_2), 42.63 (CH_2) and 32.90 (Me); *m/z* (EI) 344 (M^++H, 100).

2.2.9. 2-Benzyl-2-cyano-4-[1,3-dimethyl-2,4-bis(methylene)-1,2,3,4-tetrahydropyrimidin-5-yl]pent-4-enamide (23). Prepared from 2-benzyl-2-[2-(1,3-dimethyl-2,4-dioxohexahydro-pyrimidin-5-yl)-allyl]-malononitrile (0.334 g, 1 mmol) and KF–Al_2O_3 (0.130 g) in *t*-BuOH (10 ml) by the general procedure was heated in a sealed Schlenk tube under argon at 90 °C for 2 h. Flash column chromatography eluting with 1:20 v/v methanol/dichloromethane afforded the product (0.292 g, 83%) as colourless plates, mp 78–79 °C; R_f 0.25 (1:20 v/v methanol/dichloromethane). HRMS Found: 353.1612 $C_{19}H_{20}N_4O_3+H^+$ requires: 353.1613; IR 3416, 3330, 2240, 1701, 1647, 1455, 1370 and 914 cm^{-1}; δ (^1H, 250 MHz) 7.34 7.25 (m, 5H, ArH), 7.17 (s, 1H, CH), 6.13 and 5.82 (2×br s, 2×1H, NH_2), 5.32 and 5.30 (2×s, 2×1H, CH_2=C), 3.39 and 3.35 (2×s, 2×3H, 2×Me), 3.35 and 2.96 (AB quartet, $J=14.0$ Hz, CH_2C=C), 3.25 and 2.97 (AB quartet, $J=13.3$ Hz, CH_2Ph); δ (^{13}C) 169.14 (2×C=O), 162.79 (C=O), 151.85 (Cq), 140.82 (CH), 137.59 (Cq), 134.43 (Cq), 130.51 (2×CH), 128.97 (2×CH), 128.29 (CH), 121.50 (CH_2), 120.67 (CN), 114.55 (Cq), 51.76 (Cq), 43.75 (CH_2), 41.03 (CH_2), 37.48 (CH_2) and 28.84 (Me); *m/z* (ES) (%); 353 (M^++H, 100), 279 (35), 115 (23).

2.3. General procedure for monoamination of malononitriles

A solution of amine (1.2 mmol) in toluene (3.5 mmol) was cooled at 0 °C and trimethylaluminium (1.2 mmol, 2 M solution in hexane,) was added dropwise with stirring over 5 min. The reaction was then allowed to warm to room temperature and stirring continued for 3 h. A solution of benzylmethyl malononitrile (1 mmol) in toluene (1.5 ml) was then added, and the resulting mixture was stirred and heated at 80 °C for 17 h. The solution was cooled at room temperature and poured into a slurry of silica gel (20 g) in CH_2Cl_2/MeOH. The silica was filtered off and washed with a mixture of CH_2Cl_2/MeOH. The combined filtrate was concentrated in vacuo and the crude product purified by flash column chromatography.

2.3.1. 2-Cyano-2-methyl-3,*N*-diphenyl-propionamidine (25). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), aniline (0.1 ml, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure. The crude residue was triturated with a mixture of Et_2O/petroleum ether to afford the product (165 mg, 63%) as colourless prisms, mp 200–202 °C. (Found: C, 77.35; H, 6.50; N, 16.05 $C_{17}H_{17}N_3$ requires: C, 77.54; H, 6.51; N, 15.96%) δ (^1H, 250 MHz) 7.38–7.27 (m, 7H, ArH), 6.99 (t, 1H, ArH, $J=7.20$ Hz), 6.70 (d, 2H, ArH, $J=7.75$ Hz), 5.65 (s, 2×1H, 2×NH), 3.40 and 3.14 (AB quartet, CH_2Ph, $J=13.6$ Hz), 1.72 (s, 3H, Me). δ (^{13}C) 160.31 (Cq), 154.32 (Cq), 140.60 (Cq), 135.49 (2×CH), 134.59 (2×CH), 133.38 (2×CH), 132.60 (CH), 128.01 (CH), 127.00 (CN), 126.48 (2×CH), 50.83 (Cq), 48.95 (CH_2) and 29.39 (Me). IR (film) 3423, 3171, 2248, 1644, 1243 cm^{-1} *m/z* (ES) (%); 264 (M^++1, 100).

2.3.2. 2-Cyano-*N*-(4-methylphenyl)-phenylpropanimidamide (26). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), *p*-toluidine (129 mg, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure. Flash column chromatography eluting with 3:7 v/v Et_2O/petroleum ether afforded the product (199 mg, 72%) as colourless needles, mp 134–136 °C. (Found: C, 77.80; H, 7.20; N, 15.15 $C_{18}H_{19}N_3$ requires: C, 77.95; H, 6.90; N, 15.15%) δ (^1H, 250 MHz) 7.41–7.30 (m, 5H, ArH), 7.13 (d, 2×1H, ArH, $J=8.0$ Hz), 6.72 (d, 2×1H, ArH, $J=8.0$ Hz), 4.65 (br s, 2×1H, 2×NH), 3.38 and 3.13 (AB quartet, CH_2Ph, $J=13.4$ Hz), 2.31 (s, 3H, Me) and 1.76 (s, 3H, Me). δ (^{13}C) 154.24 (Cq), 145.74 (Cq), 135.19 (Cq), 132.76 (Cq), 130.32 (2×CH), 130.27 (2×CH), 128.39 (2×CH), 127.63 (CH), 121.90 (CN), 120.85 (2×CH), 44.89 (CH_2), 44.72 (Cq), 25.05 (Me) and 20.82 (Me). IR (film) 3422, 3310, 3173, 2242, 1642, 1605, 1505,1104 cm^{-1} *m/z* (ES) (%); 278 (M^++1, 100).

2.3.3. 2-Cyano-*N*-(4-methoxyphenyl)phenylpropanimidamide (27). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), *p*-anisidine (148 mg, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure. Flash column chromatography eluting with 1:1 v/v Et_2O/petroleum ether afforded the product (228 mg, 78%) as colourless needles, mp 133–135 °C. (Found: C, 73.50; H, 6.45; N, 14.30 $C_{18}H_{19}N_3O$ requires: C, 73.70; H, 6.53; N, 14.32%). δ (^1H, 250 MHz) 7.43–7.28 (m, 5H, ArH), 6.89 (d, 2×1H, ArH, $J=8.8$ Hz), 6.76 (d, 2×1H, ArH, $J=8.8$ Hz), 4.68 (br s, 2×1H, 2×NH), 3.74 (s, 3H, Me), 3.39 and 3.15 (AB quartet, CH_2Ph, $J=13.4$ Hz) and 1.77 (s, 3H, Me). δ (^{13}C) 156.26 (Cq), 154.98 (Cq), 141.79 (Cq), 135.61 (Cq), 130.73 (2×CH), 128.83 (2×CH), 128.08 (CH), 122.36 (CH), 115.43 (2×CH), 55.89 (Me), 45.36 (CH_2), 45.15 (Cq) and 25.47 (Me). IR (film) 3417, 3272, 3162, 3010, 2242, 1642, 1612, 1503, 1241, 1033, 871, 725 cm^{-1} *m/z* (ES) (%); 294 (M^++1, 100).

2.3.4. 2-Cyano-2-phenyl-*N*-(4-piperidin-1-ylphenyl)-propanimidamide (28). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), (4-piperidine-1-ylphenyl)amine (211 mg, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure for 7 h. Flash column chromatography eluting with 1:1 v/v Et_2O/petroleum ether afforded the product (242 mg, 70%) as colourless needles, mp 174–176 °C. (Found: C, 76.20; H, 7.45; N, 16.15 $C_{22}H_{26}N_4$ requires: C, 76.27; H, 7.56; N, 16.17%). δ (^1H, 250 MHz) 7.41–7.29 (m, 5H, ArH), 6.93 (d, 2×1H, ArH, $J=8.7$ Hz), 6.74 (d, 2×1H, ArH, $J=8.7$ Hz), 4.67 (br s, 2×1H, 2×NH), 3.39 and 3.14 (AB quartet, CH_2Ph, $J=13.4$ Hz), 3.10–3.08 (m, 2×2H, 2×CH_2), 1.76 (s, 3H, Me), 1.74–1.69 (m, 2×2H, 2×CH_2) and 1.58–1.53 (m, 2H, CH_2). δ (^{13}C) 154.75 (Cq), 149.18 (Cq), 140.89

(Cq), 135.70 (2×Cq), 130.76 (2×CH), 128.81 (2×CH), 128.04 (CH), 122.43 (CN), 122.02 (CH), 118.70 (CH), 51.86 (CH_2), 45.39 (CH_2), 45.16 (Cq), 26.42 (4×CH_2), 25.52 (CH) and 24.63 (Me). IR (film) 3414, 3269, 3161, 2932, 2808, 2238, 1641, 1611, 1504, 1232, 1129 cm^{-1} *m/z* (ES) (%); 347 ($M^+ + 1$, 100).

2.3.5. *N*-(3-Chloro-4-fluorophenyl)-2-cyano-2-methyl-3-phenylpropanimidamide (29). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), 3-chloro-4-fluoroaniline (175 mg, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure. Flash column chromatography eluting with 2:8 v/v Et_2O/petroleum ether afforded the product (85 mg, 40, 68% conversion) as colourless prisms, mp 123–125 °C. (Found: C, 64.75; H, 5.00; Cl, 11.30; N, 13.15 $C_{17}H_{15}ClFN_3$ requires: C, 64.66; H, 4.79; Cl, 11.23; N, 13.31%). δ (^{1}H, 300 MHz) 7.41–7.31 (m, 5H, ArH), 7.11 (t, 1H, ArH, J=8.7 Hz), 6.86 (dd, 1H, ArH, J=2.5 Hz), 6.70–6.65 (m, 1H, ArH), 4.73 (br s, 2×1H, 2×NH), 3.35 and 3.16 (AB quartet, CH_2Ph, J=13.5 Hz) and 1.76 (s, 3H, Me). δ (^{13}C) 154.97 (d, Cq, J=243.0 Hz), 155.67 (Cq), 145.53 (d, Cq, J=3.7 Hz), 135.31 (2×CH), 130.66 (2×CH), 128.93 (CH), 123.37 (CH), 122.22 (CN), 122.00 (Cq), 121.10 (d, CH, J=6.0 Hz), 117.89 (d, CH, J=21.7 Hz), 45.33 (CH_2), 45.22 (Cq) and 25.45 (Me). IR (film) 3422, 3273, 3163, 2245, 1644, 1614, 1489, 1275, 1260, 764, 749 cm^{-1} *m/z* (ES) (%); 316 ($M^+ + 1$, 100), 318 (45).

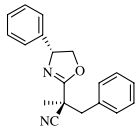
2.3.6. 2-Cyano-*N*-[1-methyl-3-(2-thienyl)-1*H*-pyrazol-5-yl]-2-phenylpropanimidamide (30). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), 5-amino-1-methyl-3-(2-thienyl)pyrazole (215 mg, 1.2 mmol), and trimethylaluminium (0.6 ml, 2 M solution in hexane, 1.2 mmol) by the general procedure. Flash column chromatography eluting with 1:1 v/v Et_2O/petroleum ether afforded the product (133 mg, 54, 71% conversion) as pale green prisms, mp 51–53 °C. (HRMS Found: 350.1430 $C_{19}H_{19}N_5S^-$ requires: 350.1434) δ (^{1}H, 250 MHz) 7.32–7.21 (m, 7H, ArH), 7.04 (dd, 1H, ArH, J=7.20 Hz), 5.98 (s, 1H, ArH), 5.45 (br s, 2H, 2×NH), 3.74 (s, 3H, Me), 3.35 and 3.16 (AB quartet, CH_2Ph, J=13.6 Hz) and 1.79 (s, 3H, Me). δ (^{13}C) 156.15 (Cq), 145.66 (Cq), 145.35 (Cq), 137.11 (Cq), 134.69 (Cq), 130.02 (2×CH), 128.59 (2×CH), 127.88 (CH), 127.39 (CH), 124.22 (CH), 123.13 (CH), 121.24 (CN), 90.88 (CH), 45.68 (Cq), 45.36 (CH_2), 34.78 (Me) and 24.83 (Me). IR (film) 3454, 3355, 3196, 2938, 2245, 1652, 1603, 1513, 1455, 923, 768, 705 cm^{-1} *m/z* (ES) (%); 349 (M^+, 18), 91 (100), 84 (22), 44 (76).

2.4. General procedure for the synthesis of oxazolines in the presence of zinc chloride

A mixture of zinc chloride (0.5 mmol), benzylmethyl malononitrile 24 (1 mmol) and amino alcohol (1.3 mmol) in chlorobenzene (3 ml) was heated in a Schlenk flask at 100 °C for 3–5 days. The solvent was removed under reduced pressure and the residue purified by flash column chromatography.

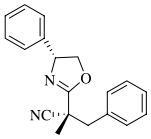
2.4.1. 2-(4,5-Dihydro-oxazol-2-yl)-2-methyl-3-phenyl-propionitrile (31). Prepared from benzylmethyl malononitrile **24** (170 mg, 1 mmol), ethanolamine (0.08 ml, 1.3 mmol), and $ZnCl_2$ (68 mg, 0.5 mmol) and chlorobenzene (3 ml) over 5 days by the general procedure. Flash column chromatography eluting with 1:1 v/v Et_2O/petroleum ether afforded the product (32 mg, 50, 30% conversion) as colourless oil. (HRMS Found: 215.1179 $C_{13}H_{14}N_2O$ requires: 215.1179). δ ^{1}H NMR; 7.31–7.29 (m, 5H, ArH), 4.37 and 3.88 (2×t, 2×2H, 2×CH_2, J=9.6 Hz), 3.24 and 3.09 (AB quartet, CH_2Ph, J=13.5 Hz) and 1.62 (s, 3H, Me). δ ^{13}C NMR; 165.18 (C=N), 134.25 (Cq), 130.07 (2×CH), 128.49 (2×CH), 127.81 (CH), 120.08 (CN), 68.68 (CH_2), 54.48 (CH_2), 43.69 (CH_2), 39.71 (Cq) and 23.03 (Me). IR (film) 3417, 2972, 2236, 1658, 1531, 1454, 743, 702 cm^{-1} *m/z* (ES) (%); 215 (M^++H, 100).

2.4.2. 2-Methyl-3-phenyl-2-(4-phenyl-4,5-dihydro-oxazol-2-yl)-propionitrile (32). Prepared from benzylmethyl malononitrile (170 mg, 1 mmol), (*R*)-(2)-amino-2-phenyl-ethanol (164 mg, 1.3 mmol) and $ZnCl_2$ (68 mg, 0.5 mmol) in chlorobenzene (3 ml) over 3 days by the general procedure. Flash column chromatography eluting with 3:7 v/v Et_2O/petroleum ether afforded the separated products (**32a**) and (**32b**) ratio 1:1 (174 mg, 75, 80% conversion);



(*S*)-2-Methyl-3-phenyl-2-((*R*)-4-phenyl-4,5-dihydro-oxazol-2-yl)-propionitrile (**32a**) was obtained as colourless needles, mp 82–85 °C $[\alpha]_D^{20}$ +35 ($CHCl_3$),

(Found: C, 78.3; H, 6.15; N, 9.70 $C_{19}H_{18}N_2O$ requires: C, 78.59; H, 6.25; N, 9.65%). δ ^{1}H NMR; 7.33–7.28 (m, 8H, Ar), 7.13–7.11 (m, 2H, Ar), 5.22 (dd, 1H, CH, J=8.7, 9.9 Hz), 4.75 (dd, 1H, CH, J=8.5, 9.9 Hz), 4.20 (dd, 1H, CH, J=8.5, 8.7 Hz), 3.33 and 3.19 (AB quartet, CH_2Ph, J=13.5 Hz) and 1.71 (s, 3H, Me). δ ^{13}C NMR; 165.83 (C=N), 141.52 (Cq), 134.56 (Cq), 130.72 (2×CH), 129.20 (2×CH), 128.99 (2×CH), 128.26 (2×CH), 126.98 (2×CH), 120.59 (CN), 76.24 (CH_2), 70.08 (CH), 44.10 (CH_2), 39.96 (Cq) and 23.65 (Me). IR (film) 3063, 3030, 2242, 1663, 1495, 1454, 1186, 1102, 973 cm^{-1} *m/z* (ES) (%); 291 (M^++H, 100).



(*R*)-2-Methyl-3-phenyl-2-((*R*)-4-phenyl-4,5-dihydro-oxazol-2-yl)-propionitrile (**32b**) was obtained as colourless needles, mp 95–97 °C, $[\alpha]_D^{20}$ +44 ($CHCl_3$), (Found: C, 78.40; H, 6.20; N, 9.70 $C_{19}H_{18}N_2O$ requires: C, 78.59; H, 6.25; N, 9.65%). δ ^{1}H NMR; 7.35–7.26 (m, 8H, Ar), 6.99–6.95 (m, 2H, Ar), 5.21 (dd, 1H, CH, J=8.5, 9.9 Hz), 4.71 (dd, 1H, CH, J=8.5, 9.9 Hz), 4.14 (dd, 1H, CH, J=8.5, 8.5 Hz), 3.30 and 3.19 (AB quartet , CH_2Ph, J=13.5 Hz) and 1.71 (s, 3H, Me). δ ^{13}C NMR; 165.83 (C=N), 141.52 (Cq), 134.79 (Cq), 130.58 (2×CH), 129.14 (2×CH), 129.05 (2×CH), 128.25 (CH), 126.95 (2×CH), 120.59 (CN), 76.41 (CH_2), 70.07 (CH), 44.21 (CH_2), 40.43 (Cq)

and 24.15 (Me). IR (film) 3311, 3032, 2917, 2244, 1662, 1455, 1192, 1105, 758, 701 cm^{-1} *m/z* (ES) 291 ($M^+ + H$, 100%).

2.5. Single-crystal X-ray analysis

Crystallographic data for **32a** and **32b** was measured on a Nonius Kappa CCD area-detector diffractometer using ϕ and ω-scans and graphite monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Both structures were solved by direct methods using SHELXS-86[35] and were refined by full-matrix least-squares (based on F^2) using SHELXL-97.[36] The weighting schemes used were $w = [\sigma^2(F_o^2) + (0.0455P)^2]^{-1}$ (for **32a**) and $w = [\sigma^2(F_o^2) + (0.0518P)^2 + 0.0452P]^{-1}$ (for **32b**) where $P = (F_o^2 + 2F_c^2)/3$. All non-hydrogen atoms were refined with anisotropic displacement parameters whilst hydrogen atoms were constrained to predicted positions using a riding model. The residuals wR_2 and R_1, given below, are defined as $wR_2 = (\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[wF_o^2]^2)^{1/2}$ and $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$. For both structures, the absolute configuration could not be confirmed from the diffraction data because of the absence of significant anomalous scattering effects and Friedel pairs were merged. However, for both **32a** and **32b**, the models were assigned on the basis of the known stereochemistry at the chiral centre C3.

Crystal data for **32a**. $C_{19}H_{18}N_2O$, $0.53 \times 0.05 \times 0.03$ mm, $M = 290.35$, monoclinic, space group $P2_1$, $a = 9.3068(4)$ Å, $b = 6.1360(2)$ Å, $c = 14.1944(8)$ Å, $\beta = 98.7550(15)°$, $U = 801.15(6)$ $Å^3$, $Z = 2$, $D_c = 1.204$ Mg m^{-3}, $\mu = 0.075$ mm^{-1}, $F(000) = 308$, $T = 150(2)$ K.

Data collection. $2.83 \leq \theta \leq 26°$; 1725 independent reflections were collected [$R_{int} = 0.0883$]; 1243 reflections with $I > 2\sigma(I)$.

Structure refinement. Number of parameters = 200, goodness of fit, $s = 1.004$; $wR_2 = 0.0956$, $R_1 = 0.0417$.

Crystal data for **32b**. $C_{19}H_{18}N_2O$, $0.46 \times 0.20 \times 0.03$ mm, $M = 290.35$, monoclinic, space group $P2_1$, $a = 5.9287(2)$ Å, $b = 8.0405(2)$ Å, $c = 16.5085(8)$ Å, $\beta = 98.8640(13)°$, $U = 777.56(5)$ $Å^3$, $Z = 2$, $D_c = 1.240$ Mg m^{-3}, $\mu = 0.078$ mm^{-1}, $F(000) = 308$, $T = 150(2)$ K.

Data collection. $3.48 \leq \theta \leq 26°$; 1646 independent reflections were collected [$R_{int} = 0.0551$]; 1409 reflections with $I > 2\sigma(I)$.

Structure refinement. Number of parameters = 200, goodness of fit, $s = 1.029$; $wR_2 = 0.0889$, $R_1 = 0.0352$.

CCDC 272642 (**32a**) and CCDC 272729 (**32b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Radical cyclization of *exo*-methylene furanose derivatives: an expedient approach to the synthesis of chiral tricyclic nucleosides and benzannulated oxepine derivatives

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Abstract—Tributyltin radical mediated cyclization of the glucose derived *exo*-methylene furanose derivatives **5a–c** led to the highly functionalized *cis*-fused bicyclic ethers **6a–c**. The product could subsequently be transformed to the optically active tricyclic nucleoside analogue **8** or oxepine derivative **9**.

1. Introduction

Seven-membered oxacycles are structural units present in a wide variety of natural products[1] including the monocyclic zoapatanol,[2] the polycyclic hemibrevetoxin B,[3] and more complex polyether toxins such as ciguatoxins and brevetoxins A and B.[4] Numerous synthetic routes for functionalized oxepine heterocycles have been developed based on ring expansion,[5] ring closing metathesis,[6] palladium induced reactions,[7] reductive intramolecular cyclization with SmI_2,[8] and several other methods.[9] Interest in the use of the easily accessible carbohydrates from the chiral pool for the synthesis of optically active oxepine derivatives has been growing rapidly.[10] In a continuation of our interest in the carbohydrate based synthesis of *cis*- and *trans*-fused tricyclic ethers,[11] we felt that the use of the chiron approach along with the application of free radical reaction methodology offers a better and more convenient route for the synthesis of *cis*-fused tricyclic furobenzoxepine derivatives.[12] The possibility of converting the intermediate furanose derivatives to nucleoside analogues was an added attraction. It should be mentioned that the design of conformationally restricted nucleosides as monomers in oligonucleotide analogues and as potent antiviral agents[13] has attracted considerable attention recently. Anticipating better biological activities, nucleosides with bi- and tricyclic carbohydrate moieties[14,15] have been synthesized in order to restrict the conformational flexibility of the nucleoside into conformers, which are ideal for nucleic acid recognition. Herein we report the synthesis of a new tricyclic nucleoside analogue in which the furanose ring is linearly *cis*-fused with a benzannulated oxepine moiety. Besides nucleoside synthesis, the cleavage of the furanose ring in the cyclized product provides an expedient entry into chiral functionalized benzoxepines. We believe that this study would, therefore, be of significant interest for synthesizing novel molecules including seven-membered ring ethers in optically pure form.

2. Results and discussion

The key starting material 1,2:5,6-di-*O*-isopropylidene glucofuranose **1** could be smoothly converted to the respective *O*-2-bromobenzylated glucofuranosides **3a–c** on reaction with the bromides **2a–c** under phase transfer catalysis conditions. Treatment of each of the benzylated products **3a–c** with 70% aq acetic acid at rt selectively removed the 5,6-*O*-isopropylidene group. On $NaIO_4$ oxidation, the diol generated the nor-aldehyde, which was reduced with $NaBH_4$. Subsequent iodination with I_2–Ph_3P-imidazole in dry benzene at rt furnished the iodides **4a–c**. Dehydroiodination of **4a–c** in the presence of a base such as ^{t}BuOK furnished the desired *exo*-methylene derivatives **5a–c** (Scheme 1) in 69–72% yield.

Radical cyclization of each of the *exo*-methylene derivatives **5a–c** with TBTH and a catalytic amount of AIBN in benzene at reflux, furnished the respective crystalline tricyclic ethers **6a–c** (Scheme 2) as the only isolable

Keywords: Benzoxepines; Free radical reaction; Tricyclic nucleoside; Carbohydrate.
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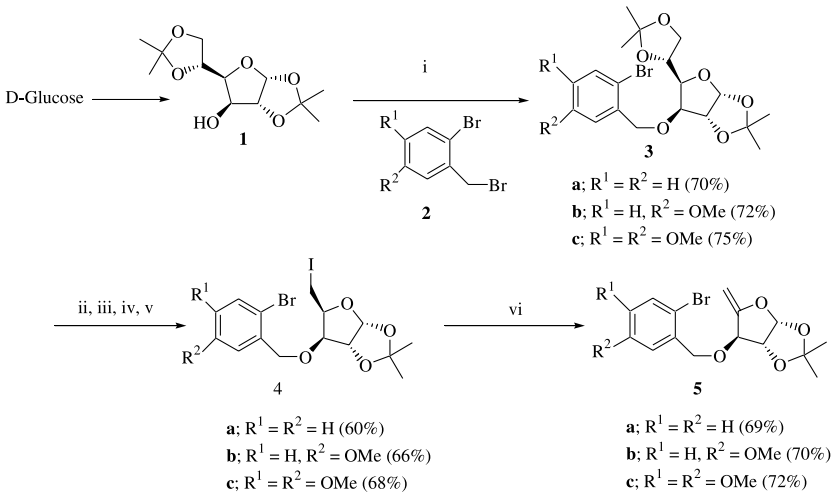
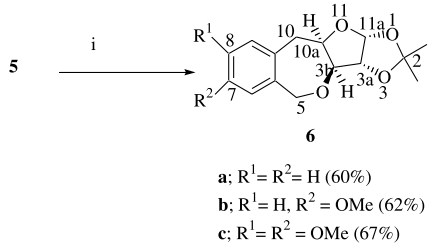


Scheme 1. Construction of *exo*-methylene sugar derivatives **5a–c**. Reagents and conditions: (i) 50% aq NaOH, TBAB, CH_2Cl_2, rt, 12 h; (ii) 70% AcOH (v/v), rt, 12 h; (iii) aq $NaIO_4$, MeOH, rt, 2.5 h; (iv) $NaBH_4$, dry EtOH, rt, 3 h; (v) PPh_3, imidazole, iodine, dry benzene, rt, 4 h; (vi) ^{t}BuOK, dry THF, 0 °C, 2.5 h, N_2.



Scheme 2. Synthesis of *cis*-fused furo 2-benzoxepines. Reagents and conditions: (i) TBTH (1.8 equiv), AIBN (cat), dry benzene, reflux (300 W lamp), 6 h, N_2.

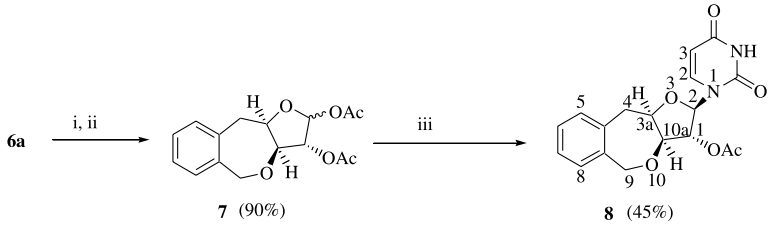
product after separation of tin compounds[16] followed by chromatography. The assigned structures of the products **6a–c** were based upon spectroscopic data. For example the stereochemistry of H-3b, the signal for which appeared at δ 4.10 (d, $J_{3b,10a}=2.4$ Hz) is similar based upon the comparison of the reported J values for comparable products prepared by us.[11a] Assignment of the *cis*-geometry of furo oxepine ring is further supported by ^{1}H–^{1}H COSY results and decoupling studies. The structures of the products showed that the cyclization followed the 7-*endo-trig* pathway.[17] This is in agreement with predictions by MO calculation and experimental corroboration by Beckwith.[18]

As an application of our methodology, a nucleobase could be successfully installed on **6a** by cleavage of the acetonide group, acetylation to form an anomeric mixture of the diacetates **7**, and reaction with 2,4-bis(trimethylsilyloxy)uracil in presence of TMS–OTf in CH_3CN at rt. The presence of two doublets at δ 5.26 and 6.73 and a broad singlet at 8.7 (olefin and NH protons of uracil) in the ^{1}H NMR of **8** confirmed the presence of the nucleobase in the product. Anchimeric assistance by the neighbouring acetoxy group directs the incoming nucleobase to the β-face,[19] forming the nucleoside derivative **8** (Scheme 3).

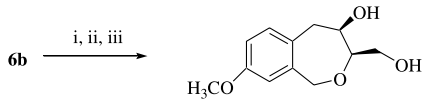
The feasibility of synthesizing chiral benzoxepines from the annulated sugar derivatives thus obtained could be realized using **6b**. Thus, **6b** was converted to the functionalized benzoxepine **9** through a sequence of reactions involving removal of the 1,2-*O*-isopropylidene group with 4% H_2SO_4 in CH_3CN/H_2O (3:1), $NaIO_4$ cleavage of the diol, and $NaBH_4$ reduction (Scheme 4). The formation of **9** was deduced from the appearance of three methylene carbon signals at δ 40.8, 64.2 and 74.9 in its ^{13}C NMR spectrum.

3. Conclusion

In summary, it has been demonstrated that the aryl radical cyclization reaction can be applied to D-glucose derived substrates to synthesize tricyclic nucleoside analogues and chiral benzannulated oxepine derivatives. This simple protocol is capable of being extended to many other carbohydrate derived precursors leading to a unity of structural types.



Scheme 3. Conversion of **6a** to modified nucleoside. Reagents and conditions: (i) H_2SO_4 (4%), acetonitrile/H_2O (3:1), rt, 24 h; (ii) Ac_2O, pyridine, rt, 12 h, 90%; (iii) 2,4-bis-(trimethyl silyloxy)pyrimidine, TMS–OTf, dry acetonitrile, rt, 5 h, N_2, 45%.



9 (70%)

Scheme 4. Conversion of **6b** to benzoxepine **9**. Reagents and conditions: (i) H_2SO_4 (4%), acetonitrile/H_2O (3:1), rt, 24 h; (ii) aq $NaIO_4$, MeOH, rt, 12 h; (iii) $NaBH_4$, dry MeOH, rt, 3 h, 70%.

4. Experimental

4.1. General

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in a Bruker AM 300L spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were obtained using either JEOL AX-500 or Micromass Q-Tofmicro™ spectrometer. IR spectra were obtained from JASCO FT/IR model 410. Elemental analyses were carried out with a C, H, N analyzer. Specific rotations were measured at 589 nm on a JASCO P-1020 polarimeter. TLC was performed on pre-coated plates (0.25 mm, silica gel 60 F_{254}). Column chromatography and flash chromatography were carried out using commercial-grade silica gel (60–120 mesh or 230–400 mesh). PS, EA stand for petroleum spirit (60–80 °C) and ethyl acetate.

4.2. General procedure for the synthesis of compounds 3a–c

To a magnetically stirred solution of 1,2:5,6-di-*O*-isopropylidene glucofuranoside (260 mg, 1 mmol) and the appropriate 2-bromobenzyl bromide **2a–c** (1.2 mmol) in CH_2Cl_2 (20 mL) was added Bu_4NBr (50 mg) followed by aq NaOH (50%, 20 mL) at 0 °C. The reaction mixture was stirred at rt for 12 h and extracted with CH_2Cl_2 (4×25 mL). The combined organic layer was washed with H_2O (3× 25 mL), dried (Na_2SO_4) and evaporated to afford a syrup, which on column chromatography over silica gel yielded the corresponding bromobenzyl derivatives.

4.2.1. (3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (3a). Thick oil; yield 70% (eluent PS/EA 13:1); [Found: C, 53.00; H, 5.75. $C_{19}H_{25}BrO_6$ requires C, 53.16; H, 5.87]; $[\alpha]_D^{25}$ −21.6 (*c* 0.25, $CHCl_3$); ν_{max} (liquid flim) 2985, 1450, 1376, 1215, 1078, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.00 (dd, 1H, J= 5.8, 8.4 Hz, H-5), 4.07–4.18 (m, 3H), 4.39 (dd, 1H, J=13.6, 6.0 Hz, H-6), 4.65–4.69 (d-like, 2H, H-6a signal overlapped by H^a of $ArCH_2$), 4.76 (d, 1H, J=12.8 Hz, H^b of $ArCH_2$), 5.92 (d, 1H, J=3.6 Hz, H-3a), 7.15–7.54 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7 (CH_3), 26.6 (CH_3), 27.1 (CH_3), 27.2 (CH_3), 67.8 (CH_2), 70.0 (CH_2), 72.8 (CH), 81.7 (CH), 82.6 (CH), 82.9 (CH), 105.7 (CH), 109.4 (C), 112.2 (C), 123.0 (C), 127.7 (C), 129.5 (CH), 129.6 (CH), 132.9 (CH), 137.4 (C); ESIMS, *m*/*z*: 451, 453 (M^+ + Na for Br^{79}, Br^{81}).

4.2.2. (3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-5-methoxy-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (3b). Thick oil; yield 72% (eluent PS/EA 10:1); [Found: C, 52.17; H, 5.88. $C_{20}H_{27}BrO_7$ requires C, 52.30; H, 5.92]; $[\alpha]_D^{25}$ −24.5 (*c* 0.22, $CHCl_3$); ν_{max} (liquid film) 2986, 1577, 1473, 1375, 1215, 1079, 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.00 (dd, 1H, J=8.4, 5.8 Hz, H-5), 4.08–4.18 (m, 3H), 4.41 (dd, 1H, J=12.1, 5.9 Hz, H-6), 4.61–4.66 (d-like, 2H, H-6a signal overlapped by H^a of $ArCH_2$), 4.72 (d, 1H, J=13.1 Hz, H^b of $ArCH_2$), 5.92 (d, 1H, J=3.6 Hz, H-3a), 6.71 (dd, 1H, J=8.6, 2.9 Hz, ArH), 7.07 (d, 1H, J=2.8 Hz, ArH), 7.41 (d, 1H, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.3 (CH_3), 26.2 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 55.4 (OCH_3), 67.3 (CH_2), 71.4 (CH_2), 72.4 (CH), 81.2 (CH), 82.1 (CH), 82.4 (CH), 105.2 (CH), 109.0 (C), 111.8 (C), 112.5 (C), 114.4 (CH), 114.9 (CH), 133.0 (CH), 137.9 (C), 159.1 (C); ESIMS, *m*/*z*: 481, 483 (M^+ + Na for Br^{79}, Br^{81}).

4.2.3. (3a*R*,5*R*,6*S*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-5-(2,2-dimethyl-[1,3]dioxolan-4-yl)-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (3c). Thick oil; yield 75% (eluent PS/EA 9:1); [Found: C, 51.40; H, 5.85. $C_{21}H_{29}BrO_8$ requires C, 51.54; H, 5.97]; $[\alpha]_D^{25}$ −30.5 (*c* 0.65, $CHCl_3$); ν_{max} (liquid film) 2946, 1509, 1269, 1210, 1163, 1026 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.32 (s, 3H, CH_3), 1.34 (s, 3H, CH_3), 1.42 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.03–4.18 (m, 4H), 4.39 (dd, 1H, J=13.6, 5.9 Hz, H-6), 4.60 (d, 1H, J=12.1 Hz, H^a of $ArCH_2$), 4.65 (d, 1H, J=3.7 Hz, H-6a), 4.71 (d, 1H, J=12.1 Hz, H^b of $ArCH_2$), 5.90 (d, 1H, J= 3.7 Hz, H-3a), 6.98 (s, 1H, ArH), 7.01 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.8 (CH_3), 26.6 (CH_3), 27.2 (2×CH_3), 56.5 (OCH_3), 56.6 (OCH_3), 67.7 (CH_2), 71.9 (CH_2), 73.0 (CH), 81.6 (CH), 82.3 (CH), 82.9 (CH), 105.6 (CH), 109.4 (C), 112.2 (C), 112.9 (CH), 113.4 (C), 115.9 (CH), 129.4 (C), 148.9 (C), 149.6 (C); ESIMS, *m*/*z*: 511, 513 (M^+ + Na for Br^{79}, Br^{81}).

4.3. General procedure for the synthesis of compounds 4a–c

The appropriate bromobenzyl derivative **3a–c** (2 mmol) was stirred overnight with 70% aq HOAc (v/v, 50 mL) at rt (monitored by TLC till disappearance of starting material). Removal of HOAc on a rotary evaporator under reduced pressure (temperature 40 °C) using dry toluene (4×25 mL) afforded the intermediate diol as a viscous syrup. A solution of the intermediate diol in the minimum volume of methanol was cooled to 0 °C and treated with aq $NaIO_4$ (0.51 g, 2.4 mmol, dissolved in 20 mL of water) dropwise with stirring (45 min). The reaction mixture was evaporated under reduced pressure and the residual syrup was extracted with $CHCl_3$ (4×25 mL). The combined organic layer was washed with water (3×25 mL), dried (Na_2SO_4) and evaporated to furnish the crude aldehyde. Without further purification, this was dissolved in absolute ethanol (30 mL) at 0 °C and treated with $NaBH_4$ (0.11 g, 3 mmol) in small portions over a period of 1 h and the stirring was continued for another 1 h at rt to complete the reaction. The solvent was evaporated under reduced pressure and the residue was extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were washed with water and dried (Na_2SO_4). Evaporation of solvent afforded the alcohol as crude oil. A solution of this crude alcohol, imidazole (0.54 g, 8 mmol)

and Ph_3P (2.09 g, 8 mmol) in dry benzene (50 mL) was stirred and cooled to 0 °C, while I_2 (1.52 g, 6 mmol) was added in small portions over a period of 1 h. After completion of addition, the reaction mixture was stirred at rt for 3 h. The solid mass was extracted with diethyl ether (6×25 mL). The combined organic layer was washed with saturated aq $Na_2S_2O_3$ (3×50 mL), water and dried (Na_2SO_4) and concentrated under reduced pressure to afford an oily material. The oil on column chromatography over silica gel furnished the iodo derivatives **4a**–**c**.

4.3.1. (3a*R*,5*S*,6*R*,6a*R*)-6-(2-Bromo-benzyloxy)-5-iodomethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (4a). Yellow liquid; yield 60% (eluent PS/EA 24:1); [Found: C, 38.29; H, 3.80. $C_{15}H_{18}BrIO_4$ requires C, 38.40; H, 3.87]; $[\alpha]_D^{25}$ −52.6 (*c* 2.12, $CHCl_3$); ν_{max} (liquid film) 2984, 2930, 1569, 1445, 1377, 1216, 1163, 1079, 1023 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.29–3.40 (m, 2H, CH_2I), 4.16 (d, 1H, J=3.0 Hz, H-6), 4.47–4.53, (m, 1H, H-5), 4.61 (d, 1H, J=12.1 Hz, H^a of $ArCH_2$), 4.71 (d, 1H, J=3.6 Hz, H-6a), 4.80 (d, 1H, J=12.1 Hz, H^b of $ArCH_2$), 5.98 (d, 1H, J=3.7 Hz, H-3a), 7.18 (td, 1H, J=7.8, 1.6 Hz, ArH), 7.32 (td, 1H, J=7.5, 1.1 Hz, ArH), 7.46 (dd, 1H, J=7.6, 1.3 Hz, ArH), 7.55 (dd, 1H, J=8.1, 0.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (CH_3), 26.8 (CH_3), 71.3 (CH_2), 71.6 (CH_2), 80.9 (CH), 81.7 (2×CH), 105.6 (CH), 111.9 (C), 122.8 (C), 127.4 (CH), 129.3 (CH), 129.4 (CH), 132.5 (CH), 136.4 (C); ESIMS, *m/z*: 491, 493 (M^+ + Na for Br^{79}, Br^{81}).

4.3.2. (3a*R*,5*S*,6*R*,6a*R*)-6-(2-Bromo-5-methoxy-benzyloxy)-5-iodomethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (4b). Yellow liquid; yield 66% (eluent PS/EA 24:1); [Found: C, 38.29; H, 4.00. $C_{16}H_{20}BrIO_5$ requires C, 38.50; H, 4.04]; $[\alpha]_D^{25}$ −54.4 (*c* 1.20, $CHCl_3$); ν_{max} (liquid film) 2984, 2933, 1577, 1474, 1377, 1296, 1238, 1164, 1079, 1020 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.33 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.29–3.40 (m, 2H, CH_2I), 3.80, (br s, 3H, OCH_3), 4.16 (d, 1H, J=3.0 Hz, H-6), 4.47–4.52 (m, 1H, H-5), 4.56 (d, 1H, J=12.3 Hz, H^a of $ArCH_2$), 4.71 (d, 1H, J=3.7 Hz, H-6a), 4.76 (d, 1H, J=12.3 Hz, H^b of $ArCH_2$), 5.98 (d, 1H, J=3.7 Hz, H-3a), 6.73 (dd, 1H, J=8.7, 3.0 Hz, ArH), 7.03 (d, 1H, J=3.0 Hz, ArH), 7.42 (d, 1H, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.1 (CH_3), 26.7 (CH_3), 55.3 (OCH_3), 60.2 (CH_2), 71.5 (CH_2), 80.9 (CH), 81.6 (CH), 81.8 (CH), 105.6 (CH), 111.8 (C), 112.7 (C), 114.7 (CH), 115.0 (CH), 133.0 (CH), 137.4 (C), 158.9 (C); ESIMS, *m/z*: 521, 523 (M^+ + Na for Br^{79}, Br^{81}).

4.3.3. (3a*R*,5*S*,6*R*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-5-iodomethyl-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxole (4c). Yellow liquid; yield 68% (eluent PS/EA16:1); [Found: C, 38.38; H, 4.00. $C_{17}H_{22}BrIO_6$ requires C, 38.59; H, 4.19]; $[\alpha]_D^{25}$ −31.8 (*c* 2.30, $CHCl_3$); ν_{max} (liquid film) 2981, 2933, 1601, 1507, 1459, 1379, 1262, 1214, 1163, 1076, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.36 (s, 3H, CH_3), 1.52 (s, 3H, CH_3), 3.31–3.35 (m, 2H, CH_2I), 3.87, (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 4.13 (d, 1H, J=2.9 Hz, H-6), 4.49–4.52 (m, 1H, H-5), 4.53 (d, 1H, J=11.6 Hz, H^a of $ArCH_2$), 4.71 (d, 1H, J=3.6 Hz, H-6a), 4.77 (d, 1H, J=11.5 Hz, H^b of $ArCH_2$), 5.97 (d, 1H, J=3.6 Hz, H-3a), 6.99 (s, 1H, ArH), 7.02 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 26.2 (CH_3), 26.8 (CH_3), 56.1 (2×OCH_3), 60.2 (CH_2), 71.6 (CH_2), 80.9 (CH), 81.5 (CH), 81.7 (CH), 105.6 (CH), 111.9 (C), 112.7 (CH), 113.4 (C), 115.2 (CH), 128.3 (C), 148.4 (C), 149.2 (C); ESIMS, *m/z*: 551, 553 (M^+ + Na for Br^{79}, Br^{81}).

4.4. General procedure for the synthesis of compounds 5a–c

Each of the iodides **4a**–**c** (1 mmol) in dry THF (20 mL) was added dropwise under inert atmosphere to a stirred solution of $KOBu^t$ (0.17 g, 1.5 mmol) in dry THF (20 mL) cooled to 0 °C. After completion of addition, the reaction mixture was stirred at 0 °C for 1.5 h. The reaction was quenched with saturated aq NH_4Cl (30 mL) and the aq layer was extracted with ethyl acetate (6×25 mL), the combined organic layer was washed with water, dried (Na_2SO_4) and evaporated under reduced pressure to provide a liquid. The liquid was purified by flash chromatography on silica gel using PS:EA as eluent to afford *exo*-methylene sugar derivatives **5a**–**c**.

4.4.1. (3a*R*,6*R*,6a*R*)-6-(2-Bromo-benzyloxy)-2,2-dimethyl-5-methylene-tetrahydro-furo[2,3-*d*][1,3]dioxole (5a). Colorless liquid; yield 69% (eluent PS/EA 49:1); [Found: C, 52.60; H, 5.00. $C_{15}H_{17}BrO_4$ requires C, 52.80; H, 5.02]; $[\alpha]_D^{25}$ −19.0 (*c* 2.62, $CHCl_3$); ν_{max} (liquid film) 2989, 2937, 1662, 1569, 1440, 1378, 1224, 1109, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 4.32 (s-like, 2H, overlapped by H-6 signal, H^a of $=CH_2$), 4.58 (d, 1H, J=12.3 Hz, H^a of $ArCH_2$), 4.63 (d, 1H, J=3.2 Hz, H-6a), 4.67 (d, 1H, J=1.4 Hz, H^b $=CH_2$), 4.71 (d, 1H, J=12.3 Hz, H^b of $ArCH_2$), 6.10 (d, 1H, J=3.2 Hz, H-3a), 7.16 (t, 1H, J=7.7 Hz, ArH), 7.30 (t, 1H, J=6.7 Hz, ArH), 7.42 (d, 1H, J=7.2 Hz, ArH), 7.54 (d, 1H, J=7.9 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 27.1 (CH_3), 27.9 (CH_3), 69.9 (CH_2), 81.2 (CH), 83.0 (CH), 88.9 ($=CH_2$), 106.7 (CH), 113.7 (C), 122.9 (C), 127.3 (CH), 129.2 (CH), 129.3 (CH), 132.6 (CH), 136.6 (C), 158.4 (C); ESIMS, *m/z*: 363, 365 (M^+ + Na for Br^{79}, Br^{81}).

4.4.2. (3a*R*,6*R*,6a*R*)-6-(2-Bromo-5-methoxy-benzyloxy)-2,2-dimethyl-5-methylene-tetrahydro-furo[2,3-*d*][1,3]dioxole (5b). Colorless liquid; yield 70% (eluent PS/EA 49:1); [Found: C, 51.56; H, 5.00. $C_{16}H_{19}BrO_5$ requires C, 51.77; H, 5.16]; $[\alpha]_D^{25}$ −32.0 (*c* 1.00, $CHCl_3$); ν_{max} (liquid film) 2989, 2938, 1665, 1590, 1576, 1472, 1378, 1235, 1110, 1004 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.32 (s-like, 2H, overlapped by H-6 signal, H^a of $=CH_2$), 4.54 (d, 1H, J=12.7 Hz, H^a of $ArCH_2$), 4.63–4.68 (m, 3H, H^b of $=CH_2$ overlapped by H^b of $ArCH_2$ and H-6a signal), 6.10 (d, 1H, J=3.2 Hz, H-3a), 6.71 (dd, 1H, J=8.7, 3.0 Hz, ArH), 6.98 (d, 1H, J=3.0 Hz, ArH), 7.41 (d, 1H, J=8.7 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 27.6 (CH_3), 28.3 (CH_3), 55.8 (OCH_3), 70.3 (CH_2), 81.7 (CH), 83.5 (CH), 89.4 ($=CH_2$), 107.2 (CH), 113.4 (C), 114.2 (C), 115.2 (CH), 115.4 (CH), 133.6 (CH), 138.0 (C), 158.9 (C), 159.5 (C); ESIMS, *m/z*: 393, 395 (M^+ + Na for Br^{79}, Br^{81}).

4.4.3. (3a*R*,6*R*,6a*R*)-6-(2-Bromo-4,5-dimethoxy-benzyloxy)-2,2-dimethyl-5-methylene-tetrahydro-furo[2,3-*d*][1,3]dioxole (5c). Colorless liquid; yield 72% (eluent PS/EA 32:1); [Found: C, 50.67; H, 5.00. $C_{17}H_{21}BrO_6$ requires

C, 50.89; H, 5.28]; $[\alpha]_D^{25}$ −11.1 (*c* 2.67, $CHCl_3$); ν_{max} (liquid film) 2986, 2938, 1660, 1600, 1507, 1461, 1442, 1380, 1263, 1213, 1162, 1087 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.39 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.87 (br s, 6H, 2×OCH_3), 4.31 (s, 1H, H-6), 4.32 (s, 1H, H^a of $=CH_2$), 4.52 (d, 1H, J=11.8 Hz, H^a of $ArCH_2$), 4.62–4.66 (d-like, 3H, H^b of $=CH_2$ overlapped by H^b of $ArCH_2$ and H-6a signal), 6.09 (d, 1H, J=3.0 Hz, H-3a), 6.92 (s, 1H, ArH), 7.02 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 27.1 (CH_3), 27.8 (CH_3), 55.9 (OCH_3), 56.0 (OCH_3), 69.9 (CH_2), 81.1 (CH), 83.0 (CH), 88.7 ($=CH_2$), 106.6 (CH), 112.4 (CH), 113.4 (C), 113.7 (C), 115.3 (CH), 128.4 (C), 148.3 (C), 149.1 (C), 158.5 (C); ESIMS, *m/z*: 423, 425 (M^++Na for Br^{79}, Br^{81}).

4.5. General procedure for radical cyclization of the *exo*-olefins

To a gently refluxing (300 W lamp) solution of appropriate *exo*-methylene derivative **5a–c** (1 mmol) and AIBN (10 mg) in dry benzene (120 mL) under N_2 atmosphere was added a solution of Bu_3SnH (1.8 mmol) and AIBN (10 mg) in dry benzene (150 mL) slowly over a period of 5 h. After complete addition the mixture was heated at reflux for 6 h. The solvent was removed under vacuum and the residue was dissolved in diethyl ether (100 mL) and stirred vigorously for 10 h with a saturated solution of aq KF (75 mL). The white precipitate was filtered off and washed with diethyl ether. After separation of ether layer, the aq layer was extracted with diethyl ether (6×25 mL), the combined organic layer was washed with water (3×30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give a thick oil, this was purified by flash chromatography on silica gel using PS:EA as eluent to furnish **6a–c**.

4.5.1. (3a*R*,3b*S*,10a*R*,11a*R*)-2,2-Dimethyl-3a,3b,5,10,10a,11a-hexahydro-1,3,4,11-tetraoxa-benzo[*f*]cyclopenta[*a*]azulene (6a). White crystalline solid; yield 60% (eluent PS/EA 13:1); mp 108 °C; [Found: C, 68.39; H, 6.80. $C_{15}H_{18}O_4$ requires C, 68.68; H, 6.92]; $[\alpha]_D^{25}$ −3.4 (*c* 1.28, $CHCl_3$); ν_{max} (KBr) 2934, 1636, 1456, 1378, 1252, 1211, 1164, 1131, 1084 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.28–3.30 (m, 2H, $ArCH_2$), 4.11 (d, 1H, $J_{3b,10a}$=2.4 Hz, H-3b), 4.42–4.45 (m, 1H, H-10a), 4.49 (d, 1H, $J_{3a,11a}$=3.8 Hz, H-3a), 4.76 (d, 1H, J=13.8 Hz, H^a of $ArCH_2O$), 4.85 (d, 1H, J=13.8 Hz, H^b of $ArCH_2O$), 5.84 (d, 1H, $J_{11a,3a}$=3.8 Hz, H-11a), 7.08–7.25 (m, 4H, aromatic protons); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.5 (CH_3), 27.1 (CH_3), 35.3 (CH_2), 72.7 (CH_2), 78.4 (CH), 84.2 (CH), 84.8 (CH), 105.4 (CH), 111.6 (C), 127.3 (CH), 127.9 (CH), 128.4 (CH), 130.9 (CH), 136.2 (C), 137.9 (C); ESIMS, *m/z*: 285 (M^++Na).

4.5.2. (3a*R*,3b*S*,10a*R*,11a*R*)-7-Methoxy-2,2-dimethyl-3a,3b,5,10,10a,11a-hexahydro-1,3,4,11-tetraoxa-benzo[*f*]cyclopenta[*a*]azulene (6b). White crystalline solid; yield 62% (eluent PS/EA 13:1); mp 104 °C; [Found: C, 65.53; H, 6.69. $C_{16}H_{20}O_5$ requires C, 65.74; H, 6.90]; $[\alpha]_D^{25}$ −2.2 (*c* 2.44, $CHCl_3$); ν_{max} (KBr) 2910, 1617, 1585, 1503, 1457, 1381, 1264, 1124, 1086 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H, CH_3), 1.47 (s, 3H, CH_3), 3.21–3.24 (m, 2H, $ArCH_2$), 3.77 (s, 3H, OCH_3), 4.10 (d, 1H, $J_{3b,10a}$=2.4 Hz, H-3b), 4.37–4.42 (m, 1H, H-10a), 4.49 (d, 1H, $J_{3a,11a}$=3.8 Hz, H-3a), 4.71 (d, 1H, J=13.8 Hz, H^a of $ArCH_2O$), 4.80 (d, 1H, J=13.8 Hz, H^b of $ArCH_2O$), 5.85 (d, 1H, $J_{11a,3a}$=3.8 Hz, H-11a), 6.66 (d, 1H, J=2.5 Hz, ArH), 6.74 (dd, 1H, J=8.2, 2.6 Hz, ArH), 7.12 (d, 1H, J=8.2 Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.6 (CH_3), 27.1 (CH_3), 34.4 (CH_2), 55.6 (OCH_3), 72.8 (CH_2), 78.5 (CH), 84.3 (CH), 84.8 (CH), 105.4 (CH), 111.6 (C), 112.9 (CH), 114.1 (CH), 128.0 (C), 131.9 (CH), 139.1 (C), 158.9 (C); ESIMS, *m/z*: 315 (M^++Na).

4.5.3. (3a*R*,3b*S*,10a*R*,11a*R*)-7,8-Dimethoxy-2,2-dimethyl-3a,3b,5,10,10a,11a-hexahydro-1,3,4,11-tetraoxa-benzo[*f*]cyclopenta[*a*]azulene (6c). White crystalline solid; yield 67% (eluent PS/EA 12:1); mp 100 °C; [Found: C, 63.22; H, 6.65. $C_{17}H_{22}O_6$ requires C, 63.34; H, 6.88]; $[\alpha]_D^{25}$ −1.7 (*c* 2.00, $CHCl_3$); ν_{max} (KBr) 2931, 1605, 1517, 1460, 1381, 1254, 1119, 1080 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.29 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 3.24 (d, 2H, J=3.5 Hz, $ArCH_2$), 3.84 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.11 (br s, 1H, H-3b), 4.40 (m, 1H, H-10a), 4.49 (d, 1H, $J_{3a,11a}$=3.4 Hz, H-3a), 4.69 (d, 1H, J=13.6 Hz, H^a of $ArCH_2O$), 4.76 (d, 1H, J=13.6 Hz, H^b of $ArCH_2O$), 5.86 (d, 1H, $J_{11a,3a}$=3.4 Hz, H-11a), 6.64 (s, 1H, ArH), 6.73 (s, 1H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.0 (CH_3), 26.5 (CH_3), 34.2 (CH_2), 55.7 (OCH_3), 55.8 (OCH_3), 71.8 (CH_2), 77.5 (CH), 83.8 (CH), 84.1 (CH), 104.8 (CH), 111.0 (C), 111.3 (CH), 113.8 (CH), 127.9 (C), 129.5 (C), 147.1 (C), 147.9 (C); ESIMS, *m/z*: 345 (M^++Na).

4.5.4. (1*R*,3a*R*,10a*S*) Acetic acid 2-acetoxy-1,2,3a,4,9,10a-hexahydro-3,10-dioxa-benzo[*f*]azulen-1-yl ester (7). Compound **6a** (2 mmol) was dissolved in acetonitrile/water 3:1 containing 4% H_2SO_4 and stirred at rt for 24 h. The acidic solution was neutralized with $NaHCO_3$ at 0 °C, filtered, and the filtrate was evaporated under reduced pressure. The residue was extracted with ethyl acetate (6×25 mL), and the combined organic layer was dried (Na_2SO_4) and concentrated. The colorless oil was dissolved in dry pyridine (5 mL), and treated with Ac_2O (0.5 mL), stirred at rt for 12 h. Pyridine was evaporated under reduced pressure and the residue was extracted with $CHCl_3$ (6×25 mL). The combined organic layer was washed with cold aq HCl (1%, 2×30 mL), water, dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The crude mass was purified by flash chromatography over silica gel to furnish **7** as a colorless liquid; yield 90% (eluent PS:EA 9:1); [Found: C, 62.50; H, 5.68. $C_{16}H_{18}O_6$ requires C, 62.74; H, 5.92]; $[\alpha]_D^{25}$ −1.0 (*c* 3.00, $CHCl_3$); ν_{max} (liquid film) 2933, 1752, 1496, 1445, 1374, 1219, 1084, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.05 (s, 3H, CH_3), 2.10 (s, 3H, CH_3), 2.82 (m, 1H, H^a of $ArCH_2$), 3.55 (m, 1H, H^b of $ArCH_2$), 4.36 (t, 1H, J=5.6 Hz, H-10a), 4.48–4.54 (m, 1H, H-3a), 4.83 (d, 1H, J=15.3 Hz, H^a of $ArCH_2O$), 5.21 (d, 1H, J=4.9 Hz, H-1), 5.22 (d, 1H, J=15.3 Hz, H^b of $ArCH_2O$), 6.41 (d, 1H, J=4.4 Hz, H-2), 7.14–7.26 (m, 4H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.9 (CH_3), 21.3 (CH_3), 35.8 (CH_2), 74.1 (CH_2), 77.9 (CH), 80.2 (CH), 82.0 (CH), 94.1 (CH), 126.0 (CH), 127.4 (CH), 127.5 (CH), 134.1 (CH), 137.2 (C), 137.5 (C), 169.8 (C), 170.2 (C); ESIMS, *m/z*: 329 (M^++Na).

4.5.5. (1*R*,2*R*,3a*R*,10a*S*) Acetic acid 2-(2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-1,2,3a,4,9,10a-hexahydro-3,

10-dioxa-benzo[*f*]azulen-1-yl-ester (8). 2,4-Bis-(trimethyl silyloxy)uracil was prepared by heating a mixture of uracil (336 mg, 3.0 mmol) and trimethylsilyl chloride (2 drops) dissolved in hexamethyl disilazane (5 mL) under N_2 for 10 h. The residue obtained after evaporation of solvent in vacuum was dissolved in dry CH_3CN (5 mL) and added to a solution of diacetate **7** (306 mg, 1.0 mmol) in dry CH_3CN (5 mL) and TMS–OTf (0.5 mL). The mixture was stirred at rt under N_2 for 5 h. TLC showed the completion of reaction. The solution was neutralized with $NaHCO_3$ and the solvent was evaporated under vacuum. The gummy material was extracted with $CHCl_3$ (3×25 mL) and organic layer washed with brine (3×30 mL), dried (Na_2SO_4) and concentrated under vacuum. The crude product was purified by flash chromatography over neutral alumina to afford **8** as a foam (160 mg); yield 45% (eluent $CHCl_3$/MeOH 49:1); [Found: C, 60.06; H, 4.80; N, 7.65. $C_{18}H_{18}N_2O_6$ requires C, 60.33; H, 5.06; N, 7.82]; $[\alpha]_D^{25}+25.0$ (*c* 2.00, $CHCl_3$); ν_{max} (KBr) 3355, 2932, 1744, 1664, 1498, 1449, 1374, 1230, 1041 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 2.12 (s, 3H), 3.31–3.51 (m, 2H), 4.17 (d, 1H, $J=2.0$ Hz), 4.36–4.44 (m, 1H), 4.76 (d, 1H, $J=13.5$ Hz), 4.81 (d, 1H, $J=13.6$ Hz), 5.03 (br s, 1H), 5.26 (d, 1H, $J=8.2$ Hz), 5.88 (d like, 1H), 6.73 (d, 1H, $J=$ 8.1 Hz), 7.15–7.28 (m, 4H), 8.7 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.7 (CH_3), 34.7 (CH_2), 71.8 (CH_2), 79.7 (CH), 80.1 (CH), 82.6 (CH), 88.8 (CH), 101.5 (CH), 127.5 (CH), 128.1 (CH), 128.6 (CH), 130.9 (CH), 135.1 (C), 137.5 (C), 140.2 (CH), 149.9 (C), 163.0 (C), 169.1 (C); ESIMS, *m/z*: 381 ($M^+ +Na$).

4.5.6. (3*R*,4*R*)-3-Hydroxymethyl-8-methoxy-1,3,4,5-tetrahydro-benzo[*c*]oxepin-4-ol (9). Compound **6b** (1 mmol) was dissolved in CH_3CN/H_2O 3:1 containing 4% H_2SO_4 and the mixture was stirred at rt for 24 h. The acidic solution was neutralized with solid $NaHCO_3$ at 0 °C, filtered and the filtrate was evaporated in vacuum. The residue was extracted with ethyl acetate (6×25 mL), and the combined organic layer was dried (Na_2SO_4) and concentrated under vacuum. The colorless residue was dissolved in a minimum volume of methanol and treated with aq $NaIO_4$ (256 mg, 1.2 mmol) at 0 °C with stirring for 45 min at rt. Usual workup followed by $NaBH_4$ reduction of the crude in dry methanol (20 mL) afforded the diol. This was purified by silica gel flash chromatography to afford **9** as a sticky liquid; yield 70% (eluent $CHCl_3$/MeOH 49:1); [Found: C, 64.00; H, 7.09. $C_{12}H_{16}O_4$ requires C, 64.27; H, 7.19]; $[\alpha]_D^{25}-2.06$ (*c* 2.90, $CHCl_3$); ν_{max} (KBr) 3397 (br), 2916, 1564, 1124, 1092, 1030 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.89 (s, 2H, 2×OH), 3.10 (dd, 1H, $J=14.8$, 6.4 Hz, H^a of $ArCH_2$), 3.21 (d, 1H, $J=14.7$ Hz, H^b of $ArCH_2$), 3.71 (dd, 2H, $J=9.6$, 2.4 Hz, CH_2OH), 3.79 (br s, 3H, OCH_3), 3.84 (d, 1H, $J=2.8$ Hz, H-3), 3.97 (d, 1H, $J=$ 6.4 Hz, H-4), 4.64 (d, 1H, $J=13.4$ Hz, H^a of $ArCH_2O$), 4.73 (d, 1H, $J=13.4$ Hz, H^b of $ArCH_2O$), 6.76–6.79 (m, 2H, ArH), 7.17 (d, 1H, $J=8.5$ Hz, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): 40.6 (CH_2), 55.2 (OCH_3), 64.0 (CH_2), 67.3 (CH), 74.8 (CH_2), 87.7 (CH), 112.7 (CH), 114.6 (CH), 127.1 (C), 133.1 (CH), 140.5 (C), 158.5 (C); ESIMS, *m/z*: 247 ($M^+ +Na$).

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Solid-phase synthesis of 6-hydroxy-2,4-diaminoquinazolines

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Abstract—A new method for the solid-phase synthesis of 6-hydroxy-2,4-diaminoquinazolines has been developed. The synthesis utilizes solid-phase bound 6-hydroxy-2,4-dichloroquinazoline as a key intermediate. Sequential substitution of the two chlorines furnishes the title compounds regioselectively with high purity. A library of 18×22 compounds demonstrates the general utility of this approach.

1. Introduction

The solid-phase synthesis of small-molecule libraries is now a widespread methodology to provide large numbers of candidates for drug discovery programs.[1] Quinazolines are interesting targets for new method development due to their importance in a broad range of therapeutic areas.[2] Recently, antitumor[3] and anti-HIV activities[4,5] of quinazolines have been disclosed as well. As a result of this attractive pharmacological profile, a number of solid-phase approaches for the synthesis of quinazoline libraries have been developed. A review of these methods was reported recently by Vögtle and Marzinzik.[2]

2,4-Diaminoquinazolines are of pharmacological interest as reversible inhibitors of the gastric (H+/K+)-ATPase,[6] as antagonists of the neurokinin-2 receptor[7] and as antimalarial agents.[8] One of the most important classes of quinazolines is 2,4-diamino-6,7-dimethoxyquinazolines as they exhibit versatile biological and pharmacological properties. Among these can be found several marketed drugs such as alfuzosin hydrochloride,[9] prazosin hydrochloride,[10] doxazosine mesylate,[11] and terazosine hydrochloride[12] (α_1-receptor blocking agents/prostate disorders), trimetrexate glucuronate[13] (dihydrofolate reductase inhibitor), bunazosin hydrochloride[14] and trimazosin hydrochloride[15] (antihypertension agents). The 2,4-diamino-6,7-dimethoxyquinazoline skeleton is present in CP-101816-1 as well, which can bind to CD4 receptors of helper T lymphocytes playing a role in virus cell fusion and infection with HI-Virus-1.[16] It has been reported that 6- and 7-hydroxy-metabolites of 2,4-diamino-6,7-dimethoxyquinazolines inhibited Cu^{2+} mediated oxidative modification of LDL and may be useful for the prevention of atherosclerosis in hypertensive individuals.[17]

There were three main reasons that made 2,4-diamino-6-hydroxy-7-methoxyquinazoline scaffold an attractive target for us: (i) the above mentioned wide pharmacological profile; (ii) the fact that only a few examples of 2,4-diamino-6-hydroxy-7-methoxyquinazolines can be found in the literature[18] (they are studied as metabolites of the above mentioned drugs);[19–23] (iii) in one of our ongoing projects exploring NR2B selective NMDA antagonists, related structures (benzofused nitrogen containing heterocycles substituted with a hydroxyl group on a benzene ring) proved to be effective.[24] Moreover, 6-hydroxyquinazoline is ideally suited as a scaffold for combinatorial library generation, because it has a rigid core that possesses two sites available for diversification, and a linker appendage at the hydroxyl group.[25–27] Herein, we report an efficient synthesis of 2,4-dichloro-6-hydroxy-7-methoxyquinazoline and a solid-phase synthesis of 6-hydroxy-7-methoxy-2,4-diaminoquinazolines.

2. Results and discussion

Our approach is based on the idea that 6-hydroxy-2,4-dichloroquinazoline derivatives can be coupled to benzyl alcohol type resins via the phenolic hydroxyl group and then the two chlorines can be replaced selectively by nucleophiles. In spite of the fact that the introduction of the diversity elements consists of only two steps, we decided to use the solid-phase approach, since our preliminary solution

Keywords: Quinazolines; Solid-phase synthesis; Library; Regioselectivity; Amination; Mitsunobu; NMDA; Demethylation.
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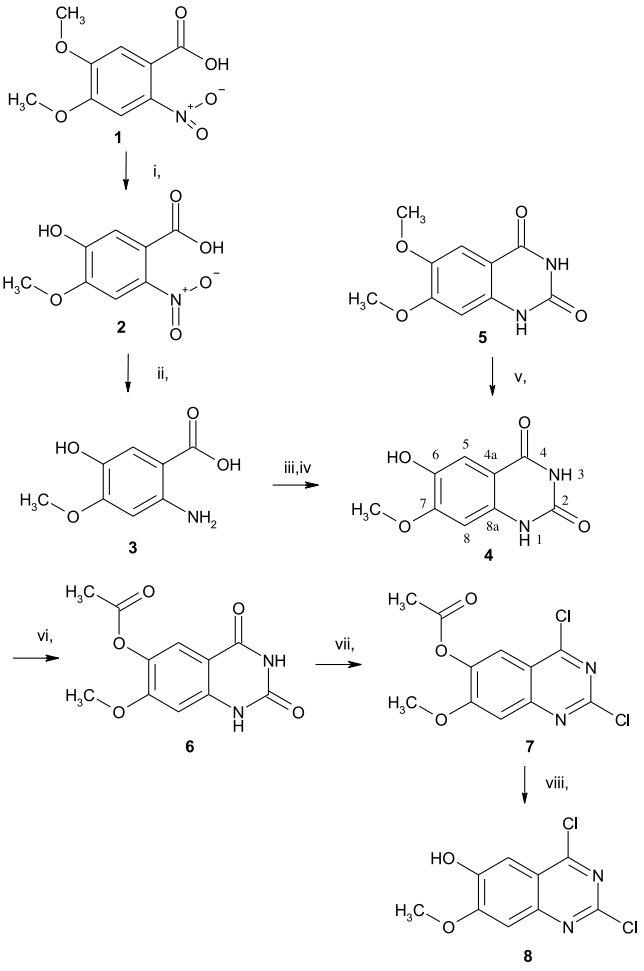


Scheme 1. Reagents and conditions: (i) KOH, H_2O, 100 °C, 24 h; (ii) Pd/C, H_2, rt; (iii) HOCN, H_2O, MeOH, 24 h, rt; (iv) KOH, H_2O, MeOH, 100 °C; (v) HBr, H_2O, 150 °C, 30 min; (vi) Ac_2O, Py, 115 °C, 30 h; (vii) $POCl_3$, $PhNEt_2$, reflux, 5 h; (viii) MeOMgCl, THF, 68 °C, 3 h.

phase experiments showed that protection of the phenolic hydroxyl group has a positive effect on the purities of the products. Our synthetic strategy is outlined in Schemes 1 and 2.

The central 6-hydroxy-7-methoxyquinazolin scaffold was prepared by solution phase chemistry in six steps (Scheme 1). Commercially available 4,5-dimethoxy-2-nitrobenzoic acid (**1**) was treated with sodium hydroxide to afford 5-hydroxy-4-methoxy-2-nitrobenzoic acid[28] (**2**). Reduction of the nitro group gave the 2-amino derivative[29] (**3**), which was converted to 6-hydroxy-7-methoxy-2,4-quinazolindione (**4**) in good yield. An alternative method for the synthesis of **4** was also investigated. Selective demethylation of 6,7-dimethoxy-2,4(1*H*, 3*H*)-quinazolindione[30] (**5**) by HBr solution under pressure furnished 6-hydroxy-7-methoxyquinazoline, however, the purity and yield of this route were considerably lower than of the route described earlier in this paragraph. Acetylation of **4** with acetic anhydride in pyridine furnished the 6-acetoxy derivative (**6**), which was treated with $POCl_3$ to yield 6-acetoxy-7-methoxy-2,4-dichloroquinazoline (**7**). Deprotection of the phenolic hydroxyl group gave 2,4-dichloro-6-hydroxy-7-methoxyquinazoline (**8**) suitable for coupling to the solid-phase.

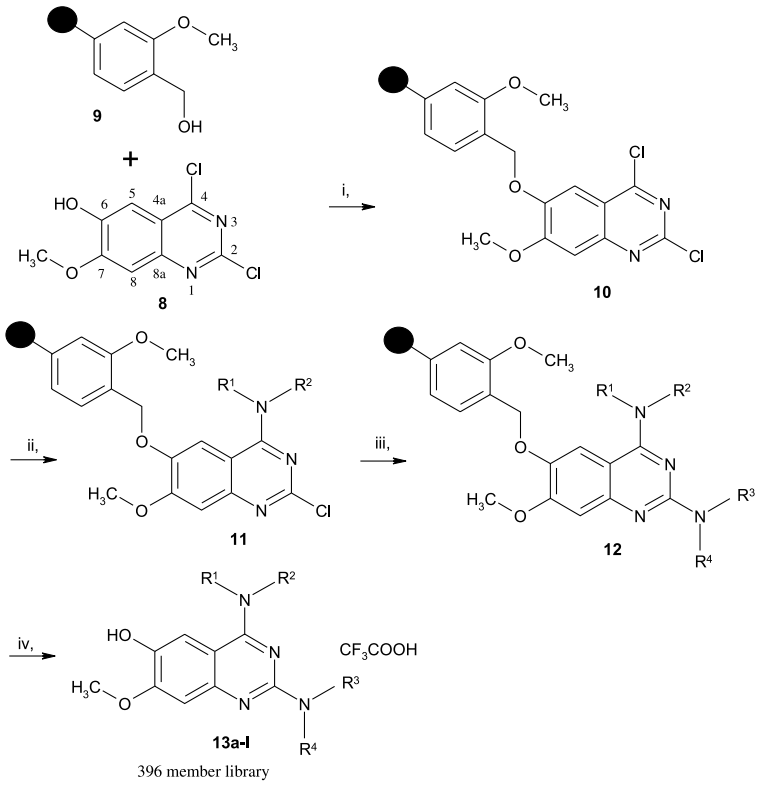
As a first step of the solid-phase synthesis, a resin having an *o*-methoxybenzyl alcohol (**9**) linker was reacted with **8** under Mitsunobu conditions. The best results were obtained in the presence of DIAD at 10–15 °C. However, along with the expected product (**10**), we observed the formation of **4**, which precipitated from the solvent. The very poor solubility of **4** made it difficult to wash it away from the resin. This led us to decrease the water content of the solvent to avoid the hydrolysis of **8**. The loading of **10** was quantified by measuring the chlorine content of the resin. Routine loadings ranged from 68 to 84% (as percentage of theoretical loading calculated on the basis of original benzyl alcohol substitution).

Selective reaction of the chlorine atom at the C4 position by amines afforded the solid-phase bound 4-aminoquinazoline derivative (**11**). This step was carried out at room temperature in THF. Primary amines and secondary amines not branched at the alpha position gave pure product (Table 1 entries 1–3, 5, 7–9, 11, and 12). However, secondary amines having a substituent at the alpha position did not afford pure products even under harsher conditions (longer reaction time, higher amine concentration, higher temperature) (Table 1 entry 4). The conversion of **11** to **12** was successfully achieved by reacting **11** with unbranched secondary amines in *n*-BuOH at 90 °C (Table 1 entries 1–3, 5, 7–9, 11, and 12). Attempts to displace the chlorine of **11** by primary amines and branched secondary amines resulted in mixtures of the expected products, monoaminated quinazolines and unknown side products (Table 1 entries 6 and 10). When the substitution of the second chlorine by *n*-hexylamine was attempted in DMAC at 100 °C, the 2-dimethylamino derivative (see Section 4, compound **14**) was isolated from the product. The 2,4-diamino-6-hydroxy-quinazoline derivatives (**13**) were released from resin **12** by treatment with 10% TFA in moderate to excellent overall yields.

The solid-phase method was translated to an 18×22 array using commercially available cyclic six-membered secondary amines. The synthesis was carried out by a Tecan combitec synthesizer on a 0.1 mmol scale (≈100 mg resin). The library was characterized by LC-MS. The purities of the individual compounds were determined by LC integration without calibration at 254 nm. The average purity of the library was 86% with 84% of the products having purities above 80%. The average molecular weight and clogP of the library were 504 and 5.3, respectively.

3. Conclusion

A simple and efficient four step strategy has been described for the solid-phase syntheses of 2,4-diamino-6-hydroxy-7-methoxyquinazolines. The feasibility of this method has been demonstrated by the automated synthesis of a 396 member library having 86% average purity. The significance of the library is increased by the widespread biological effects of related structures, and also by the fact



Scheme 2. Reagents and conditions: (i) DIAD, PPh_3, THF, 10–15 °C, 24 h; (ii) 15 equiv HNR^1R^2, THF, rt, 24 h; (iii) 20 equiv HNR^3R^4, *n*-BuOH, 100 °C, 48 h; (iv) TFA/DCM = 1:9, 2 h, rt.

Table 1. The purities and yields of 2,4-diamino-6-hydroxy-7-methoxyquinazolines

Entry	Compound	NR^1R^2	NR^3R^4	Yield (%)[a]	Purity (%)[b]
1	**13a**	*n*-Hexylamino	Piperidin-1-yl	82	93
2	**13b**	*sec*-Butylamino	Piperidin-1-yl	91	91
3	**13c**	bis(*n*-Butyl)amino	Piperidin-1-yl	87	89
4	**13d**	*N*-Isopropyl-ethylamino	Piperidin-1-yl	—	17
5	**13e**	Pyrrolidin-1-yl	Piperidin-1-yl	84	91
6	**13f**	Piperidin-1-yl	*n*-Hexylamino	—	12
7	**13g**	Piperidin-1-yl	bis(*n*-Butyl)amino	—	87
8	**13h**	Piperidin-1-yl	Piperidin-1-yl	84	96
9	**13i**	Piperidin-1-yl	Morpholin-4-yl	78	94
10	**13j**	Piperidin-1-yl	2-Methylpiperidin-1-yl	—	48
11	**13k**	Piperidin-1-yl	4-Phenylpiperazin-1-yl	88	94
12	**13l**	Piperidin-1-yl	Pyrrolidin-1-yl	84	96

[a] The overall yield was determined by weight based on the loading of **10**.
[b] The purities and MWs of the crude products were determined by HPLC-MS at 254 nm.

that not a member of the library has been described in the literature before.

4. Experimental

4.1. General

Reagents were obtained from Sigma-Aldrich. The typical loading of 4-hydroxy-2-methoxybenzyl alcohol resin (cat. number: 54-073-0, 50–90 mesh, 1% cross-linked) was 0.3–0.6 mmol/g. Solvents were obtained from Merck and were used as received if not indicated otherwise. Small scale parallel solid-phase reactions were performed using an Advanced ChemTech PLS 4×6 system in 8 mL glass reaction vials (1.5 cm×5 cm) with Teflon-lined screw-caps. Cleavage and washing of the resins were performed in 8 mL Teflon vials (1.5 cm×5 cm) equipped with a filter at the bottom. The synthesis of an 18×22 library was carried out by a Tecan combitec synthesizer on a same scale.

Purity was determined by HPLC (Hewlett-Packard HP 1100) using an acetonitrile/water gradient (100% water to 95% acetonitrile v/v, with 0.1% TFA with a run time of 20 min) on a Discovery RP C_{16}-amide column (5 cm× 4.6 mm, 5 μm) operating at a flow rate of 1 mL/min; analysis was conducted at 254 nm wavelength, and retention times were recorded. Molecular parent ion identity was confirmed via mass spectrometry using electrospray ionization and a probe voltage of 4.0 kV. Capacity factors (k') were calculated according to $k'=(t_r-t_0)/t_r$, where t_r= retention time, t_0=dead time.

The structures of compounds having a purity at least 80% were confirmed by nuclear magnetic resonance (NMR) spectroscopy. NMR spectra were recorded either at 300 or 500 MHz for ^{1}H and 125 or 75 MHz for ^{13}C on a Varian INOVA spectrometer. The chemical shifts are reported in ppm relative to TMS in $CDCl_3$ or in DMSO-d_6 at 30 °C.

Melting points are uncorrected.

The following abbreviations are used: AcOH, acetic acid; Ac_2O, acetic anhydride; DCM, dichloromethane; DIAD, diisopropyl azodicarboxylate; DMAC, *N*,*N*-dimethylacetamide; Morp, morpholine; NMDA, *N*-methyl-D-aspartate; NR2B, a subunit of NMDA receptor; Pip, piperidine; Pip-C(2,6), carbon atoms of piperidine at the 2- and 6-positions; Pip-H(2,6), hydrogen atoms connected to Pip-C(2,6); Py, pyridine; Pyr, pyrrolidine; TFA, trifluoroacetic acid; THF, tetrahydrofuran.

4.1.1. 5-Hydroxy-4-methoxy-2-nitrobenzoic acid (2). 4,5-Dimethoxy-2-nitrobenzoic acid (100 g, 0.436 mol) was added to a sodium hydroxide solution (500 mL, 20%) and the resulting suspension was stirred for 48 h at 100 °C. The solution was acidified with HCl to pH 2 (20% solution). The solid was filtered off, washed with water, and dried to give **2** (81.7 g, 0.380 mol, 87.1%). Mp published[31] 181–182 °C. Mp found 182–183 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=3.90$ (s, 3H), 7.08 (s, 1H), 7.55 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=56.3$, 108.0, 114.8, 122.1, 139.8, 148.9, 150.8, 166.2. $M^+=215$ (EI).

4.1.2. 2-Amino-5-hydroxy-4-methoxybenzoic acid (3). Compound **2** (75 g, 0.348 mol) was reduced with hydrogen in MeOH (1000 mL) using Pd on carbon (loading: 10 wt %, 2.0 g). The solution was filtered and the solvent was evaporated to give crude **2** (62 g, 97%). Mp published[31] 214–215 °C. Mp found 194–195 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=3.73$ (s, 3H), 6.29 (s, 1H), 7.09 (s, 1H), 8.1–8.4 (br s, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=55.1$, 99.1, 101.4, 115.9, 136.3, 146.7, 153.7, 169.1. $M^+=183$ (EI).

4.1.3. 6-Hydroxy-7-methoxy-2,4(1*H*, 3*H*)-quinazolindione (4). Method a: compound **3** (60 g, 0.289 mol) was suspended in a mixture of MeOH (600 mL) and acetic acid (27 mL). A solution of KOCN (35.0 g, 0.43 mol) in water (200 mL) was added dropwise at room temperature over 5 h. The resulted slurry was added dropwise to a hot solution of sodium hydroxide (25%, 1000 mL, 100 °C) at a rate that the temperature of the sodium hydroxide solution did not fall below 95 °C (solvent is distilled off at the rate of addition). Water (300 mL) was added, the solution was acidified with formic acid (pH=4) and was stirred at room temperature for 2 h. The solid was filtered off, washed with water, and dried to give **4** (58.1 g, 96%). Mp >300 °C. Method b: a mixture of **5** (5.0 g, 22.5 mmol) and HBr in AcOH (60 mL, 33%) was heated in an autoclave at 220 °C for 30 min. The solvent was evaporated and the residue was purified by column chromatography ($CHCl_3$/MeOH=4:1) to give **4** (0.80 g, 17.1%). Mp>300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=$ 3.83 (s, 3H, MeO), 6.70 [s, 1H, H(8)], 7.23 [s, 1H, H(5)], 8.59 (s, 1H, OH). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=55.7$ MeO, 97.9 C(8), 106.7 C(4a), 110.7 C(5), 135.1 C(8a), 143.2 C(6), 150.5 C(2), 154.4 C(7), 162.5 C(4). $M^+=208$ (EI). Anal. Calcd for: $C_9H_8N_2O_4$; C, 51.93; H, 3.87; N, 13.46%. Found: C, 51.86; H, 3.88; N, 13.42%.

4.1.4. 6-Acetoxy-7-methoxy-2,4(1*H*, 3*H*)-quinazolindione (6). Compound **4** (225 g, 1.08 mol) was dissolved in a mixture of pyridine (4800 mL) and acetic anhydride (215 mL, 2.28 mol). The solution was refluxed for 30 h then it was concentrated to 600 mL. The resulted slurry was allowed to cool to room temperature. The solid was filtered off, washed with water and acetone, and dried to give **6** (251 g, 92%). Mp 168–169 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=2.26$ (s, 3H), 3.84 (s, 3H), 6.83 (s, 1H), 7.53 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=20.3$, 56.2, 98.4, 106.7, 120.4, 135.0, 140.8, 150.5, 156.3, 162.0, 168.7. $M^+=250$ (EI). Anal. Calcd for: $C_{11}H_{10}N_2O_5$; C, 52.80; H, 4.03; N, 11.20%. Found: C, 52.65; H, 4.01; N, 11.17%.

4.1.5. 6-Acetoxy-2,4-dichloro-7-methoxyquinazoline (7). Compound **6** (56.2 g, 0.25 mol) was dissolved in a mixture of $POCl_3$ (120 mL) and *N*,*N*-diethylaniline (80 mL, 0.50 mol). The mixture was refluxed for 3 h, $POCl_3$ was distilled off, and the residue was poured onto ice. The slurry was stirred for 1 h at 0–5 °C. The solid was filtered off, washed with water, and dried to give **7** (45 g, 0.157 mol, 62.8%). Mp 149–150 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): $\delta=2.36$ (s, 3H), 4.03 (s, 3H), 7.63 (s, 1H), 8.04 (s, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz): $\delta=20.3$, 57.3, 107.7, 116.6, 118.5, 142.2, 152.4, 154.2, 158.8, 161.4, 168.3. $M^+=286$ (EI). Anal. Calcd for: $C_{11}H_8Cl_2N_2O_2$; C, 46.02; H, 2.81; Cl, 24.70; N, 9.76%. Found: C, 46.11; H, 2.82; Cl, 24.76; N, 9.73%.

4.1.6. 2,4-Dichloro-6-hydroxy-7-methoxyquinazoline (8). To a mixture of abs THF (1600 mL) and MeOH (120 mL) was added dropwise a solution of MeMgCl (320 mL, THF, 0.96 mol). Compound **8** (84 g, 0.294 mol) was added to this mixture and the solution was refluxed for 3 h. The solution was allowed to cool to room temperature then acetic acid (54.4 mL, 0.95 mol) was added dropwise. The solution was concentrated to 400 mL and ethyl acetate was added (2500 mL) to the residue. The solution was washed with water (1×2000 mL) and brine (1000 mL), then it was dried ($MgSO_4$), filtered and the solvent was evaporated to give **8** (64.4 g, 89%). Mp 169–170 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): $\delta=4.02$ (s, 3H), 7.39 (s, 1H), 7.42 (s, 1H), 10.85–10.95 (br s, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): $\delta=56.6$, 105.4, 106.4, 117.6, 149.2, 150.2, 151.1, 157.7, 158.4. $M^+=244$ (EI). Anal. Calcd for: $C_9H_6Cl_2N_2O_2$; C, 44.11; H, 2.47; Cl, 28.93; N, 11.43%. Found: C, 44.02; H, 2.46; Cl, 28.97, N, 11.47%.

4.1.7. Solid-phase bound 2,4-dichloro-6-hydroxy-7-methoxyquinazoline (10). Compound **8** (11.3 g, 46 mmol) and PPh_3 (6.0 g, 23 mmol) were dissolved in abs THF (230 mL, water content <0.01%), and then **9** (23 g 4-hydroxy-2-methoxybenzyl alcohol resin, 9.2 mmol polymer bound benzyl alcohol) was added. To this mixture was added dropwise at 15–20 °C a solution of DIAD (3.64 g, 18 mmol) in abs THF (30 mL) over 2 h, then it was shaken overnight. The resin was filtered off, washed with THF (3×250 mL), MeOH (3×250 mL), DCM (3×250 mL), THF (3×250 mL), MeOH (3×250 mL), DCM

(3×250 mL), and dried in vacuo to give **10.** Capacities of the resins ranged from 0.27 to 0.34 mmol/g based on Cl content ranging from 0.54 to 0.68 mmol/g.

4.1.8. Solid-phase bound 4-amino-2-chloro-6-hydroxy-7-methoxyquinazolines (11). To a suspension of **10** (100 mg, ≈0.03 mmol polymer bound quinazoline) and THF (1.5 mL) was added a primary or secondary amine (0.45 mmol). The mixture was shaken for 24 h then the resin was filtered off and washed with THF (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL).

4.1.9. Solid-phase bound 2,4-diamino-6-hydroxy-7-methoxyquinazolines (12). To a suspension of **11** (100 mg, ≈0.03 mmol polymer-bound quinazoline) and *n*-BuOH (1.5 mL) was added a secondary amine (0.6 mmol). The mixture was shaken for 48 h at 100 °C then the resin was filtered off and washed with THF (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL).

4.1.10. 2,4-Diamino-6-hydroxy-7-methoxyquinazolines (13). Compound **12** (100 mg, ≈0.03 mmol polymer-bound 2,4-diaminoquinazoline) was shaken in DCM–TFA (9/1) (2 mL) for 2 h, then the resin was filtered off. The filtrate was combined with washes of DCM (2×1 mL) and MeOH (2×1 mL), the solvent was evaporated then the residue was dried under vacuo overnight to give **13**. The products as trifluoroacetate salts were obtained as brownish or yellowish oils or semisolids.

4.1.11. 4-(*n*-Hexylamino)-6-hydroxy-7-methoxy-2-(piperidin-1-yl)quinazoline (13a). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=0.85 [t, 3H, J=7 Hz, CH_3(CH$_2$)$_3$CH$_2$CH$_2$-NH–], 1.20–1.40 [m, 6H, CH$_3$(*CH*$_2$)$_3$CH$_2$CH$_2$NH–], 1.50–1.70 [m, 8H, Pip-H(3,4,5), CH$_3$(CH$_2$)$_3$*CH*$_2$CH$_2$NH–], 3.45–3.55 [m, 2H, CH$_3$(CH$_2$)$_3$CH$_2$*CH*$_2$NH–], 3.80–3.90 [m, 4H, Pip-H(2,6)], 3.89 (s, 3H, MeO), 7.56 [br s, 1H, H(8)], 7.57 [s, 1H, H(5)], 8.90 [br s, 1H, CH$_3$(CH$_2$)$_3$CH$_2$CH$_2$*NH*–], 9.42 (br s, 1H, OH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ=13.8, 21.9, 23.7, 24.1, 26.1, 28.1, 30.9, 40.9, 45.6, 55.9, 99.8, 102.6, 107.6, 136.0, 144.0, 151.3, 154.1, 158.3. HPLC-MS: M$^+$=358 (EI); k'=7.81.

4.1.12. 4-(*sec*-Butylamino)-6-hydroxy-7-methoxy-2-(piperidin-1-yl)quinazoline (13b). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=0.89 [t, 3H, J=7.5 Hz, CH$_3$CH(NH–)CH$_2$*CH*$_3$], 1.25 [d, 3H, J=6.5 Hz, *CH*$_3$CH(NH–)CH$_2$CH$_3$], 1.50–1.75 [m, 8H, Pip-H(3,4,5), CH$_3$CH(NH–)*CH*$_2$CH$_3$], 3.80–3.87 [m, 4H, Pip-H(2,6)], 3.90 [s, 3H, MeO], 4.20–4.35 [m, 1H, CH$_3$*CH*(NH–)CH$_2$CH$_3$], 7.62, 7.70 [s, 2×1H, H(5), H(8)], 9.36 [s, 1H, OH], 12.3 [br s, 1H, NH$^+$]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ=10.7, 19.4, 23.7, 25.1, 28.3, 45.7, 48.7, 55.9, 99.9, 102.6, 108.0, 132.0, 143.9, 151.2, 154.1, 158.0. HPLC-MS: M$^+$=386 (EI); k'=6.22.

4.1.13. 4-[Bis(*n*-butyl)amino]-6-hydroxy-7-methoxy-2-(piperidin-1-yl)quinazoline (13c). ^{1}H NMR (DMSO-d_6, 300 MHz): δ=0.91 [t, 6H, J=7.2 Hz, (*CH*$_3$CH$_2$CH$_2$CH$_2$)$_2$-N–], 1.26–1.42 [m, 4H, (CH$_3$*CH*$_2$CH$_2$CH$_2$)$_2$N–], 1.46–1.78 [m, 10H, (CH$_3$CH$_2$*CH*$_2$CH$_2$)$_2$N–, Pip-H(3,4,5)], 3.56–3.78 [m, 8H, (CH$_3$CH$_2$CH$_2$*CH*$_2$)$_2$N–, Pip-H(2,6)], 3.87 [s, 3H, MeO], 7.18, 7.22 [s, 2×1H, H(5), H(8)], 8.5–11.0 [br s, 1H, NH$^+$], 11.67 [s, 1H, OH]. ^{13}C NMR (DMSO-d_6, 75 MHz): δ=13.7, 19.6, 23.6, 25.1, 29.0, 45.6, 51.2, 55.9, 99.5, 102.5, 109.7, 136.7, 143.4, 148.9, 154.1, 159.3. HPLC-MS: M$^+$=330 (EI); k'=8.84.

4.1.14. 6-Hydroxy-4-(*N*-isopropyl-etilamino)-7-methoxy-2-(piperidin-1-yl)quinazoline (13d). HPLC-MS: M$^+$=344 (EI); k'=9.1.

4.1.15. 2-Hydroxy-7-methoxy-2-(piperidin-1-yl)-4-(pyrrolidin-1-yl)quinazoline (13e). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.58–1.72 [br m, 6H, Pip-H(3,4,5)], 1.86–2.12 [br m, 4H, Pyr(2,3)], 3.73–3.79 [br m, 4H, Pip(2,6)], 3.90 [s, 3H, MeO], 3.92–4.10 [br m, 4H, Pyr(2,5)], 7.24, 7.60 [s, 2×1H, H(5,8)], 11.61 [s, 1H, OH]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ=23.6, 25.0, 45.4, 51.0, 55.8, 99.2, 103.3, 110.5, 135.9, 143.6, 149.2, 153.8, 157.1. MS: M$^+$=328 (EI).

4.1.16. 2-(*n*-Hexylamino)-6-hydroxy-7-methoxy-4-(piperidin-1-yl)quinazoline (13f). HPLC-MS: M$^+$=358 (EI); k'=7.68.

4.1.17. 6-[Bis(*n*-butyl)amino]-6-hydroxy-7-methoxy-4-(piperidin-1-yl)quinazoline (13g). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=0.91 [t, 6H, J=7 Hz, (*CH*$_3$(CH$_2$)$_3$)$_2$NH–], 1.20–1.40 [m, 4H, (CH$_3$*CH*$_2$(CH$_2$)$_2$)$_2$NH–], 1.45–1.80 [m, 10H, Pip-H(3,4,5), (CH$_3$CH$_2$*CH*$_2$CH$_2$)$_2$NH–], 3.2–3.7 [m, 8H, (CH$_3$CH$_2$CH$_2$*CH*$_2$)$_2$NH–], 3.86 [s, 3H, MeO], 7.08, 7.12 [s, 2×1H, H(5), H(8)], 9.40 [s, 1H, OH]. HPLC-MS: M$^+$=386 (EI); k'=8.15.

4.1.18. 6-Hydroxy-7-methoxy-2,4-bis(piperidin-1-yl)quinazoline (13h). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.59–1.77 [m, 12H, 2-Pip-H(3,4,5), 4-Pip-H(3,4,5)], 3.74–3.80 [m, 4H, 2-Pip-H(2,6)], 3.80–3.88 [m, 4H, 4-Pip-H(2,6)], 3.90 (s, 3H, MeO), 7.24 [br s, 1H, H(5)], 7.26 [br s, 1H, H(8)], 10.01 (br s, 1H, OH) 11.86 (br s, 1H, NH$^+$). ^{13}C NMR (DMSO-d_6, 125 MHz): δ=23.6, 23.7, 25.1, 25.6 [2-Pip-C(3,4,5), 4-Pip-C(3,4,5)], 45.6 [2-Pip-C(2,6)], 49.8 [4-Pip-C(2,6)] 55.9 (OMe), 99.5, C(8), 102.6 C(4a), 109.8 C(5) 137.2 C(8a), 143.8 C(6), 149.7 C(2), 154.5 C(7), 161.2 C(4); HPLC-MS: M$^+$=342 (EI).

4.1.19. 6-Hydroxy-7-methoxy-2-(morpholin-4-yl)-4-(piperidin-1-yl)quinazoline (13i). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.67–1.78 [m, 6H, Pip-H(3,4,5)], 3.70–3.75 [m, 4H, Morp-H(2,6)], 3.75–3.81 [m, 4H, Morp-H(3,5)], 3.82–3.89 [m, 4H, Pip-H(2,6)], 3.91 (s, 3H, MeO), 7.24 [s, 1H, H(8)] 7.26 [s, 1H, H(5)], 9.9–10.2 (br s, OH), 11.8–12.2 (br s, 1H, NH$^+$), ^{13}C NMR (DMSO-d_6, 125 MHz): δ=23.7 Pip-C(3,5), 25.6 Pip-C(4), 44.7 Morp-C(3,5), 49.9 Pip-C(2,6), 55.9 MeO, 65.4 Morp-C(2,6), 99.6 C(8), 102.8 C(4a), 109.7 C(5), 137.3 C(8a), 143.9 C(6), 150.4 C(2), 154.5 C(7), 161.1 C(4); HPLC-MS: M$^+$=344 (EI).

4.1.20. 6-Hydroxy-7-methoxy-2-(2-methylpiperidin-1-yl)-4-(piperidin-1-yl)quinazoline (13j). HPLC-MS: M$^+$=356 (EI); k'=7.33.

4.1.21. 6-Hydroxy-7-methoxy-2-(4-Phenylpiperazin-1-yl)-4-(piperidin-1-yl)quinazoline(13k). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.69–1.78 [s, 6H, Pip-H(3,4,5)], 3.30–3.36 [m, 4H, Piperazine], 3.85–3.92 [br m, 4H, Pip-H(2,6)], 3.93 [s, 3H, MeO], 3.93–4.0 [br m, 4H, Piperazine], 6.85 [m, 1H, Phenyl-H(4)], 7.03 [s, 2H, J= 8 Hz, Phenyl-H(2,6)], 7.22–7.32 [m, 4H, Phenyl-H(2,6), H(5,8)]. ^{13}C NMR (DMSO-d_6, 125 MHz): δ=23.7, 25.6, 44.3, 47.7, 49.8, 55.9, 99.4, 102.7, 109.9, 115.8, 119.5, 129.0, 136.8, 144.0, 149.9, 150.3, 154.6, 161.0. HPLC-MS: M^+=419 (EI); k'=6.29.

4.1.22. 6-Hydroxy-7-methoxy-4-(piperidin-1-yl)-2-(pyrrolidin-1-yl)quinazoline (13l). ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.66–1.76 [m, 6H, Pip-H(3,4,5)], 1.90–2.10 [br m, 4H, Pyr-H(3,4)], 3.50–3.66 [br m, 4H, Pyr-H(2,5)], 3.81–3.89 [m, 4H, Pip-H(2,6)], 3.90 (s, 3H, MeO), 7.21 [s, 1H, H(8)], 7.23 [s, 1H, H(5)] 11.53 (s, 1H, OH), 12.2–13.2 (br s, 1H, NH^+). ^{13}C NMR (DMSO-d_6, 500 MHz): δ=23.9, 25.7 Pip-C(3,4,5), 24.4 Pir-C(3,4), 46.8 Pir-C(2,5), 50.0 [Pip-C(2,6)], 56.0 (MeO), 99.3 C(8), 102.6 C(4a), 110.2 C(5), 136.9 C(8a), 143.6 C(6), 148.7 C(2), 154.6 C(7), 161.4 C(4); HPLC-MS: M^+=328 (EI).

4.1.23. 2-Dimethylamino-6-hydroxy-7-methoxy-4-(piperidin-1-yl)quinazoline (14). To a suspension of **11** (100 mg, ≈0.03 mmol polymer-bound quinazoline, NR^1R^2=piperidin-1-yl) and DMAC (1.5 mL) was added a secondary amine (0.6 mmol). The mixture was shaken for 48 h at 100 °C then the resin was filtered off and washed with THF (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL), MeOH (3×3 mL), DCM (3×3 mL). The resin was shaken in DCM–TFA (9/1) (2 mL) for 2 h, then it was filtered off. The filtrate was combined with washes of DCM (2×1 mL) and MeOH (2×1 mL), the solvent was evaporated then the residue was dried under vacuo overnight. The crude product was purified by column chromatography ($CHCl_3$/*n*-hexane= 98:2) to give **14** and **13**, respectively. ^{1}H NMR (DMSO-d_6, 500 MHz): δ=1.67–1.80 [m, 6H, Pip-H(3,4,5)], 3.22 (s, 6H, NMe_2), 3.80–3.89 [m, 4H, Pip-H(2,6)], 3.90 (s, 3H, MeO), 7.24 [s, 1H, H(5)] 7.31 [s, 1H, H(8)], 10.01 (br s, 1H, OH), 11.77 (br s, 1H, NH). ^{13}C NMR (DMSO-d_6, 125 MHz): δ= 23.7, 25.6, [Pip-C(3,4,5)], 37.4 (NMe_2), 49.8 [Pip-C(2,6)], 55.9 (MeO), 99.5 C(8), 102.4 C(4a), 109.9 C(5), 137.0 C(8a), 143.7 C(6), 150.7 C(2), 154.5 C(7), 161.0 C(4); HPLC-MS: M^+=302 (EI).

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Towards highly powerful neutral organic superacids—a DFT study of some polycyano derivatives of planar hydrocarbons

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Abstract—Density functional theory (DFT) calculations at B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level have been carried out on indene, cyclopentaphenanthrene and 1*H*-phenalene and their heptacyano and nonacyano derivatives, respectively, in order to examine their acidities in the gas-phase and DMSO. It is found that polycyano derivatives represent powerful organic superacids, the most acidic being nonacyano-1*H*-phenalene. The origin of the highly pronounced acidity is identified as a strong anionic resonance in the resulting conjugate base. Comparison of the calculated ΔH_{acid} value for 1*H*-phenalene with the experimental NIST value shows that the latter is too large by 8–11 kcal mol^{-1}. A possible reason for this error is briefly discussed.

1. Introduction

The name superacid was first proposed by Hall and Conant to describe compounds stronger than conventional Brønsted mineral acids.[1] An arbitrary, but useful and widely accepted definition was put forward later on by Gillespie and Peel for substances stronger than 100% sulfuric acid.[2] Recently, considerable attention has been focused on carboranes[3–5] as precursors of highly stable anions and design of neutral organic superacids, based either on the notion of the electron superacceptor substituents,[6,7] or on systems undergoing aromatic stabilization upon deprotonation assisted by judiciously chosen substituents[8–12] participating in a very strong anionic resonance. This ever increasing interest in the topic is not surprising, because strong organic acids have some distinct advantages over their mineral counterparts being reactive in mild chemical environments. The latter is of particular importance, since superacids are essential ingredients in general acid catalysis, where the catalytic activity does not depend only on the concentration of H^+ ions, but also on the presence of superacid itself.[13] In particular, stable and weakly coordinating anions exhibiting chemical inertness and high solubility proved useful in numerous applications including olefin polymerization,[14] development of a new Li battery technology,[15] the isolation and stabilization of new strongly reactive and notoriously elusive cations such as HC_{60}^+ and $C_{60}^{\cdot+}$,[16] $C_6H_7^+$,[17] Bu_3Sn^+,[18] $Cu(CO)_4^+$,[19] S_8^+,[20] and Xe_2^+.[21] Consequently, the design of neutral organic superacids, which easily give up a proton, is vital from both scientific and practical points of view.

In attempts to tailor neutral organic superacids, we observed that the cyano groups provided very efficient assistance in stabilization of the planar carbon skeletons via an anionic resonance mechanism[8–12] upon deprotonation at the C(sp^3) site. It turned out that the cyano group was very convenient since it embodied the best compromise between a modest steric requirement and a highly pronounced electron withdrawing power. Hence, the CN groups seem to be ideal in accommodating the excess negative charge. Another interesting finding was given by the fact that planar polycyano hydrocarbon derivatives often underwent prototropic tautomerism, for example, in pentacyanocyclopentadiene,[10] where the most stable structure of neutral acid possessed keteneimine C=C=NH moiety, instead of the HC(sp^3)–CN structural fragment. This theoretical prediction is confirmed by a parallel experimental investigation of Richardson and Reed,[22] who found that a very stable planar $C_5(CN)_5^-$ anion could be protonated only at the nitrogen yielding a fulvene-like structure.[9] Protonation at the carbon atom of the five-membered ring, which would give a cyclopentadiene molecular architecture instead, was not observed.

Keywords: Acidity; Neutral organic acids; Superacidity; Aromaticity; Prototropic tautomerism.
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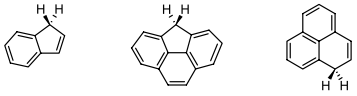
A strong acidifying effect of the CN functional group adds up to a number of its remarkable properties. Its versatility deserves some comments. The cyano group is considered second in abundance on the earth, next to the amino group,[23] being also present in significant amounts in dense interstellar clouds[24] and comets.[25] The possible important role of HCN and polycyano compounds in prebiotic syntheses and chemical evolution has interested researchers for decades.[26] Roughly 2000 plants produce cyano compounds, some of them being cyanogenic glycosides.[27] The universality of the CN group is reflected in polycyano compounds, which act as dyes or organic metals.[28] Finally, polycyano anions are important ingredients of materials exhibiting very strong electrical conductivity.[29] It is quite possible that polycyano derivatives of organic molecules will play a significant role in superacid–superbase chemistry[8–12,22] in the future.

It should be mentioned that a formation of a dense ladder of organic superacids, which match powerful organic superbases in their strength, is highly desirable in view of the expected spontaneous proton transfer. Building on the earlier results, we would like to show in the present report that polycyano derivatives of indene **I**, cyclopentaphenanthrene **II** and 1*H*-phenalene **III** (Fig. 1) are candidates for superacids in the gas-phase and in dimethylsulfoxide (DMSO) thus, providing additional important rungs on the superacidity ladder established in silico earlier.[8–12]



I **II** **III**

Figure 1. Schematic representation of indene (**I**), cyclopentaphenanthrene (**II**) and 1*H*-phenalene (**III**).

2. Theoretical methods

A good measure of the gas-phase acidity is given by the enthalpy change ΔH_{acid} for the proton dissociation reaction:

$$\text{AH(g)} \rightarrow \text{A}^-\text{(g)} + \text{H}^+\text{(g)} \quad (1)$$

which is calculated as:

$$\Delta H_{\text{acid}} = \Delta E_{\text{acid}} + \Delta(pV) \quad (2)$$

where ΔE_{acid} is the change in the total molecular energies of all species participating in reaction 1. It also includes the zero-point vibrational energy (ZPVE) and the finite temperature (298.15 K) correction. The pressure–volume work term is denoted by $\Delta(pV)$ as usual. It is useful to keep in mind that stronger acids have smaller numerical ΔH_{acid} values, which implies easier release of the acidic proton. Furthermore, acidity will be discussed in terms of ΔH_{acid} values, instead of the changes in the Gibbs free energy for the sake of simplicity and easier interpretation.

It is well documented that the G3 computational scheme is very successful in predicting gas-phase acidities.[30] Unfortunately, it is not feasible for the large molecules being examined here. Therefore, a more practical model is required, which still provides a good compromise between accuracy and practicality. Our choice is the DFT-B3LYP method[31,32] employing an appropriate basis set. It was shown by Handy and co-workers[33] that Pople's triple-zeta basis set, which includes the polarization and diffuse functions, yields practically converged energies at this level of the density functional theory. Specifically, the basis sets used in our calculations of acidities[8–12] are B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) implying that geometries are optimized by the very economical 6-31G(d) functions, whereas the energies are estimated by the flexible 6-311+G(2d,p) basis set necessary for a satisfactory description of anions. Moreover, it has been demonstrated that density functional theory,[34] and in particular its hybrid B3LYP functional,[35] gives a satisfactory description of the deprotonation process. It should also be pointed out that the DFT-B3LYP approach proved useful in reproducing electron affinities of molecules as shown by Schaefer and co-workers in a number of papers.[36–39] This lends credence to the method utilized here and puts all superacids examined so far[8–12] on the same theoretical scale. The latter is of importance, because their relative acidities should be highly reliable. Finally, it should be mentioned that the ZPVEs and thermal corrections were estimated at the B3LYP/6-31G(d) level without any scaling factors.

There is a widely accepted opinion that theory can predict the acidity and basicity of molecules quite accurately in the gas-phase.[40,41] The situation is less satisfactory in solution, where one has to resort on more approximate models. One of the possibilities is offered by the use of the complete bases set CBS-QB3 method in conjuction with the polarizable conductor model (CPCM),[42] which gives good agreement with experiment as evidenced by root-mean-square errors less than 0.4 pK_a units.[43–45] Unfortunately, this approach is not applicable to large systems like **I–III**. It is gratifying, however, that a simpler and more practical procedure is available with a relatively small sacrifice in accuracy. It is based on the isodensity polarized continuum model (IPCM) developed by Miertuš and Tomasi.[46,47] The cavity within the aprotic solvent of medium polarity is defined by the molecular surface with a constant density of 0.0004 eB^{-3} as proposed by Wiberg and co-workers.[48,49] This model accounts for the long-range bulk solvent effects for moderately polar solvents rather well. It will be utilized to assess the influence of DMSO on the acidity of systems **I–III** and their multiply substituted CN derivatives. Further, the present calculations are based on the proton-transfer reaction between solvated acid and the DMSO solvent molecule:

$$\text{AH} + \text{DMSO} \rightarrow \text{A}^- + \text{DMSOH}^+ + \Delta_r H_{\text{DMSO}} \quad (3)$$

which ultimately yields the conjugate base A^- in solution. The total molecular enthalpies of all species entering Eq. 3 contribute to the reaction enthalpy of proton transfer in solution, which is denoted as $\Delta_r H_{\text{DMSO}}$. The latter value is obtained by the IPCM/B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) model, which includes the thermal correction enthalpy obtained at the B3LYP/6-31G(d) level. Extensive calculations and comparison with experimental data for a large variety of neutral organic CH acids gave a good linear

Table 1. Total molecular energies of studied molecules in the gas phase (GP) and in dimethylsulfoxide (DMSO) obtained at B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory

Molecule	E_{GP}[a]	E_{DMSO}[a]	H_{corr}[a]	ΔH_{acid}[b]	ΔH_{acid}(exp)[b,c]	$\Delta_r H_{DMSO}$[b]	pK_a(theor)
CPD(CN)[d]	−655.47119	−655.50407	0.09938	263.9		−18.9	−20.2
CPD(CN)$^-$	−655.04175	−655.11471	0.08818				
1a	−347.86033	−347.86417	0.14825	351.8	351.9±2.1	42.9	20.7[e]
1a$^-$	−347.28728	−347.37277	0.13345				
2a	−993.66434	−993.71540	0.14952	257.1		−18.1	−19.7
2a$^-$	−993.24497	−993.32415	0.13757				
2b	−993.67231	−993.72260	0.14897	262.5		−13.3	−16.5
2b$^-$	−993.24497	−993.32415	0.13757				
3a	−577.79255	−577.80034	0.21181	351.0		52.8	27.2
3a$^-$	−577.22045	−577.29296	0.19673				
4a	−1408.10036	−1408.15321	0.21260	260.6		−14.1	−17.0
4a$^-$	−1407.67521	−1407.75818	0.20033				
4b	−1408.10360	−1408.16533	0.21198	263.0		−8.0	−13.0
4b$^-$	−1407.67521	−1407.75818	0.20033				
5a	−501.54964	−501.55560	0.19846	342.0	350.9±3.8	37.8	17.3
5a$^-$	−500.99175	−501.07182	0.18319				
6a	−1331.84307	−1331.88947	0.19924	249.0		−21.6	−22.0
6a$^-$	−1331.43599	−1331.50307	0.18663				
6b	−1331.85064	−1331.89792	0.19796	254.6		−15.5	−17.9
6b$^-$	−1331.43599	−1331.50307	0.18663				

H_{corr} denotes thermal correction to enthalpy obtained by the B3LYP/6-31G(d) model. Theoretical pK_a values are obtained by Eq. 4.
[a] In atomic units.
[b] In kcal mol^{-1}.
[c] Experimental data are taken from Refs. 51 and 54.
[d] Pentacyanocyclopentadiene is denoted by CPD(CN).
[e] Experimental value of Bordwell and Satish is 20.1 (Ref. 59).

correlation between the measured pK_a values and computed $\Delta_r H_{DMSO}$ enthalpies for reaction 3,[12] giving Eq. 4:

$$pK_a(exp) = 0.661\Delta_r H_{DMSO} - 7.7 \quad (4)$$

with an average absolute error of 1.1 pK_a and the correlativity factor $R^2=0.985$. This accuracy is sufficient for our purposes. All computations are carried out with the GAUSSIAN 98 suite of programs.[50]

3. Results and discussion

3.1. Indene and heptacyanoindene

The gas-phase deprotonation enthalpies are given in Table 1. The tautomeric forms of indene are depicted in Figure 2 together with their relative energies.

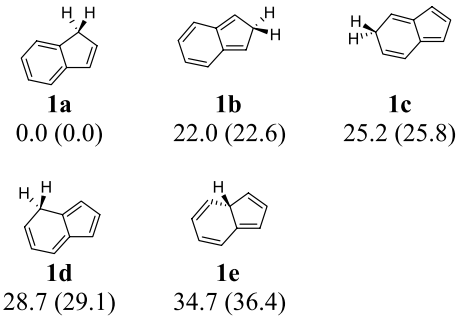
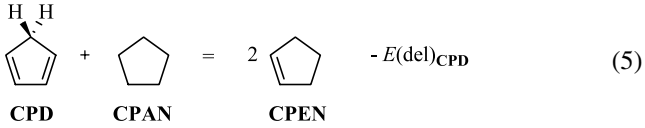


Figure 2. Schematic representation of indene tautomers and their relative energies obtained by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) and B3LYP/6-31G(d) models. The latter are given within parentheses (in kcal mol^{-1}).

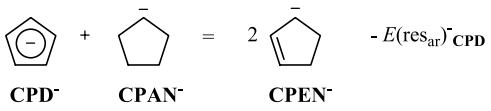
The most stable tautomer is **1a**, since it preserves the aromaticity of the benzene fragment to a great extent upon fusion of the five-membered ring. The difference in the ground state energy between **1a** and **1b** of 22 kcal mol^{-1} corresponds roughly to the aromatization energy of the six-membered benzene ring. The least stable tautomer is **1e** presumably due to the strain energy imposed by the distorted tetrahedral structure of the sp^3 carbon atom and nonplanarity, which diminishes the π-electron conjugation. It appears that the B3LYP/6-31G(d) results reproduce the relative stabilities of tautomers rather well and in accordance with the more advanced B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) calculations and chemical intuition (Fig. 2).

Deprotonation of all tautomers **1a**–**1e** results in a unique anion structure with completely delocalized negative charge over the π-electron framework. The resonance structures describing delocalization are easily obtained and visualized by replacing one of the two out of plane CH bond by a lone pair placed in the π AO in all tautomeric forms (Fig. 2). The rest of the resonance structures are obtained by taking into account the C_{2v} symmetry of the indene anion. The B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) deprotonation energy of **1a** is 351.8 kcal mol^{-1}, which shows that the parent indene is a rather moderately acidic compound (Table 1). This value is in perfect agreement with the experimentally determined acidity of indene being 351.9±2.1.[51] It is of interest to compare the acidity of indene with that of cyclopentadiene (**CPD**). The latter is 352.6 kcal mol^{-1} implying a somewhat lesser acidity. Since we shall use **CPD** and its pentacyano derivative as standards, we should shed some light on the origin of their acidities. For that purpose we shall make use of the homodesmotic reactions[52] 5 and 6:



(5)

and



(6)

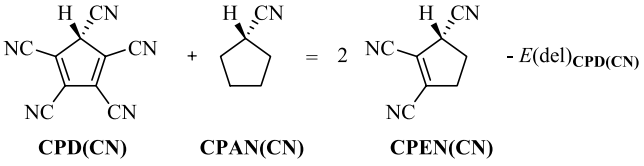
Here $E(\mathrm{del})_{\mathbf{CPD}}$ and $E(\mathrm{res_{ar}})^{-}{}_{\mathbf{CPD}}$ stand for the π-electron conjugation in **CPD** and the aromatic stabilization in $\mathbf{CPD}^{-}$ due to a cyclic anionic resonance gauged against the double anionic resonance in allyl anion occurring in $\mathbf{CPEN}^{-}$, respectively. They are defined as positive quantities. **CPAN** and **CPEN** denote cyclopentane and cyclopentene, respectively. Subtracting Eq. 5 from Eq. 6, one can write Eq. 7:

$$E(\mathrm{res_{ar}})^{-}_{\mathbf{CPD}} = -\{[\Delta H_{\mathrm{acid}}(\mathbf{CPD}) - \Delta H_{\mathrm{acid}}(\mathbf{CPAN})] - 2[\Delta H_{\mathrm{acid}}(\mathbf{CPEN}) - \Delta H_{\mathrm{acid}}(\mathbf{CPAN})]\} + E(\mathrm{del})_{\mathbf{CPD}} \quad (7)$$

The π-electron conjugation energy in **CPD**, $E(\mathrm{del})_{\mathbf{CPD}}$ is 2.6 kcal mol^{-1} thus, being in accordance with a pronounced localization of the double bonds in linear polyenes. It follows that the aromatic stabilization due to a cyclic anionic resonance in $\mathbf{CPD}^{-}$ relative to two allylic anions, taken as a reference and corrected by the π-conjugation in the initial **CPD**, is 23.4 kcal mol^{-1} as obtained by Eq. 7. This is comparable to the extrinsic aromatic stabilization of benzene measured against the linear zig-zag polyenes.[53] The anionic resonance in $\mathbf{CPEN}^{-}$ is by no means negligible being a difference between ΔH_{acid}(**CPAN**) and ΔH_{acid}(**CPEN**). It is 18.9 kcal mol^{-1}. The total anionic resonance in the cyclic $\mathbf{CPD}^{-}$ anion is, therefore, given by Eq. 8:

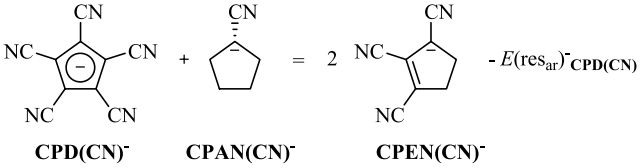
$$E(\mathrm{res})^{-}_{\mathbf{CPD}} = E(\mathrm{res_{ar}})^{-}_{\mathbf{CPD}} - 2[\Delta H_{\mathrm{acid}}(\mathbf{CPEN}) - \Delta H_{\mathrm{acid}}(\mathbf{CPAN})] - E(\mathrm{del})_{\mathbf{CPD}} \quad (8)$$

This yields the total stabilization of the $\mathbf{CPD}^{-}$anion gauged against the localized negative charge in $\mathbf{CPAN}^{-}$. The calculation gives $E(\mathrm{res})^{-}{}_{\mathbf{CPD}}$= 58.6 kcal mol^{-1}, which is significantly larger than the total aromatic stabilization in benzene that lies around 43 kcal mol^{-1}, if it is gauged against the localized π-double bond.[53] The present analysis convincingly illustrates the overwhelming importance of the anionic resonance in determining the acidity of organic compounds possessing the C(sp^3)H center attached to an (extended) π-network. The anionic resonance is dramatically amplified by cyano substituents as reflected in a large increase in acidity of polycyano derivatives. In this case the notion of the anionic resonance is more complex, since it involves a strong σ-inductive effect. It is clear that a depletion of the electronic density of the ring carbon atoms induced by the CN groups is compensated to a large extent by redistribution of the π-electrons. Obviously, the inductive and (anionic) resonance effects are strongly interlocked, which cannot be delineated at present. Hence, we shall retain the term anionic resonance keeping in mind that it also includes the inductive effect. In order to get a feeling about extent of the anionic resonance effect, let us analyze pentacyanocyclopentadiene. The corresponding homodesmotic reactions are given by Eqs. 9 and 10:



(9)

and



(10)

One obtains Eq. 11:

$$E(\mathrm{res_{ar}})^{-}_{\mathbf{CPD(CN)}} = -\{[\Delta H_{\mathrm{acid}}(\mathbf{CPD(CN)}) - \Delta H_{\mathrm{acid}}(\mathbf{CPAN(CN)})] - 2[\Delta H_{\mathrm{acid}}(\mathbf{CPEN(CN)}) - \Delta H_{\mathrm{acid}}(\mathbf{CPAN(CN)})]\} + E(\mathrm{del})_{\mathbf{CPD(CN)}} \quad (11)$$

It appears that $E(\mathrm{del})_{\mathbf{CPD(CN)}}$ is −2.2 kcal mol^{-1} implying that the two double bonds in **CPD(CN)** are slightly destabilized by tetracyano substitution. An interesting finding is that the cyclic resonance in pentasubstituted $\mathbf{CPD(CN)}^{-}$ is practically nil relative to the two anionic resonance interactions occurring in the allylic fragments of $\mathbf{CPEN(CN)}^{-}$ anion as evidenced by $E(\mathrm{res_{ar}})^{-}{}_{\mathbf{CPD(CN)}}$= 0.3 kcal mol^{-1}. In spite of that, the increase in acidity in pentacyanocyclopentadiene relative to the *ipso*-substituted cyanocyclopentadiene is very large due to the concerted anionic resonance of five CN groups in $\mathbf{CPD(CN)}^{-}$. It is given by $E(\mathrm{res_{ar}})^{-}{}_{\mathbf{CPD(CN)}}$ +2{ΔH_{acid}[**CPEN(CN)**]− ΔH_{acid}[**CPAN(CN)**]}−*E*(del), in full analogy with Eq. 8. It turns out that this quantity is as high as 108.1 kcal mol^{-1}. It is practically equal to the very strong anionic resonance within the triple substituted allylic fragment in $\mathbf{CPEN(CN)}^{-}$ (52.8 kcal mol^{-1}) multiplied by a factor of 2.

Let us consider heptacyanoindene now. This system undergoes a very interesting prototropic tautomerism (Fig. 3).

It turns out that the hydrogen atom can 'walk' from the sp^3 carbon to one of the cyano nitrogens thus, forming the keteneimine C═C═NH group. This process involves significant rehybridization at the atoms belonging to the

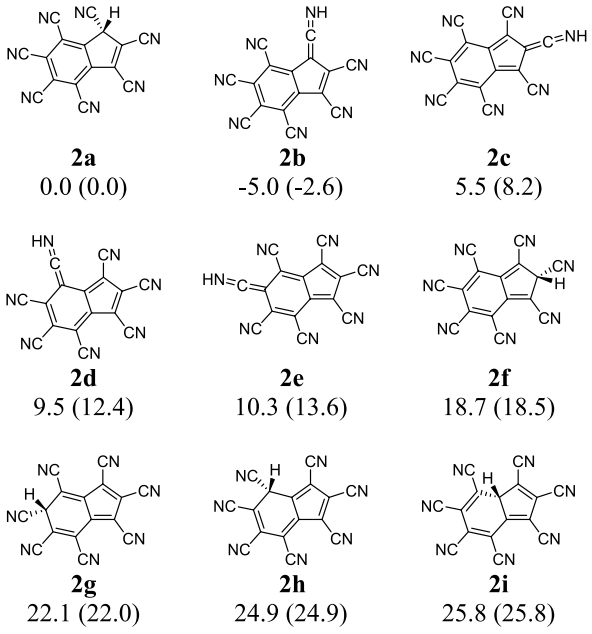


Figure 3. Prototropic tautomerism in heptacyanoindene. The relative stabilities (in kcal mol^{-1}) are calculated by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) (B3LYP/6-31G(d)) methods.

C(sp^3)–C≡N fragment and formation of two double bonds in a new C=C=NH moiety. One of the new double bonds (C=C) becomes a part of the extended π-framework, which stabilizes the system. It follows as a consequence that there is always one prototropic tautomer involving the keteneimine functionality, which is more stable than the rest of the tautomeric forms, and that holds as a rule. To be more specific, it is obtained by the hydrogen 'walk' from the C(sp^3)–H bond to the cyano group attached to the same C(sp^3) carbon. This rule applies to all polycyano systems examined earlier,[8–12] and it is corroborated by the present study. It is also worth noting that tautomers **2a** and **2b** retain the aromaticity of the benzene ring and are, therefore, considerably more stable than the other seven tautomers **2c**–**2f** (Fig. 3). Since all tautomers end up as the same anion upon deprotonation, differences in their stabilities straightforwardly give the differences in deprotonation energies. It suffices, therefore, to consider ΔH_{acid} energies of the two most stable tautomers **2a** and **2b**. They are 257.1 and 262.5 kcal mol^{-1}, respectively (Table 1). The rest of the prototropic tautomers are more acidic. It is interesting to put these results into perspective by comparison with some well known very strong Brønsted mineral acids like HNO_3, H_2SO_4 and $HClO_4$. The corresponding experimental gas-phase ΔH_{acid} values are 324.5, 306.3 and 288.0 kcal mol^{-1}.[54] Thus, one can safely conclude that heptacyanoindenes **2a** and **2b** represent powerful neutral organic superacids in the gas-phase. It should be noted that cyanation of **1a** leading to **2a** increases acidity by 95 kcal mol^{-1}. Finally, it is interesting to compare **2a** and **2b** acids with acidity of pentacyanocyclopentadiene and its keteneimine prototropic tautomer. The corresponding ΔH_{acid} values are 256.5 and 263.5 kcal mol^{-1}, respectively.[10] It follows that the acidities of pentacyanocyclopentadiene and heptacyano systems are comparable. The latter are somewhat less acidic in DMSO (see later).

3.2. Cyclopentaphenanthrene and nonacyanocyclopentaphenanthrene

Due to a bigger molecular skeleton, cyclopentaphenanthrene possesses a larger number of possible prototropic tautomers than indene. There are eight of them in total, which are depicted in Figure 4 together with their energies relative to the most stable species, **3a**.

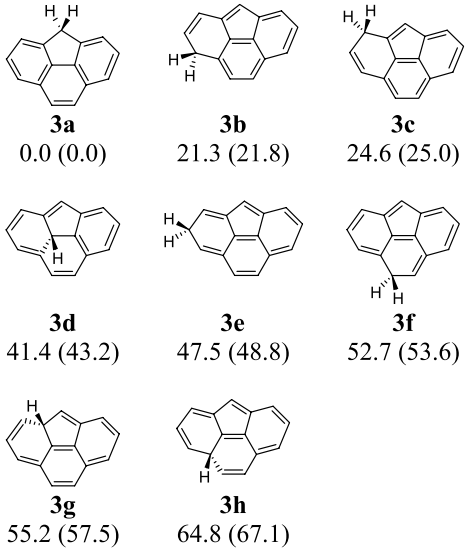


Figure 4. Schematic representation of cyclopentaphenanthrene tautomers and their relative energies obtained by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) and B3LYP/6-31G(d) models. The latter are given within parentheses (in kcal mol^{-1}).

The latter preserves the aromatic phenanthrene structure, which is the main cause of its large stability. The next two most stable structures are **3b** and **3c**, since they retain acenaphthene π-electron pattern. They are higher in energy than **3a** by 21.3 and 24.6 kcal mol^{-1}, respectively, because the acenaphthene fragment has one benzene ring less than phenanthrene. On the other hand, the least stable tautomers are **3g** and **3h**, since they do not have a single benzene or any other aromatic moiety, being considerably nonplanar and angularly strained at the same time. It is useful to note that a simple B3LYP/6-31G(d) model gives again practically the same relative stabilities as the more involved B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) method. Another remarkable observation is that the same proton, which participates in the prototropic tautomerism, is always the most acidic one. This implies that the resulting anions are the same irrespective of the position of the proton cleavage, which holds in general for all compounds studied here, as well as in the related systems explored earlier.[8–12] It appears that the parent cyclopentaphenanthrene molecule **3a** is not a very acidic compound, since its deprotonation enthalpy, obtained at the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) level of theory, is ΔH_{acid}=351.0 kcal mol^{-1}. This is practically identical to the corresponding gas-phase acidity of indene discussed above (Table 1). As in the case of indene, nonacyano substitution of cyclopentaphenanthrene backbone enables a large number of possible tautomers and has enormous influence on the acidity of the parent molecule **3a**. As seen in Figure 5, the number of

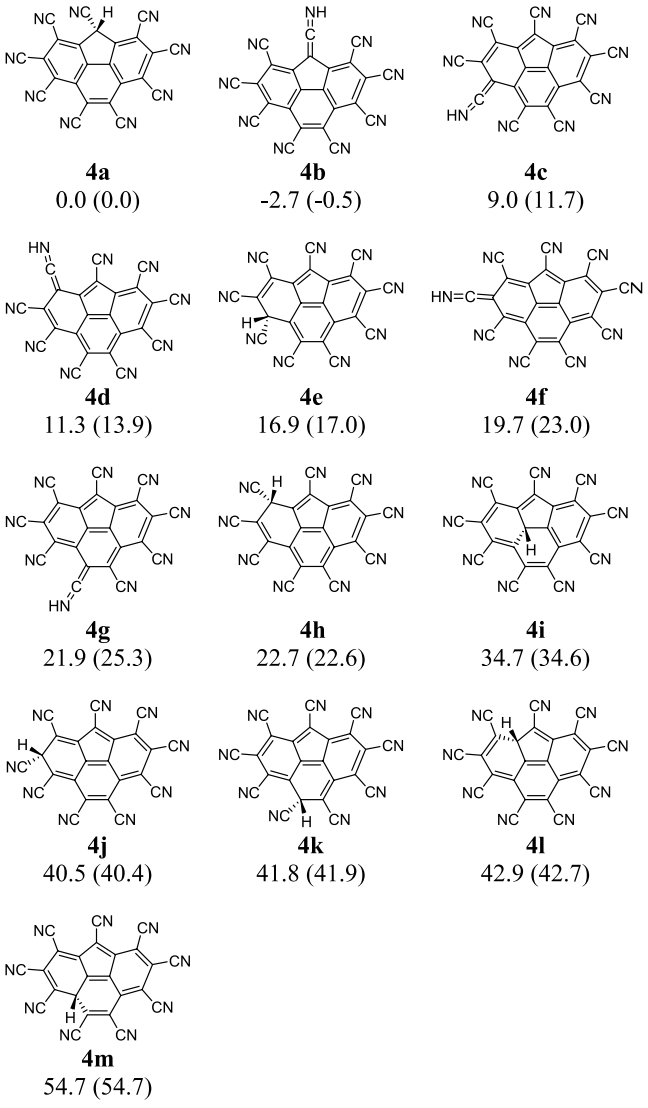


Figure 5. Prototropic tautomerism in nonacyanocyclopentaphenanthrene. The relative stabilities (in kcal mol^{-1}) are calculated by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) (B3LYP/6-31G(d)) methods.

all possible tautomers in nonacyanocyclopentaphenanthrene is 13.

However, tautomers **4a** and **4b** are significantly more stable than the other ones, for the same reasons as in the parent cyclopentaphenanthrene: they have the largest number of benzene rings. It should be noticed that the form **4b** possessing keteneimine C=C=NH fragment, which contributes one additional C=C double bond to the π-electron network, is more stable (by 2.7 kcal mol^{-1}) thus, conforming to the general rule stated earlier. Keeping in mind that all other tautomers are considerably less stable, we shall focus only on these two most stable tautomers in discussing the acidity of nonacyanocyclopentaphenanthrenes. If other tautomers were synthetically prepared, they would exhibit even higher acidities. Our calculations reveal that gas-phase acidities of compounds **4a** and **4b** are 260.6 and 263.0 kcal mol^{-1} (Table 1), respectively, the latter value representing the upper bound for all nonacyanocyclopentaphenanthrenes. Hence, their acidities are slightly higher than that of the keteneimine form of pentacyanocyclopentadiene (ΔH_{acid}[**CPD(CN)**] = 263.9 kcal mol^{-1}). It is worth pointing out that the 9-fold substitution of the parent cyclopentaphenanthrene **3a** enhances its acidity by as much as 90.4 kcal mol^{-1}, as far as **4a** tautomer is concerned. Another point of great importance is that anion derived by detachment of proton in nonacyano derivative of cyclopentaphenanthrene has antiaromatic (16) number of π-electrons, and yet the anionic resonance supported by CN groups is very strong leading to a very stable conjugate base. Hence, this system provides convincing evidence that the anionic resonance with cyano substituents prevails both in aromatic and antiaromatic π-electron frameworks of the planar polycyclic carbon anions leading to their outstanding stability. This is in line with analysis of the stability of pentacyanocyclopentadiene anion [viz. Eq. 11] presented earlier. It can be safely concluded that nonacyanocyclopentaphenanthrene tautomers **4a** and **4b** provide ultrastrong neutral organic superacids in the gas-phase. The corresponding acidity enhancement is lower than in indene in spite of the fact that nonacyanocyclopentaphenanthrene has nine CN substituents. However, this has some positive consequences, because the negative charge of the conjugate base is dispersed over a larger number of centers. Concomitantly, the anion should be less nucleophilic and thus, chemically more useful. Finally, it should be noticed that the relative stabilities of the prototropic tautomers are relatively well predicted at the B3LYP/6-31G(d) level (Fig. 5), just as in the parent unsubstituted tautomers. However, the acidities of **4a** and **4b** are significantly less accurate by the B3LYP/6-31G(d) method being 266.0 and 266.9 kcal mol^{-1}, respectively. The point is that one needs a very flexible basis set to describe deprotonation in a satisfactory way, that is the total molecular energies of both the initial acid and the final conjugate base should be reproduced with the same accuracy.

3.3. 1*H*-Phenalene and nonacyano-1*H*-phenalene

Let us turn attention now to the last compound in the present series of potential organic superacids: 1*H*-phenalene and its polycyano derivatives, which in turn represent a new structural and π-bonding pattern. The systems explored are depicted in Figures 6 and 7, which illustrate a relatively small number of possible prototropic tautomers.

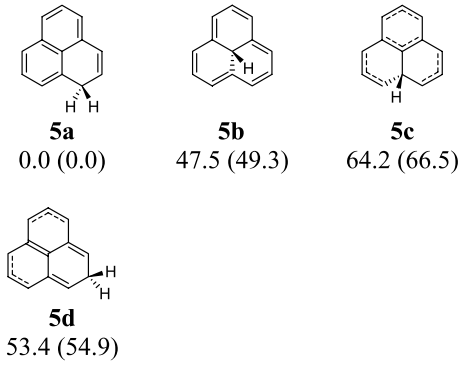


Figure 6. Schematic representation of 1*H*-phenalene tautomers and their relative energies obtained by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) and B3LYP/6-31G(d) models. The latter are given within parentheses (in kcal mol^{-1}).

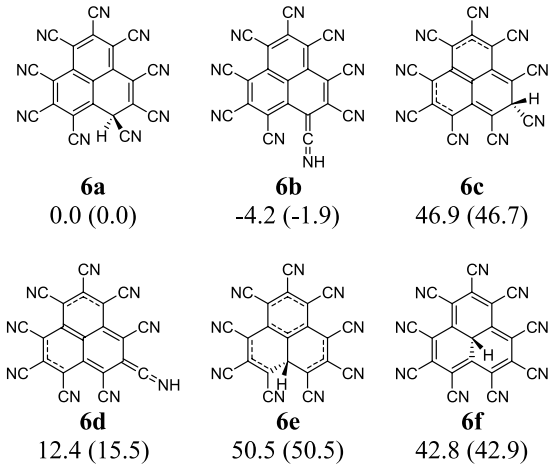


Figure 7. Prototropic tautomerism in nonacyano-1*H*-phenalene. The relative stabilities (in kcal mol^{-1}) are calculated by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) (B3LYP/6-31G(d)) methods.

This is due to the fact that 1*H*-phenalene is a molecule of moderate size and that phenalene backbone in its anionic conjugate base form is highly symmetric (D_{3h}). Thus, the number of different carbon atoms in the molecular skeleton is small. The most stable tautomer of 1*H*-phenalene is by far the **5a** species, which includes the naphthalene core. The difference between its total molecular energy and that of other tautomers is no less than 47.5 kcal mol^{-1}. It is, therefore, sufficient to consider gas-phase acidity of **5a** only, which is 342.0 kcal mol^{-1} (Table 1). Thus, it is more acidic than cyclopentadiene (ΔH_{acid}(**CPD**)=354.1 kcal mol^{-1}). This provides the upper boundary for the ΔH_{acid} values and lower boundary for acidities of 1*H*-phenalene tautomers. It is of importance to mention that the theoretical estimate is at variance with the available experimental result of 350.9±3.8 kcal mol^{-1} listed in the NIST data.[54] In order to test another theoretical method, rooted this time in the molecular orbital formalism, we carried out MP2(fc)/6-311+G(2d,p)//MP2(fc)/6-31G(d) calculations. The resulting ΔH_{acid} was 339.1 kcal mol^{-1}, thus being lower than experiment by some 11 kcal mol^{-1}. Hence, this discrepancy is appreciable and calls for some attention. We notice that the experimental result is based on the photodetachment measurement of the electron affinity of the perinaphthenyl radical[55] and the kinetic measurements of the C–H bond energy of 1*H*-phenylene.[56] However, the cross section in the photodetachment measurements exhibited extreme shallowness thus, prohibiting the use of the data close to threshold. Therefore, one had to resort to approximate theoretical calculations by using the method of partial orthogonal plane waves.[57] Moreover, the geometry of the perinaphthenyl anion **5a**$^-$ was fixed in the calculations and a unique C–C bond distance of 1.395 Å (found in benzene) was used for all bonds.[55] Consequently, the quoted experimental result is not 100% experimental, but includes also a use of approximate theoretical model in interpreting the measured data. It follows that some more experimental and theoretical investigations are desirable in this case in order to settle the problem. The acidity of tautomer **5a** is roughly 9–10 kcal mol^{-1} higher than that of all other unsubstituted hydrocarbons examined here. Concomitantly, its ΔH_{acid}(**5a**) is lower by that amount. It appears that the same also holds for its cyano derivatives too (Fig. 7).

The most stable tautomer **6b** possesses an *exo*-keteneimine fragment C=C=NH, in accordance with a general rule (vide supra). The prototropic tautomer **6b** is followed in stability by **6a** containing the HC(sp^3)–CN structural group. Our calculations show that the latter tautomer is less stable by 4.2 kcal mol^{-1} as obtained by the B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d) method. The gas-phase acidities of compounds **6a** and **6b** are 249.0 and 254.6 kcal mol^{-1}, respectively, thus reaching record gas-phase values. They are significantly lower than that of the most stable pentacyanocyclopentadiene tautomer (ΔH_{acid}=263.9 kcal mol^{-1}). It should be kept in mind that the remaining tautomers **6c**–**6f** are substantially less stable. Hence, they would exhibit even more pronounced acidity once synthetized. The corresponding values are easily deduced from data given in Figure 7. These remarkably low deprotonation enthalpies lead to a conclusion that nonacyano-1*H*-phenalene is a neutral organic superacid of extreme strength. The situation will be, however, somewhat different in DMSO solution, as we shall see shortly. It is noteworthy that the 9-fold cyano substitution of the parent hydrocarbon yields an enhancement in acidity of about 90 kcal mol^{-1}.

To reiterate, the multiple cyanation leading from the parent pure hydrocarbons to polycyano derivatives studied in this work **1a**→**2a**, **3a**→**4a** and **5a**→**6a** decreases the corresponding ΔH_{acid} values by 94.7, 90.4 and 93.0 kcal mol^{-1}, respectively. The influence of the cyano groups is dramatic indeed.

3.4. Acidity in dimethylsulfoxide (DMSO)

A point of significant importance is the behaviour of strong superacids in nonprotic solvents of low polarity. The nonpolar medium has at least three advantages: (1) perturbation of the examined solvated compounds is small; (2) it enables investigation of species of both high and low acidity and (3) it provides a good model for technological processes, since the latter usually take place in nonpolar solvents. Large polycyano hydrocarbons are particularly suitable systems, because the anionic negative charge is dispersed over many centers due to the mobile π-electrons. This feature prevents excessive aggregation of solutes. One of the suitable inert solvents in this respect is DMSO, since measurements in this medium are free from ion association effects in general.[58] Moreover, DMSO is a strongly dissociating solvent with a large dielectric constant implying that the relative acidities do not depend on the choice of the anchor acid.[59] Hence, the most stable tautomers of the systems studied here are immersed in DMSO in our computational experiment in silico and their behaviour is examined by the simple isodensity polarized continuum model (IPCM). As already described (vide supra), our approach is based on the proton transfer reaction 3 taking place in the DMSO solution. The corresponding $\Delta_r H_{DMSO}$ enthalpies are given in Table 1. It is worth pointing out that these values are negative for the polycyano substituted hydrocarbons, which shows that proton transfer to solvent molecules is particularly favoured. Making use of Eq. 4, one obtains pK_a values 20.7, 27.2 and 17.3 for

unsubstituted hydrocarbons **1a**, **3a** and **5a**, respectively. They demonstrate that these compounds are moderately acidic molecules in DMSO as well as in the gas-phase. It is worth mentioning that the estimated pK_a(DMSO) value for indene **1a** is in good agreement with the experimental result of Bordwell and Satish (pK_a=20.1).[60] On the other hand, the corresponding pK_a values for the most stable pairs of tautomers of heptacyanoindene (**2a**, **2b**), nonacyanocyclopentaphenanthrene (**4a**, **4b**) and nonacyano-1*H*-phenalene (**6a**, **6b**) are extremely low being (−19.7, −16.5), (−17.0, −13.0) and (−22.0, −17.9), respectively. Hence, it is fair to say that multiply substituted cyano hydrocarbons studied here represent hyperstrong acids both in the gas-phase and in dimethylsulfoxide. In order to put the present results into a proper perspective, we shall compare them with the pK_a(DMSO) values of pentacyanocyclopentadiene in its conventional and most stable keteneimine forms, which are −25.4 and −20.2, respectively (in pK_a units). Although the considered systems are less acidic in DMSO, they represent in principle important rungs on the superacidity ladder.

Finally, it is interesting to mention that the DMSO acidities correlate very well with the corresponding gas-phase data for the families of related compounds composed of a parent molecule substituted by a variety of substituents.[60] This is, however, not generally the case as exemplified by different superacids studied here.

4. Concluding remarks

An important impetus for examining the present systems was given by the fact that the parent compounds indene[61–63] (**1a**), cyclopentaphenanthrene[64–66] (**3a**) and 1*H*-phenalene[67,68] (**5a**) were already synthetized thus, being available. Since the chemistry of the cyano group is well known,[23,27,28,69,70] it is hoped that their cyano derivatives will be synthetized in the future too. It is quite possible that it will be easier to produce their anions first, in view of their enormous stability.[29] Protonation of these anions will be most likely a difficult task, but it is probably still feasible as shown by Richardson and Reed[22] in the case of a very stable $C_5(CN)_5^-$ anion.

In order to put the present results into perspective, we list gas-phase (GP) ΔH_{acid} and DMSO pK_a values of some of the most superacidic species considered so far, taking into account only the most stable keteneimine tautomer forms. They are given in the form of diads [ΔH_{acid}(GP), pK_a(DMSO)]: pentacyanocyclopentadiene [263.9, −20.2], heptacyanoindene [262.5, −16.5], nonacyanofluorene[11] [263.1, −9.7], nonacyanocyclopentaphenanthrene [263.0, −13.0] and nonacyano-1*H*-phenalene [254.6, −17.9], where ΔH_{acid}(GP) values are given in kcal mol^{-1}. It appears that the ΔH_{acid}(GP) values cluster around 263 kcal mol^{-1} with an exception given by the most acidic gas phase species nonacyano-1*H*-phenalene (ΔH_{acid}= 254.6 kcal mol^{-1}). In contrast, the pK_a(DMSO) values exhibit a larger scatter. The most acidic compound in DMSO is pentacyanocyclopentadiene with pK_a=−20.2. Although the studied systems are less acidic than pentacyanocyclopentadiene in DMSO, they provide important rungs on the superacidity ladder. It should be borne in mind, however, that successful syntheses of less stable tautomers would lead to considerably more acidic species than pentacyanocyclopentadiene.

The origin of hyperstrong acidity of polysubstituted cyano hydrocarbons, possessing the keteneimine C=C=NH functionality, is a consequence of a strong anionic delocalization of the excess charge in the corresponding conjugate bases, which is grossly amplified by the multiple CN substituents and their concerted action, as exemplified by $C_5(CN)_5^-$, heptacyanoindene and nonacyano-1*H*-phenalene anions. This effect is present even in nonacyanocyclopentaphenanthrene anion, which is formally an antiaromatic system.

Finally, it is useful to mention that the variation in acidity within the same family of molecules is determined by the initial state effects, that is within the set **1a**–**1e**, or within their polycyano derivatives **2a**–**2i**. However, the change in acidity on going from the parent hydrocarbons to cyanated derivatives is governed by the final state features.

A useful by-product of the present study is a finding that both B3LYP and MP2 methodologies indicate that the experimental ΔH_{acid} value of 1*H*-phenalene is too high by 8–11 kcal mol^{-1}. Hence, additional experimental data are desired.

Acknowledgements

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Highly regio- and stereo-selective carbometallation reaction of fluorine-containing internal acetylenes with organocopper reagents

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Abstract—The carbometallation reactions of fluoroalkylated internal alkynes with various organocopper reagents derived from organolithium, Grignard, and organozinc reagents were examined. All carbocupration reactions proceeded smoothly in a highly regio- and stereo-selective manner to give the corresponding vinylcopper intermediates. The intermediates reacted with H^+ smoothly, leading to the trisubstituted alkenes in high to excellent yields, whereas they reacted only with strictly limited carbon electrophiles such as allyl-, crotyl-, methallyl bromide, etc, probably due to the low reactivity exerted by an electron-withdrawing fluoroalkyl group. Treatment of vinylcopper with iodine resulted in a high yield of the corresponding vinyl iodide, which was employed successfully for Suzuki–Miyaura and Sonogashira cross-coupling reactions. In addition, two key reactions, the carbocupration and the Suzuki–Miyaura cross-coupling reaction realized the first highly stereoselective total synthesis of anti-estrogen drug, panomifene.

1. Introduction

Much interest has been focused on fluorine-containing materials due to their unique properties derived from modified electron density, acidity, and hydrogen-bonding patterns.[1] Fluoroalkyl groups increase lipophilicity allowing for easier drug transportation, cellular absorption, blood–brain barrier penetration, and improved binding within hydrophobic pockets of receptor. Consequently, the development of novel synthetic methods for the preparation of fluoroalkylated molecules has been becoming much more important in the fluorine chemistry.[2] Among a diversity of fluoroalkylated molecules, alkenes having a fluoroalkyl group (**1**) are well known as one of the most important synthetic targets because they are found in the framework of biologically active compounds such as panomifene (Fig. 1).[3] Though several synthetic methods for such molecules have been reported thus far,[4] carbocupration of fluoroalkylated alkynes is very attractive because the C–C and C–Cu bonds are simultaneously introduced across a triple bond in a highly stereoselective fashion to give the corresponding vinylcopper intermediates, which can react with electrophiles, variously substituted ethenes being provided with retention of configuration.[5] Despite of potentially great advantages, there have been quite limited studies on the carbocupration of fluorine-containing acetylene derivatives.[6] Herein we wish to describe the highly regio- and stereo-selective carbometallation of fluoroalkylated internal alkynes with organocopper reagents prepared from lithium,[7] magnesium,[8] and zinc reagents,[9] which serves a novel synthetic approach for the preparation of **1**.

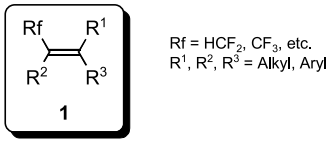

Figure 1.

2. Results and discussion

2.1. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from lithium reagents

Initially, the reaction of trifluoromethylated acetylene

Keywords: Fluorinated materials; Carbometallation; Fluorinated alkynes.
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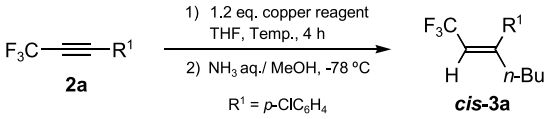
Table 1. Investigation of the reaction conditions for the carbocupration



Entry	Copper reagent[a]	Temp./°C	Yield[b]/% of **3a**	Recovery[b]/% of **2a**
1	*n*-BuCu	−78	10	81
2	*n*-BuCu	−45	73	26
3	*n*-BuCu	−20	39	13
4	*n*-Bu_2CuLi	−78	53	15
5	*n*-Bu_2CuLi	−45	97 (81)	0
6	*n*-BuCu(CN)Li	−78	42	50
7	*n*-BuCu(CN)Li	−45	75	25
8	*n*-$Bu_2Cu(CN)Li_2$	−78	77	13
9	*n*-$Bu_2Cu(CN)Li_2$	−45	96 (87)	0
10[c]	*n*-$Bu_2Cu(CN)Li_2$	−45	82	0
11[d]	*n*-$Bu_2Cu(CN)Li_2$	−45	47	0

[a] Copper reagents were prepared from Grignard reagent and CuI or CuCN.
[b] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[c] DME was employed instead of THF.
[d] Et_2O was employed instead of THF.

derivative **2a**[10] ($R^1 = p\text{-}ClC_6H_4$) with various organocopper reagents, prepared from *n*-BuLi and copper salts, was examined as shown in Table 1. Thus, to a solution of 1.2 eq. of *n*-BuCu (prepared from 1.2 eq. each of *n*-BuLi and CuI at −78 °C) in THF was added a THF solution of **2a** at −78 °C and the mixture was stirred for 4 h at that temperature. After quenching the reaction with NH_3 aq./MeOH, only *cis*-addition product **3a** was obtained in 10% yield, together with 81% of the starting material (entry 1). Raising the reaction temperature from −78 to −45 °C caused a significant improvement of the yield, **3a** being produced in 73% yield with high regio- and stereo-selectivity, though 26% of **2a** still remained unreacted (entry 2). However, the reaction at −20 °C led to a partial decomposition of the intermediate, affording the desired compound in only 39% yield (entry 3). Switching the organocopper reagent from *n*-BuCu to *n*-Bu_2CuLi brought about a dramatic change, the desired product being obtained quantitatively when the reaction was performed at −45 °C (entry 5). We next examined the reaction with cyanocuprates as shown in entries 6–9. The reaction with *n*-BuCu(CN)Li or *n*-$Bu_2Cu(CN)Li_2$ proceeded at −45 °C more smoothly than at −78 °C (entries 6 and 8 vs entries 7 and 9). In particular, the use of *n*-$Bu_2Cu(CN)Li_2$ at −45 °C resulted in complete consumption of the starting material, giving the corresponding alkene in 96% yield (entry 9). The investigation of the effect of the solvent, as shown in entries 10 and 11, revealed that THF was the solvent of choice. In all cases, the isomers such as *trans*-**3a**, *cis*-**4a**, and *trans*-**4a** were not detected at all (Fig. 2).

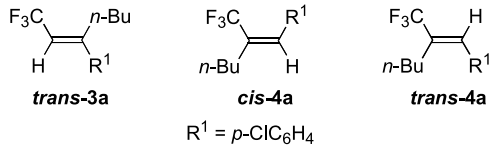
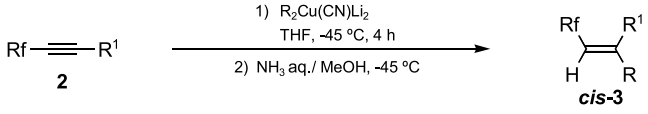


Figure 2.

With this optimised reaction conditions (Table 1, entry 9), the carbocupration reaction of various fluorine-containing acetylene derivatives was investigated in detail as listed in Table 2. As can be seen in entries 2 and 4, the use of 1.2 eq. of $Me_2Cu(CN)Li_2$ or $Ph_2Cu(CN)Li_2$ gave *cis*-**3** in only 38 or 42% yield, 57 or 56% of the starting alkyne being recovered, respectively. On the other hand, the use of 3.0 eq. of the cyanocuprate and the prolonged reaction time led to the complete consumption of the starting materials, affording the desired alkenes in high yields (entries 3 and 5). No influence of the substituents on the benzene ring in the alkynes was observed. Thus, the alkynes having either an electron-donating group (Me, MeO, entries 6 and 7) or an electron-withdrawing group (EtO_2C, entry 10) could participate nicely in the carbocupration reaction. It should be also noted that the position of the substituents on the benzene ring (*para*-; entry 7, *meta*-; entry 8, *ortho*-: entry 9) did not affect the yield. We also examined the effect of a fluoroalkyl group on the reaction as shown in entries 11–13. The alkynes bearing a difluoromethyl or hexafluoropropyl group caused a partial decomposition of the intermediate,

Table 2. The carbocupration reaction of fluoroalkylated alkynes with various organolithium reagents

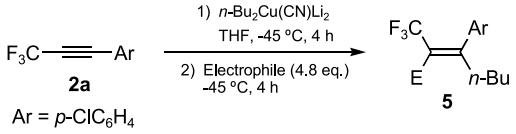


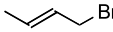
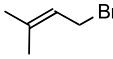
Entry	Equiv of copper reagent	R	Rf	R^1	Product	Yield[a]/% of *cis*-**3**	Recovery[a]/% of **2**
1	1.2	*n*-Bu	CF_3	$p\text{-}ClC_6H_4$	**3a**	96 (87)	0
2	1.2	Me	CF_3	$p\text{-}ClC_6H_4$	**3b**	38	57
3[b]	3.0	Me	CF_3	$p\text{-}ClC_6H_4$	**3b**	79 (73)	0
4	1.2	Ph	CF_3	$p\text{-}ClC_6H_4$	**3c**	42	56
5[b]	3.0	Ph	CF_3	$p\text{-}ClC_6H_4$	**3c**	91 (88)	0
6	1.2	*n*-Bu	CF_3	$p\text{-}MeC_6H_4$	**3d**	91 (83)	0
7	2.4	*n*-Bu	CF_3	$p\text{-}MeOC_6H_4$	**3e**	96 (94)	0
8	2.4	*n*-Bu	CF_3	$m\text{-}MeOC_6H_4$	**3f**	99 (89)	0
9	2.4	*n*-Bu	CF_3	$o\text{-}MeOC_6H_4$	**3g**	94 (84)	0
10	2.4	*n*-Bu	CF_3	$p\text{-}EtO_2CC_6H_4$	**3h**	quant. (98)	0
11	1.2	*n*-Bu	HCF_2	$p\text{-}ClC_6H_4$	**3i**	42 (27)	0
12	1.2	*n*-Bu	$HCF_2CF_2CF_2$	$p\text{-}ClC_6H_4$	**3j**	16	34
13	2.4	*n*-Bu	$HCF_2CF_2CF_2$	$p\text{-}ClC_6H_4$	**3j**	33 (33)	0

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] Stirred for 8 h.

the desired product being obtained in low yields. Next, we investigated the coupling reaction of the carbometallated adduct with a variety of electrophiles instead of H_2O. The results are collected in Table 3.

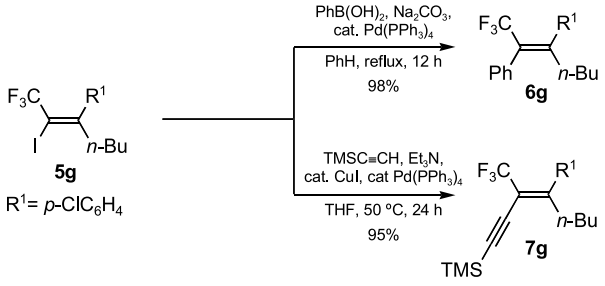
Table 3. The cross-coupling reaction of the carbocuprated adduct with various electrophiles



Entry	Electrophile (E^+)	Product	Yield[a]/% of **5**
1		**5a**	91 (86)
2		**5b**	97 (88)
3		**5c**	85 (81)
4		**5d**	88 (84)
5		**5e**	quant. (76)
6		**5f**	84 (63)
7	I_2	**5g**	90 (88)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.

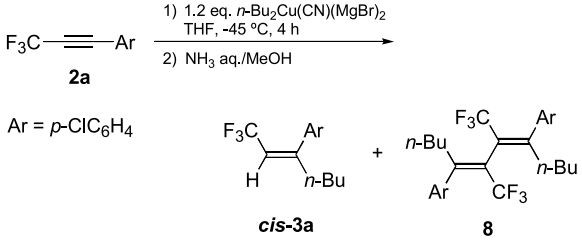
As can be seen in entries 1–5, variously-substituted allyl bromide such as allyl- methallyl-, crotyl-, prenyl-bromide, and β-(methoxycarbonyl)allyl bromide, could undergo the coupling reaction nicely to give the corresponding fluorine-containing tetrasubstituted alkenes **5a**–**e** in excellent yields. The propargyl bromide was also a good electrophile (entry 6), but other carbon electrophiles such as benzyl bromide, ethyl bromoacetate, iodomethane, and ethyl chloroformate were not subjected to the coupling reaction at all, the protonated *cis*-**3a** being obtained in moderate yield after quenching the reaction with NH_3 aq./MeOH. Additionally, trimethylsilyl chloride and tributylstannyl chloride were also found to be poor electrophiles, the desired tetra-substituted alkenes being obtained in low yields. On the other hand, the reaction with iodine took place smoothly to give the corresponding vinyl iodide **5g** in 90% yield (entry 7). Hereupon, we attempted the cross-coupling reaction of **5g** with organometallic reagents in the presence of a transition metal catalyst (Scheme 1). Thus, treatment of **5g** with phenylboronic acid and sodium carbonate in the presence of a catalytic amount of $Pd(PPh_3)_4$ in benzene at the reflux temperature for 12 h gave the corresponding coupling product **6g** almost quantitatively.[11] Furthermore, the reaction of **5g** with trimethylsilylacetylene and Et_3N in the presence of a catalytic amount of CuI and $Pd(PPh_3)_4$ took place smoothly to give the fluorine-containing enyne compound **7g** in 95% yield.[12]



Scheme 1. Suzuki–Miyaura and Sonogashira cross-coupling reactions.

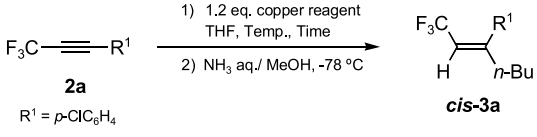
2.2. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from Grignard reagents

As an extension of the studies on the carbocupration reaction, our interest was next directed toward the reaction of fluoroalkylated alkynes with organocopper reagents derived from Grignard reagents in place of lithium reagents. Initially, the reaction was carried out under the optimised reaction conditions in the case of lithium reagents (n-$Bu_2Cu(CN)(MgBr)_2$, THF, −45 °C, 4 h), but the desired compound was given in only 43% yield together with 12% of the dimer **8** and 20% of **2a** recovered (Scheme 2). Therefore, we reexamined the feasibility of the carbometallation reaction with a series of organocopper reagents by using trifluoromethylated alkyne **2a** in order to determine the optimum linchpin (Table 4). Treatment of **2a** with n-BuCu at −45 °C for 4 h furnished *cis*-**3a** in only 5% yield, together with 48% of the starting material, after quenching the reaction with NH_3 aq./MeOH at −45 °C. The product was proved to be a *cis*-adduct as a single isomer. Using a lower ordered dibutylcuprate, generated from butylmagnesium bromide and CuBr, significantly improved the yield of *cis*-**3a** from 5 to 58% (entry 2). Furthermore, the reaction at −78 °C was found to give the desired product



Scheme 2. The carbocupration using cyanocuprate.

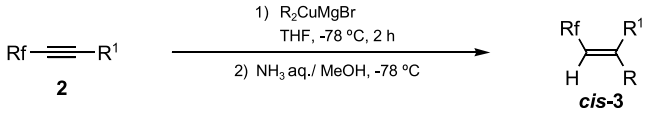
Table 4. Investigation of the reaction conditions for the carbocupration



Entry	Copper reagent[a]	Temp./°C	Time/h	Yield[b]/% of **3a**	Recovery[b]/% of **2a**
1	n-BuCu	−45	4	5	48
2	n-$Bu_2CuMgBr$	−45	4	58	0
3	n-$Bu_2CuMgBr$	−78	2	94 (85)	0
4[c]	n-$Bu_2CuMgBr$	−78	2	31	68
5	n-BuCu(CN)MgBr	−78	2	24	76
6	n-$Bu_2Cu(CN)(MgBr)_2$	−78	2	69	28

[a] Copper reagents were prepared from Grignard reagent and CuBr or CuCN, unless otherwise noted.
[b] Determined by ^{19}F NMR. Value in parentheses is of isolated yield.
[c] CuI was employed instead of CuBr.

Table 5. The carbocupration reaction of fluoroalkylated alkynes with various Grignard reagents

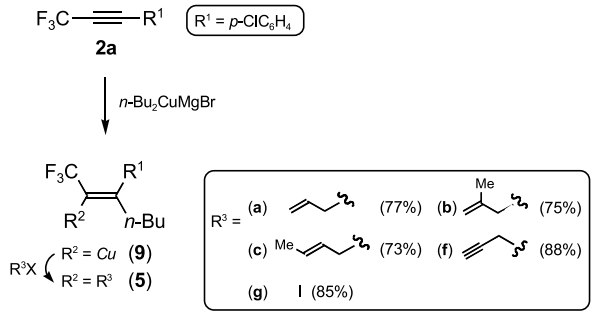


Entry	Equiv of copper reagent	R	Rf	R^1	Product	Yield[a]/% of *cis*-**3**
1	1.2	*n*-Bu	CF_3	*p*-ClC_6H_4	**3a**	93 (83)
2	2.4	*s*-Bu	CF_3	*p*-ClC_6H_4	**3k**	84 (69)
3	1.2	*c*-Hex	CF_3	*p*-ClC_6H_4	**3l**	74
4[b]	1.2	Bn	CF_3	*p*-ClC_6H_4	**3m**	quant. (69)
5[c]	1.2	Allyl	CF_3	*p*-ClC_6H_4	**3n**	98 (86)
6	2.4	Vinyl	CF_3	*p*-ClC_6H_4	**3o**	53 (41)
7	2.4	Ph	CF_3	*p*-ClC_6H_4	**3c**	93
8	2.4	*p*-$MeOC_6H_4$	CF_3	*p*-ClC_6H_4	**3p**	61[d]
9	2.4	*n*-Bu	CF_3	*m*-ClC_6H_4	**3q**	90 (70)
10	1.2	*n*-Bu	CF_3	*o*-ClC_6H_4	**3r**	89 (83)
11	1.2	*n*-Bu	CF_3	*p*-$MeOC_6H_4$	**3e**	97 (93)
12	1.2	*n*-Bu	CF_3	*p*-MeC_6H_4	**3d**	96 (90)
13	1.2	*n*-Bu	CF_3	*p*-$EtO_2CC_6H_4$	**3h**	84 (80)
14	1.2	*n*-Bu	CF_3	*p*-$(MeOC_6H_4)$-CH_2	**3s**	quant. (99)
15	1.2	*n*-Bu	HCF_2	*p*-ClC_6H_4	**3i**	65 (55)

[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] Benzylmagnesium chloride was used for the preparation of copper reagent.
[c] Allylmagnesium chloride was used for the preparation of copper reagent.
[d] CuCN was employed instead of CuBr because the copper reagents prepared from Grignard reagent and CuBr did not give a reproducible result.

cis-**3a** in 94% yield. Additional studies focused on a copper salt such as CuI and CuCN, both of which had proven to be good copper salts in the carbocupration reaction using organolithium reagents. Thus, changing a copper salt from CuBr to CuI appreciably affected the yield (entry 4). Higher ordered cyanocuprate realized the satisfactory reaction at −78 °C, resulting in the formation of *cis*-**3a** in 69% yield (entry 6), whereas lower ordered cyanocuprate did not lead to the good results (entry 5). In order to examine the scope and limitation of this carbocupration, the optimised reaction conditions were applied for various types of fluoroalkylated alkynes **2** as shown in Table 5. Primary and secondary Grignard reagents such as *n*-BuMgBr and *s*-BuMgBr (entries 1 and 2), cyclohexyl, benzyl, and allyl Grignard reagents (entries 3–5) could participate well in the carbocupration reaction to give the corresponding adducts *cis*-**3** in good to excellent yields (69–86% isolated yields). However, the yield was somewhat eroded with vinyl Grignard reagent employed (entry 6). Switching R in Grignard reagent from aliphatic to aromatic groups had no discernible effect on the yield, though 2.4 eq. of copper reagents or CuCN were required for the smooth reaction (entries 7 and 8). Changing the aromatic substituent (R^1) of the alkynes **2** from *p*-chlorophenyl to *m*-chloro- or *o*-chlorophenyl also did not significantly affect the yield (entries 1, 9 and 10). In addition, no influence of the yield on the substituents in R^1, such as the electron-donating (MeO, Me, entries 11 and 12) or the electron-withdrawing group (EtO_2C, entry 13), was observed. It is worthwhile to note that the internal alkynes having an alkyl side chain as R^1 (entry 14) or a difluoromethyl moiety as Rf (entry 15) could also undergo the smooth carbocupration reaction to afford the corresponding adducts in good to high yields.

Based on the above-described results on the regio- and stereo-selective carbometallation of the fluoroalkylated internal alkynes **2** with organocopper reagents, our interest was directed toward the cross-coupling reaction using the carbometallated adduct **9** (Scheme 3).



Scheme 3. The cross-coupling reaction.

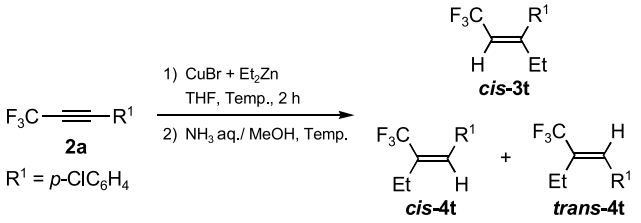
Treatment of **9** with 4.0 eq. of allyl-, methallyl-, crotyl-, propargyl bromide or iodine at −78 °C resulted in the smooth coupling reaction, affording the tetrasubstituted alkenes **5a–c,f,g** in high yields. Similar to the results on the lithium reagents, other electrophiles such as benzyl bromide, ethyl chloroformate, ethyl bromoacetate, etc. were all unreacted, leading to the formation of trisubstituted alkene *cis*-**3a** after quenching the reaction with NH_3 aq./MeOH. The coupling reaction of **9** with iodobenzene under the influence of palladium catalyst at 0 °C–rt did not give any desired product due to the decomposition of **9**.

2.3. The carbometallation reaction of fluorine-containing alkynes with organocopper reagents prepared from organozinc reagents

Organozinc reagents are well known as useful intermediates, and their chemistry has been actively investigated in the recent years. They tolerate a broad range of functionalities and undergo various reactions such as Michael addition, S_N2 reaction, and so on, in the presence

of a copper salt like CuBr, CuCN, etc.[13] Therefore, we next attempted the carbometallation reaction of various fluorine-containing alkynes with copper reagents derived from organozinc reagents (Table 6). In initial experiments, **2a** was treated with 1.2 eq. of copper reagent (prepared from 1.2 eq. each of copper bromide and Et_2Zn) at −45 °C for 2 h to give a mixture of *cis*-**3t**, *cis*-**4t**, and *trans*-**4t** in 78% yield. The ^{19}F NMR analysis showed that the ratio of *cis*-**3t**:(*cis*-**4t**+*trans*-**4t**) was 94:6 (entry 1). Interestingly, the reaction at −78 °C led to a decrease in the regioselectivity (entry 2). The use of 2.4 eq. of Et_2Zn caused a smooth carbocupration, *cis*-**3t** being produced with high regio- and stereo-selectivity (entry 3). It should be noted that the present reaction proceeded smoothly even in the presence of a catalytic amount of CuBr, 73% of the desired compounds being obtained, though the regioselectivity decreased slightly (entry 5). With the optimised reaction conditions (Table 6, entry 3), the scope of the carbocupration reaction with various organozinc reagents was examined. The results are summarized in Table 7. In the case of diorganozinc reagents, the reaction took place smoothly to afford *cis*-**3** with high regio- and stereoselectivity in high yields (entries 1–3). As can be seen in entries 5 and 6, an ester or a nitrile group in the organozinc reagents did not influence on the yield and the regioselectivity, whereas the zinc reagent derived from ethyl bromoacetate did not react with **2a** at all, the starting material being recovered quantitatively (entry 4). It is noteworthy that the carbometallation reaction with *n*-butylzinc iodide at −78 °C gave the desired molecule in a higher regioselective manner than the reaction at −45 °C (entry 7 vs 8). We also investigated the cross-coupling reaction of the carbometallated adduct **9** with various electrophiles (Scheme 4). Initially, treatment of the in situ generated carbometallated adduct with an excess amount of iodine at −78 °C did not give the corresponding vinyl iodide at all, the starting alkyne **2a** being recovered quantitatively. After several trials, we have found that the addition of DMF to the reaction mixture promoted the cross-coupling reaction significantly. Thus, to a solution of the in situ generated carbometallated adduct in THF was added the same volume of DMF as THF at −78 °C. After stirring of the reaction mixture for 10 min, then 4.8 eq. of iodine was added to the reaction mixture, and the whole was stirred for 1 h at room temperature before the reaction was quenched with NH_3 aq./MeOH. As a result, the vinyl iodide **5g** was obtained in high yield as a single isomer. The same reaction procedure could be applied for the reaction of the carbometallated adduct with allyl bromide, tetrasubstituted alkene **5a** being afforded in high yields with high regioselectivity. However, the reaction with methallyl- and crotylbromide gave the coupling products in moderate yields, 37 and 43% of **2a** being recovered, respectively.

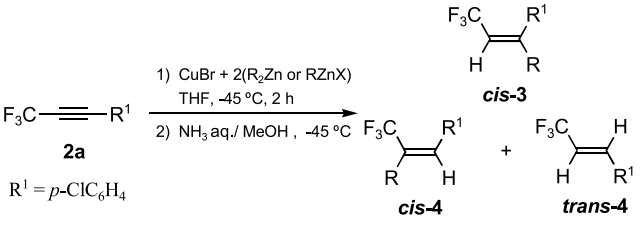
Table 6. Investigation of the reaction conditions



Entry	Eq. of CuBr	Eq. of Et_2Zn	Temp./°C	Yield[a]/% of **3**+**4**	Ratio[a,b] (**3**:**4**)	Recovery[a]/% of **2a**
1	1.2	1.2	−45	78	94:6	0
2	1.2	1.2	−78	86	85:15	0
3	1.2	2.4	−45	92 (84)	98:2	0
4	1.2	2.4	−78	92	96:4	0
5	0.2	2.4	−45	73	89:11	20
6	None	2.4	−45	0	—	99

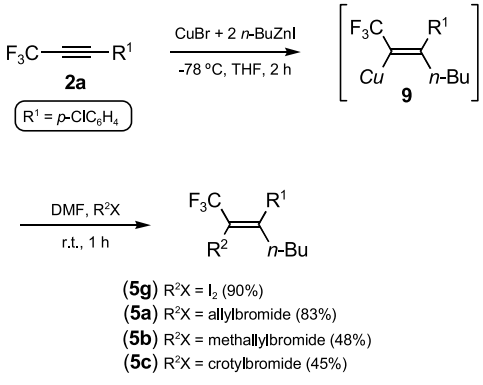
[a] Determined by ^{19}F NMR. Value in parentheses is of isolated yield.
[b] A ratio of *cis*-**4t**:*trans*-**4t** was not determined.

Table 7. The carbocupration reaction of fluoroalkylated alkynes with various organozinc reagents



Entry	Zinc reagent	Product	Yield[a]/% of **3**+**4**	Ratio[a,b] (**3**:**4**)
1	Et_2Zn	**3t**	92(84)	98:2
2	*n*-Bu_2Zn	**3a**	80(80)	100:0
3	Ph_2Zn	**3c**	80	100:0
4	$BrZnCH_2CO_2Et$	—	0	—
5	$IZnCH_2CH_2CO_2Me$	**3u**	80(79)	95:5
6	$IZnCH_2CH_2CH_2CN$	**3v**	95(90)	100:0
7	*n*-BuZnI	**3a**	80	78:22
8[c]	*n*-BuZnI	**3a**	96(96)	100:0

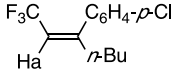
[a] Determined by ^{19}F NMR. Values in parentheses are of isolated yields.
[b] A ratio of *cis*-**4**:*trans*-**4** was not determined.
[c] Carried out at −78 °C.



Scheme 4. The cross-coupling reaction.

2.4. Determination of the stereochemistry of the carbocupration products

The stereochemistry in the carbocupration was determined as follows. Thus, the ^1H and ^{19}F NMR spectra of *cis*-**3a** showed a quartet signal due to the vinylic proton H_a and a



^1H NMR: q, J = 8.2 Hz
^{19}F NMR: d, J = 8.2 Hz

Figure 3.

doublet signal due to the CF_3 group, respectively (Fig. 3). Additionally, the NOE between H_b and H_c in **5f** was observed in the NOESY, strongly indicating that the propargyl and the butyl groups were situated in the *cis* configuration (Fig. 4). These spectral data suggest that the present carbocupration reaction occurred in a highly *cis* addition manner, in which the copper metal was attached with a carbon bearing a fluoroalkyl group.

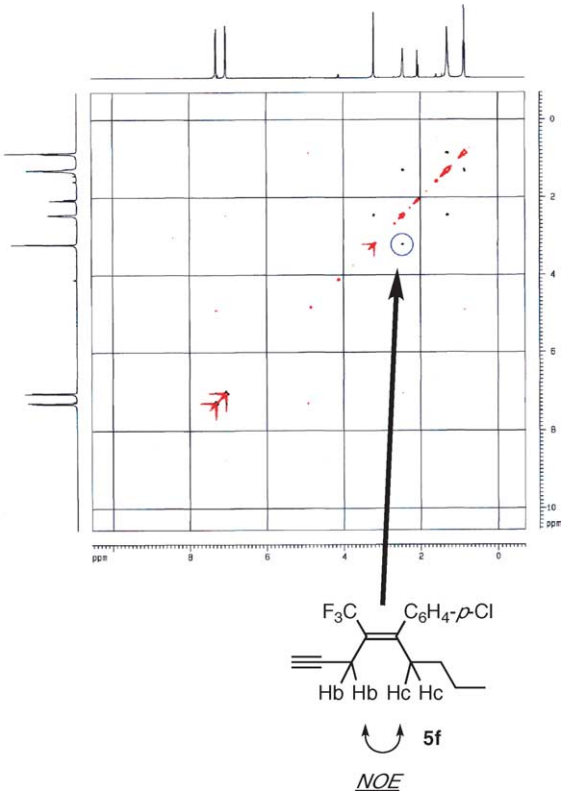
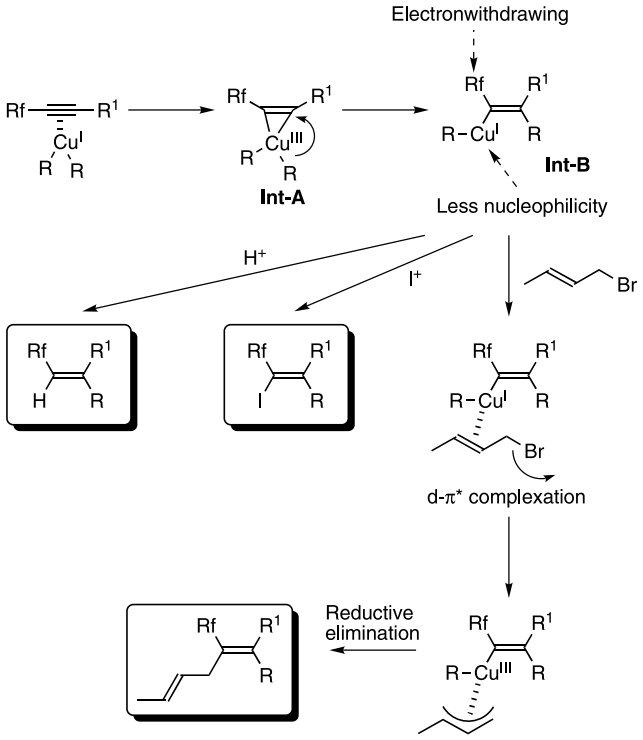


Figure 4. NOESY spectrum of **5f**.

2.5. Mechanism

Based on the results of the stereochemical assignment, the proposed mechanism for the present carbocupration reaction is outlined in Scheme 5. Thus, when copper reagent coordinates on the triple bond, oxidative addition of the alkyne to $Cu^{(I)}$ takes place to form the intermediate **Int-A**. Due to the strong electron-withdrawing effect exerted by a fluoroalkyl group (Rf), (Rf)C–$Cu^{(III)}$ bond may be stronger than (R^1)C–$Cu^{(III)}$. Accordingly, R on $Cu^{(III)}$ may transfer to the olefinic carbon distal to a fluoroalkyl group, vinylcopper intermediate **Int-B** being produced preferentially. Low nucleophilicity exerted by a fluoroalkyl group results in the coupling reaction of **Int-A** with only active electrophiles such as H^+, I^+, and variously-substituted allyl bromide. In the reaction of **Int-B** with variously-substituted allyl bromide, d-π* complexation between $Cu^{(I)}$ and the double bond may promote the generation of π-allylcopper intermediate, leading to the formation of tetrasubstituted alkenes via reductive elimination at the less hindered carbon.[14]



Scheme 5. Mechanism.

2.6. The synthetic application of the carbocupration reaction of fluorine-containing alkynes—total synthesis of anti-estrogenic drug, panomifene

As a synthetic application of the carbocupration reaction of fluorine-containing internal acetylenes, the total synthesis of panomifene **10**[3] (EGIS-5656, GYKI-13504), which is a follow-up molecule of tamoxifen **11**[15] (Nolvadex), the well-known triarylethylene type anti-estrogenic drug in the therapy of breast cancer and for the treatment of menstrual disorders (Fig. 5), was executed as follows (Scheme 6). Thus, alkyne **2x**[10] was exposed to the carbocupration reaction with $(4\text{-}MeOC_6H_4)_2Cu(CN)(MgBr)_2$ (1.2 eq.) at −45 °C for 2 h, followed by addition of 2.4 eq. of iodine at −78 °C, to afford vinyl iodide **5x** in 51% yield. The ^1H, ^{13}C, ^{19}F NMR, and GLC analyses were indicative of no other stereoisomers being formed. The stereochemically pure **5x** was treated with 4.0 eq. of phenylboronic acid under the Suzuki–Miyaura cross-coupling reaction conditions, producing the triarylethylene derivative **12x** almost quantitatively with complete retention of the stereochemistry. Surprisingly, treatment of **12x** with BBr_3 gave **13x** in low yield.[16] All attempts for improving this demethylation were unsuccessful. On the other hand, the demethylation of **5x** with BBr_3 proceeded readily to give the corresponding phenol derivative. The following nucleophilic substitution

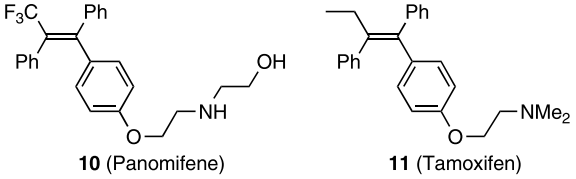
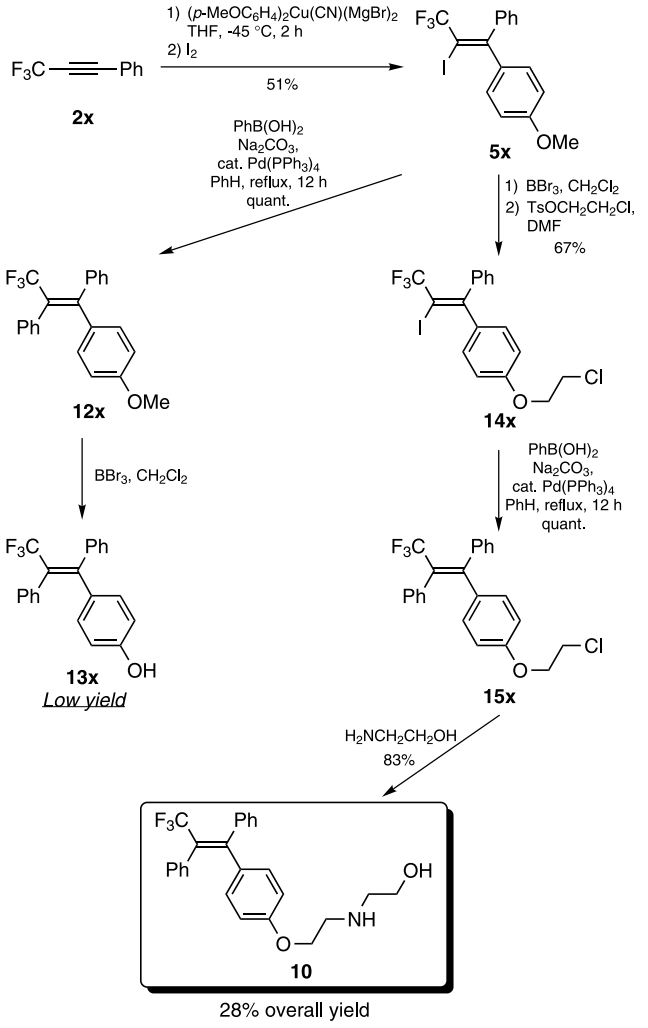


Figure 5. Panomifene and tamoxifen.



Scheme 6. A short total synthesis of panomifene.

reaction between phenoxide and 2-chloroethyl tosylate in DMF at the reflux temperature gave rise to the desired ether **14x** in 67% yield. The Suzuki–Miyaura cross-coupling reaction of **14x** with phenylboronic acid afforded the corresponding alkene **15x** quantitatively. Finally, on treating **15x** with ethanolamine in 2-methoxyethyleneglycol, the desired panomifene **10** was obtained in 83% yield (28% overall yield from **2x**).

3. Conclusion

In summary, we have investigated the carbocupration reaction of fluoroalkylated internal acetylene derivatives with various copper reagents derived from organolithium, Grignard, and organozinc reagents. The carbocupration reaction of fluoroalkylated internal alkynes proceeded in a highly regio- and stereo-selective manner to give the corresponding trisubstituted alkenes in high yields. Zinc reagents possessing a functional group such as an ester or a nitrile moiety were also applied for the reaction of the alkynes in a similar manner. The vinylcopper intermediate reacted only with a few carbon electrophiles such as allyl-, methally-, crotyl-bromide, etc, probably due to low reactivity exerted by an electron-withdrawing fluoroalkyl group. Treatment of vinylcopper with iodine resulted in the high yield of the corresponding vinyl iodide, which was employed successfully for the Suzuki–Miyaura and Sonogashira cross-coupling reactions. Two key reactions, the carbocupration and the Suzuki–Miyaura cross-coupling reaction realized the first highly stereoselective total synthesis of anti-estrogenic drug, panomifene **10** (total yield for five steps: 28%).[17]

4. Experimental

4.1. General

^{1}H NMR spectra were measured with a Bruker DRX (500.13 MHz) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. ^{13}C NMR spectra were recorded on a Bruker DRX (125.77 MHz). A JEOL JNM-EX90F (54.21 MHz, FT) spectrometer was used for determining ^{19}F NMR yield with internal C_6F_6. It was used for determining regioselectivity and stereoselectivity and was used for taking ^{19}F NMR spectra in a $CDCl_3$ solution with internal $CFCl_3$. $CFCl_3$ was used ($\delta_F=0$) as an internal standard for ^{19}F NMR. Infrared spectra (IR) were recorded on a Shimadzu FTIR-8200A (PC) spectrophotometer. Mass spectra (MS) were taken on a JEOL JMS-700.

4.2. Materials

All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Thin-layer chromatography (TLC) was done with Merck silica gel 60 F_{254} plates. Preparative thin layer chromatography (TLC) was done with Merck silica gel 60 F_{254}, 1 mm.

4.3. Typical procedure for the reaction of fluoroalkylated acetylene derivatives with cuprate derived from lithium reagents

To a solution of copper cyanide (53 mg, 0.6 mmol) in THF (2.0 mL) was added 0.76 mL (1.2 mmol) of *n*-BuLi (1.6 M hexane solution) at −78 °C and the whole was stirred for 10 min, then allowed to warm to −20 °C and stirred for 30 min. To this solution was added dropwise 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (102 mg, 0.5 mmol). The reaction was stirred for 4 h at −78 °C, and was then quenched with NH_3 aq./MeOH (1 mL/5 mL), extracted with Et_2O three times. The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane only) to afford (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-heptene (0.114 g, 0.44 mmol, 87% yield).

4.3.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3a). ^{1}H NMR ($CDCl_3$) δ 0.88 (3H, t, $J=7.0$ Hz), 1.31–1.34 (4H, m), 2.35–2.40 (2H, m), 5.67 (1H, q, $J=8.2$ Hz), 7.08 (2H, d, $J=8.3$ Hz), 7.33 (2H, d, $J=8.3$ Hz); ^{19}F NMR ($CDCl_3$) δ −56.70 (3F, d, $J=8.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.1, 29.2, 39.7, 115.7 (q, $J=33.4$ Hz), 122.7 (q, $J=271.0$ Hz), 128.3, 128.6, 133.9, 136.8, 153.2 (q, $J=5.9$ Hz); IR (neat) ν 2962, 2873, 1666, 1492, 1280 cm^{-1}; HRMS

(FAB) calcd for $C_{13}H_{14}{}^{35}ClF_3$ (M^+) 262.0736, found 262.0751. Anal. Calcd: C, 59.44; H, 5.37. Found: C, 59.03; H, 5.15.

4.3.2. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-butene (3b). ^1H NMR ($CDCl_3$) δ 2.13 (3H, q, J=2.0 Hz), 5.71 (1H, qq, J=1.5, 8.2 Hz), 7.16 (2H, d, J=8.5 Hz), 7.33 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −59.94 (3F, d, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 26.7, 116.2 (q, J=33.6 Hz), 122.4 (q, J=271.3 Hz), 128.2, 128.4, 134.1, 137.5, 148.9 (q, J=5.9 Hz); IR (neat) ν 1670, 1492 cm^{-1}; HRMS (FAB) calcd for $C_{10}H_8{}^{35}ClF_3$ (M^+) 220.0267, found 220.0260.

4.3.3. (1*Z*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1-phenylprop-1-ene (3c). ^1H NMR ($CDCl_3$) δ 6.14 (1H, q, J=8.2 Hz), 7.18 (2H, d, J=7.8 Hz), 7.23 (2H, d, J=7.8 Hz) 7.32–7.40 (5H, m); ^{19}F NMR ($CDCl_3$) δ −56.36 (3F, d, J=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 115.9 (q, J=34.0 Hz), 122.7 (q, J=264.8 Hz), 127.9, 128.4, 128.6, 129.6, 130.5, 134.7, 135.7, 139.7, 151.3 (q, J=5.8 Hz); IR (neat) ν 1643, 1492, 1361 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{10}{}^{35}ClF_3$ (M^+) 282.0423, found 282.0446.

4.3.4. (*Z*)-1,1,1-Trifluoro-3-(4-methylphenyl)-2-heptene (3d). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=7.0 Hz), 1.30–1.37 (4H, m), 2.37 (3H, s), 2.38–2.42 (2H, m), 5.66 (1H, q, J=8.3 Hz), 7.07 (2H, d, J=8.0 Hz), 7.16 (2H, d, J=8.0 Hz); ^{19}F NMR ($CDCl_3$) δ −57.99 (3F, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 21.2, 22.1, 29.3, 39.9, 114.8 (q, J=33.1 Hz), 123.0 (q, J=270.3 Hz), 127.1, 128.7, 135.5, 137.6, 154.5 (q, J=5.6 Hz); IR (neat) ν 2931, 2873, 1662 cm^{-1}. HRMS (CI) calcd for $C_{14}H_{18}F_3$ (M+H) 243.1361, found 243.1362. Anal. Calcd: C, 69.40; H, 7.07. Found: C, 69.13; H, 7.15.

4.3.5. (*Z*)-1,1,1-Trifluoro-3-(4-methoxyphenyl)-2-heptene (3e). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=7.0 Hz), 1.28–1.36 (4H, m), 2.36–2.42 (2H, m), 3.82 (3H, s), 5.62 (1H, q, J=8.3 Hz), 6.88 (2H, d, J=8.8 Hz), 7.12 (2H, d, J=8.8 Hz); ^{19}F NMR ($CDCl_3$) δ −56.62 (3F, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.1, 29.4, 39.8, 55.2, 113.4, 114.7 (q, J=33.1 Hz), 124.3 (q, J=270.6 Hz), 128.5, 130.6, 154.1 (q, J=5.6 Hz), 159.3; IR (neat) ν 2935, 2873, 1662, 1612 cm^{-1}. HRMS (FAB) calcd for $C_{14}H_{17}F_3O$ (M^+) 258.1231, found 258.1220. Anal. Calcd: C, 65.10; H, 6.63. Found: C, 65.20; H, 6.78.

4.3.6. (*Z*)-1,1,1-Trifluoro-3-(3-methoxyphenyl)-2-heptene (3f). ^1H NMR ($CDCl_3$) δ 0.81 (3H, t, J=7.0 Hz), 1.22–1.31 (4H, m), 2.29–2.34 (2H, m), 3.74 (3H, s), 5.56 (1H, q, J=8.0 Hz), 6.64 (1H, s), 6.68 (1H, d, J=7.3 Hz), 6.78 (1H, dd, J=2.3, 8.4 Hz), 7.19 (1H, dd, J=7.3, 8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −60.95 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.1, 29.3, 39.7, 55.20, 113.1, 113.1, 115.0 (q, J=33.4 Hz), 119.6, 122.8 (q, J=270.4 Hz), 129.0, 139.8, 154.2 (q, J=5.6 Hz), 159.1; IR (neat) ν 2935, 2873, 1666, 1581 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{17}F_3$ (M^+) 258.1231, found 258.1220.

4.3.7. (*Z*)-1,1,1-Trifluoro-3-(2-methoxyphenyl)-2-heptene (3g). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=7.0 Hz), 1.30–1.39 (4H, m), 2.37–2.41 (2H, m), 33.80 (3H, s), 5.69 (1H, q, J=8.0 Hz), 6.90 (1H, d, J=7.9 Hz), 6.93 (1H, t, J=7.4 Hz), 7.01 (1H, dd, J=1.3, 7.4 Hz), 7.29 (1H, td, J=7.9, 1.8 Hz); ^{19}F NMR ($CDCl_3$) δ −62.78 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 29.3, 38.3, 55.4, 110.7, 115.6 (q, J=32.9 Hz), 120.0, 122.9 (q, J=270.6 Hz), 127.5, 129.0, 129.1, 152.1 (q, J=5.6 Hz), 155.79; IR (neat) ν 2935, 2873, 1672, 1492 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{17}F_3$ (M^+) 258.1231, found 258.1237.

4.3.8. (*Z*)-Ethyl 4-(1-butyl-3,3,3-trifluoro-1-propenyl) benzoate (3h). ^1H NMR ($CDCl_3$) δ 0.80 (3H, t, J=7.0 Hz), 1.23–1.28 (4H, m), 1.32 (3H, t, J=7.0 Hz), 2.31–2.35 (2H, m), 4.31 (2H, q, J=7.0 Hz), 5.63 (1H, q, J=8.3 Hz), 7.16 (2H, d, J=8.3 Hz), 7.96 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −57.97 (3F, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 13.7, 14.3, 22.1, 29.1, 39.6, 61.0, 115.8 (q, J=33.6 Hz), 122.6 (q, J=271.4 Hz), 127.2, 129.3, 130.0, 143.1, 153.4 (q, J=5.3 Hz), 166.2; IR (neat) ν 2935, 2873, 1720, 1666 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{20}F_3O_2$ (M+H) 301.1416, found 301.1409. Anal. Calcd: C, 63.99; H, 6.38. Found: C, 64.01; H, 6.78.

4.3.9. (*Z*)-3-(4-Chlorophenyl)-1,1-difluoro-2-heptene (3i). ^1H NMR ($CDCl_3$) δ 0.87 (3H, t, J=7.0 Hz), 1.28–1.36 (4H, m), 2.38–3.42 (2H, m), 5.69 (1H, q, J=7.7 Hz), 5.86 (1H, td, J=55.5, 7.7 Hz), 7.12 (2H, d, J=8.5 Hz), 7.35 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −109.23 to −109.55 (1F, m), −109.93 to −101.18 (1F, m); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.1, 29.4, 38.4, 113.5 (t, J=229.6 Hz), 120.3 (t, J=26.4 Hz), 128.7, 129.3, 134.2, 136.6, 151.1 (t, J=1.3 Hz); IR (neat) ν 2958, 2862, 1662, 1492 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{15}{}^{35}ClF_2$ (M^+) 244.0830, found 244.0831.

4.3.10. (*Z*)-5-(4-Chlorophenyl)-1,1,2,2,3,3-hexafluoro-4-nonene (3j). ^1H NMR ($CDCl_3$) δ 0.88 (3H, t, J=7.0 Hz), 1.28–1.37 (4H, m), 2.44–2.48 (2H, m), 5.92 (1H, m), 6.02–6.29 (1H, m), 7.11 (2H, d, J=8.5 Hz), 7.33 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −127.10 to −127.50 (6F, m); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.1, 29.7, 39.6, 105–109 (3C, m), 110.5 (dt, J=15.9, 7.8 Hz), 128.6, 128.7, 134.1, 137.5, 152.8 (d, J=8.3 Hz); IR (neat) ν 2958, 2873, 1631, 1492 cm^{-1}; *m/z* (EI) 306 (93) 271 (100) 215 (86) 177 (90) 164 (60) 137 (30).

4.4. Typical procedure for the synthesis of tetrasubstituted alkenes

To a solution of copper cyanide (53 mg, 0.6 mmol) in THF (2 mL) was added 0.76 mL (1.2 mmol) of *n*-BuLi (1.6 M hexane solution) at −45 °C, and the whole was stirred for 10 min, then allowed to warm to −20 °C and stirred for 30 min. To this solution was added dropwise 1-(4-chlorophenyl)-3,3-3-trifluoropropyne (102 mg, 0.5 mmol). The reaction was stirred for 4 h at −45 °C, and then was added dropwise allyl bromide (290 mg, 2.4 mmol). The reaction was stirred for 4 h at −45 °C, and then was quenched with NH_4Cl aq. (3 mL), extracted with Et_2O three times. The combined layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (hexane only) to afford (*Z*)-5-(4-chlorophenyl)-4-trifluoromethyl-1,4-nonadiene (129 mg, 0.43 mmol, 86% yield).

4.4.1. (*Z*)-5-(4-Chlorophenyl)-4-trifluoromethyl-1,4-nonadiene (5a). ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J=7.0 Hz), 1.20–1.30 (4H, m), 2.33–2.37 (2H, m), 3.09 (2H, d, J=6.0 Hz), 5.11–5.20 (2H, m), 5.83–5.92 (1H, m), 7.04 (2H, d, J=8.3 Hz), 7.30 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −59.33 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 29.2, 32.0, 35.7, 116.1, 124.2 (q, J=276.0 Hz), 124.3 (q, J=26.7 Hz), 128.0, 128.9, 133.1, 134.5, 139.1, 148.5 (q, J=3.6 Hz); IR (neat) ν 2962, 2866, 1651 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{18}{}^{35}ClF_3$ (M^+) 302.1049, found 302.1050.

4.4.2. (*Z*)-5-(4-Chlorophenyl)-2-methyl-4-trifluoromethyl-1,4-nonadiene (5b). ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, J=7.0 Hz), 1.17–1.28 (4H, m), 1.83 (3H, s), 2.28–2.32 (2H, m), 3.00 (2H, s), 4.79 (1H, s), 4.89 (1H, s), 7.06 (2H, d, J=8.5 Hz), 7.31 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −59.13 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 23.0, 29.1, 35.5 (d, J=2.0 Hz), 35.9, 111.0, 124.1 (q, J=274.9 Hz), 124.4 (q, J=28.1 Hz), 128.0, 129.0, 133.1, 139.0, 141.8, 149.2 (q, J=3.4 Hz); IR (neat) ν 2962, 2862, 1651, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{20}{}^{35}ClF_3$ (M^+) 316.1206, found 316.1202. Anal. Calcd: C, 64.45; H, 6.36. Found: C, 64.65; H, 6.48.

4.4.3. (2*E*,5*Z*)-6-(4-Chlorophenyl)-5-trifluoromethyl-2,5-decadiene (5c). ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J=7.0 Hz), 1.19–1.30 (4H, m), 1.70 (3H, dd, J=1.3, 6.8 Hz), 2.31–2.36 (2H, m), 3.00 (2H, d, J=6.3 Hz), 5.43–5.49 (1H, m), 5.52–5.60 (1H, m), 7.03 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −56.00 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 17.9, 22.6, 29.2, 31.0, 35.6, 124.3 (q, J=276.0 Hz), 125.1 (q, J=22.5 Hz), 126.8, 127.1, 128.9, 133.0, 139.3, 147.7 (q, J=3.8 Hz); IR (neat) ν 2962, 2873, 1630 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{20}{}^{35}ClF_3$ (M^+) 316.1256, found 316.1187. Anal. Calcd: C, 64.45; H, 6.36. Found: C, 64.35; H, 6.11.

4.4.4. (*Z*)-6-(4-Chlorophenyl)-2-methyl-5-trifluoromethyl-2,5-decadiene (5d). ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J=6.8 Hz), 1.21–1.29 (4H, m), 1.70 (3H, s), 1.74 (3H, s), 2.31–2.35 (2H, m), 3.01 (2H, d, J=6.8 Hz), 5.10 (1H, t, J=6.8 Hz), 7.03 (2H, d, J=8.5 Hz), 7.29 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −62.10 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.8, 22.7, 25.7, 27.1, 29.3, 35.8, 121.1, 124.9 (q, J=276.0 Hz), 126.0 (q, J=27.3 Hz), 128.0, 128.9 (d, J=2.0 Hz), 132.8, 133.0, 139.40, 147.0 (q, J=3.6 Hz); IR (neat) ν 2962, 2862, 1651, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{22}{}^{35}ClF_3$ (M^+) 329.1283, found 329.1285.

4.4.5. (*Z*)-Methyl 5-(4-chlorophenyl)-2-methylene-4-trifluoromethyl-4-nonenate (5e). ^{1}H NMR ($CDCl_3$) δ 0.81 (3H, t, J=7.0 Hz), 1.17–1.27 (4H, m), 2.24–2.29 (2H, m), 3.35 (2H, s), 3.81 (3H, s), 5.62 (1H, s), 6.33 (1H, s), 7.06 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −61.83 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.5, 29.1, 29.6, 36.0, 52.1, 123.9 (q, J=275.8 Hz), 123.0 (q, J=28.0 Hz), 125.1, 128.1, 128.9, 133.3, 136.8, 138.5, 150.5 (q, J=3.1 Hz); IR (neat) ν 2958, 2837, 1724, 1635, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{21}{}^{35}ClF_3O_2$ (M^+) 361.1183, found 361.1180.

4.4.6. (*Z*)-5-(4-Chlorophenyl)-4-trifluoromethyl-4-nonen-1-yne (5f). ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J=6.8 Hz), 1.24–1.35 (4H, m), 2.08 (1H, t, J=2.5 Hz), 2.44–2.48 (2H, m), 3.21 (2H, d, J=2.5 Hz), 7.05 (2H, d, J=8.3 Hz), 7.31 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −59.53 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 17.6, 22.6, 28.9, 36.1, 68.9, 80.1, 121.4 (q, J=275.1 Hz), 121.9 (q, J=28.1 Hz), 128.1, 128.7, 133.4, 138.3, 149.4 (q, J=3.4 Hz); IR (neat) ν 3309, 2962, 2873, 1654 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{16}{}^{35}ClF_3$ (M^+) 300.0893, found 300.0896.

4.4.7. (*E*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (5g). ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J=7.0 Hz), 1.30–1.36 (4H, m), 2.62–2.67 (2H, m), 7.02 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −55.23 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 28.2, 46.3, 86.6 (q, J=34.2 Hz), 120.8 (q, J=273.7 Hz), 128.3, 128.4, 134.0, 137.3, 157.2 (q, J=2.9 Hz); IR (neat) ν 2958, 2862, 1593 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{13}{}^{35}ClF_3I$ (M^+) 387.9703, found 387.9694. Anal. Calcd: C, 40.18; H, 3.37. Found: C, 40.55; H, 3.23.

4.5. The Suzuki–Miyaura cross-coupling of 5g with phenyl iodide in the presence of palladium catalyst

To a solution of (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (109 mg, 0.273 mmol), $Pd(PPh_3)_4$ (34 mg, 0.024 mmol), in benzene (6 mL) was added Na_2CO_3 (72 mg, 0.68 mmol), $PhB(OH)_2$ (133 mg, 1.092 mmol), H_2O (0.35 mL), and EtOH (0.3 mL). The reaction mixture was refluxed for 12 h, then quenched with saturated NH_4Cl aq. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-phenyl-2-heptene (91 mg, 0.269 mmol, 98% yield).

4.5.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-phenyl-2-heptene (6g). ^{1}H NMR ($CDCl_3$) δ 0.66 (3H, t, J=7.1 Hz), 1.03–1.13 (4H, m), 2.13 (2H, d, J=7.2 Hz), 7.18 (2H, d, J=8.3 Hz), 7.29 (2H, d, J=8.3 Hz), 7.35–7.46 (5H, m); ^{19}F NMR ($CDCl_3$) δ −56.43 (3F, s); ^{13}C NMR ($CDCl_3$) δ 13.6, 22.2, 29.3, 36.7, 123.2 (q, J=274.9 Hz), 125.3, 127.2, 127.2, 128.2, 128.4, 128.8, 129.8, 133.4, 134.6, 138.2, 149.3 (q, J=2.4 Hz); IR (neat) ν 2929, 2862, 1643 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{18}{}^{35}ClF_3$ (M^+) 338.1049, found 338.1051.

4.6. The Sonogashira cross-coupling reaction of 8b with trimethylsilyl acetylene

To a solution of 3-(4-chlorophenyl)-2-iodo-1,1,1-trifluoro-2-heptene (100 mg, 0.260 mmol), trimethylsilylacetylene (50 mg, 0.52 mmol) and copper (I) iodide (5 mg, 0.026 mmol) in THF (2.0 mL) was added $Pd(PPh_3)_4$ (13 mg, 0.02 mmol), Et_3N (1.5 mL) and the whole was stirred for 24 h at 50 °C. The reaction mixture was quenched with NH_4Cl aq. and extracted with Et_2O three times. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel to afford (*Z*)-4-(4-chlorophenyl)-3-trifluoromethyl-1-trimethylsilyl-3-heptene-1-yne (90 mg, 0.247 mmol, 95% yield).

4.6.1. (*Z*)-4-(4-Chlorophenyl)-3-trifluoromethy-1-trimethylsilyl-3-hepten-1-yne (7g). ^{1}H NMR ($CDCl_3$) δ 0.25 (9H, s), 0.89 (3H, t, J=7.0 Hz), 1.33 (4H, m), 2.70 (2H, t, J=6.7 Hz), 7.05 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −57.42 (3F, s); ^{13}C NMR ($CDCl_3$) δ 0.3, 13.8, 22.4, 29.0, 38.8, 97.3, 102.8, 112.9 (q, J=33.2 Hz), 121.5 (q, J=274.7 Hz), 128.3, 128.4, 134.1, 137.0, 158.7 (q, J=2.6 Hz); IR (neat) ν 2862, 2152, 1488 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{22}{}^{35}ClF_3Si$ (M^+) 358.1131, found 358.1137. Anal. Calcd: C, 60.24; H, 6.18. Found: C, 60.06; H, 6.18.

4.7. Typical procedure for the carbocupration of fluorine-containing acetylene derivatives with Grignard reagents

To a solution of CuBr (47 mg, 0.328 mmol) in THF (2 mL) was added a THF solution of *n*-butylmagnesium bromide (0.66 mmol, prepared by magnesium and 1-bromobutane) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (49 mg, 0.240 mmol) in THF (2 mL). After stirring at that temperature for 2 h, the reaction was quenched with NH_3 aq./MeOH, and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-heptene (52 mg, 0.198 mmol, 83% yield).

4.7.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-4-methyl-2-hexene (3k). ^{1}H NMR ($CDCl_3$) δ 0.92 (3H, t, J=7.5 Hz), 1.05 (3H, d, J=6.5 Hz), 1.26 (1H, dq, J=7.5, 21.0 Hz), 1.46 (1H, m), 2.34 (1H, q, J=6.5 Hz), 5.65 (1H, q, J=7.8 Hz), 7.05 (2H, d, J=8.5 Hz), 7.32 (2H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −56.25 (3F, d, J=7.8 Hz); ^{13}C NMR ($CDCl_3$) δ 11.5, 18.4, 27.1, 44.1, 115.7 (q, J=33.3 Hz), 122.9 (q, J=271.2 Hz), 128.0, 129.0, 133.7, 136.1, 157.3 (q, J=5.2 Hz); IR (neat) ν 2966, 2935, 2877, 1662 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{14}{}^{35}ClF_3$ (M^+) 262.0736, found 262.0735.

4.7.2. (*Z*)-1-(4-Chlorophenyl)-1-cyclohexyl-3,3,3-trifluoropropene (3l). ^{1}H NMR ($CDCl_3$) δ 1.08–1.40 (5H, m), 1.66–1.98 (5H, m), 2.16 (1H, t, J=11.7 Hz), 5.62 (1H, q, J=8.0 Hz), 7.04 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −56.17 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 25.9, 26.3, 31.3, 46.8, 114.7 (q, J=33.3 Hz), 123.1 (q, J=271.2 Hz), 128.0, 128.9, 133.6, 136.6, 158.0 (q, J=5.4 Hz); IR (neat) ν 2931, 2856, 1664, 1595 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{16}{}^{35}ClF_3$ (M^+) 288.0893, found 288.0897.

4.7.3. (*Z*)-2-(4-Chlorophenyl)-4,4,4-trifluoro-1-phenyl-2-butene (3m). ^{1}H NMR ($CDCl_3$) δ 3.65 (2H, s), 5.59 (1H, q, J=8.0 Hz), 7.01 (2H, d, J=8.0 Hz), 7.08 (2H, d, J=8.0 Hz), 7.22–7.30 (5H, m); ^{19}F NMR ($CDCl_3$) δ −56.72 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 46.2, 117.4 (q, J=33.6 Hz), 121.6 (q, J=271.3 Hz), 127.1, 128.3, 128.7, 129.3, 134.0, 136.1, 136.4, 152.3 (q, J=5.5 Hz); IR (neat) ν 3062, 3031, 1666, 1596 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{12}{}^{35}ClF_3$ (M^+) 296.0580, found 296.0579. Anal. Calcd: C, 64.77; H, 4.08. Found: C, 65.20; H, 4.03.

4.7.4. (4*Z*)-4-(4-Chlorophenyl)-6,6,6-trifluoro-1,4-hexadiene (3n). ^{1}H NMR ($CDCl_3$) δ 3.11 (2H, d, J=5.5 Hz), 5.11 (1H, d, J=17.0 Hz), 5.16 (1H, d, J=10.0 Hz), 5.72 (2H, m), 7.13 (2H, d, J=8.0 Hz), 7.33 (2H, d, J=8.0 Hz); ^{19}F NMR ($CDCl_3$) δ −56.68 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 43.8, 116.6 (q, J=34.0 Hz), 119.0, 124.8 (q, J=270.4 Hz), 128.4, 128.6, 132.9, 134.1, 136.7, 151.2 (q, J=5.0 Hz); IR (neat) ν 3082, 1670, 1639, 1596 cm^{-1}; HRMS (FAB) calcd for $C_{12}H_{10}{}^{35}ClF_3$ (M^+) 246.0423, found 246.0420. Anal. Calcd: C, 58.43; H, 4.08. Found: C, 58.15; H, 3.98.

4.7.5. (3*Z*)-3-(4-Chlorophenyl)-5,5,5-trifluoro-1,3-pentadiene (3o). ^{1}H NMR ($CDCl_3$) δ 5.01 (1H, d, J=17.2 Hz), 5.43 (1H, d, J=10.4 Hz), 5.82 (1H, q, J=8.1 Hz), 6.56 (2H, dd, J=10.4, 17.2 Hz), 7.11 (2H, d, J=8.4 Hz), 7.37 (2H, d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −56.56 (3F, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$) δ 118.8 (q, J=33.6 Hz), 122.8 (q, J=270.5 Hz), 123.4, 128.3, 128.6, 130.0, 132.8, 134.2, 149.1 (q, J=5.5 Hz); IR (neat) ν 2360, 1643, 1610, 1596 cm^{-1}; HRMS (EI) calcd for $C_{11}H_8{}^{35}ClF_3$ (M^+) 262.0736, found 262.0735.

4.7.6. (*Z*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1-(4-methoxyphenyl)-propene (3p). ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.06 (1H, q, J=8.3 Hz), 6.85 (2H, d, J=8.9 Hz), 7.1δ 6 (2H, d, J=8.3 Hz), 7.17 (2H, d, J=8.9 Hz), 7.37 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −57.23 (3F, d, J=8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 55.4, 113.9 (q, J=34.1 Hz), 113.9, 123.1 (q, J=270.5 Hz), 128.3, 129.3, 131.9, 134.5, 135.9, 150.6 (q, J=5.8 Hz), 160.8; IR (neat) ν 1604, 1512, 1490 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{12}{}^{35}ClF_3O$ (M^+) 312.0529, found 312.0526.

4.7.7. (*Z*)-3-(3-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3q). ^{1}H NMR ($CDCl_3$) δ 0.89 (3H, t, J=7.0 Hz), 1.33 (4H, m), 2.37 (2H, m), 5.67 (1H, q, J=8.0 Hz), 7.05 (1H, d, J=7.0 Hz), 7.16 (1H, s), 7.24–7.32 (2H, m); ^{19}F NMR ($CDCl_3$) δ −56.62 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.1, 29.1, 39.6, 115.8 (q, J=33.4 Hz), 122.6 (q, J=271.2 Hz), 125.5, 127.1, 128.0, 129.3, 133.9, 140.2, 152.8 (q, J=5.7 Hz); IR (neat) ν 2963, 2936, 2874, 2500, 1666, 1600 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{14}{}^{35}ClF_3$ (M^+) 262.0736, found 262.0739. Anal. Calcd: C, 59.44; H, 5.17. Found: C, 59.67; H, 5.17.

4.7.8. (*Z*)-3-(2-Chlorophenyl)-1,1,1-trifluoro-2-heptene (3r). ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, J=6.5 Hz), 1.25–1.37 (4H, m), 2.32 (2H, t, J=7.0 Hz), 5.69 (1H, q, J=7.5 Hz), 7.01 (1H, d, J=9.0 Hz), 7.16–7.21 (2H, m), 7.32 (1H, d, J=9.0 Hz); ^{19}F NMR ($CDCl_3$) δ −58.72 (3F, d, J=7.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 29.0, 38.0, 116.5 (q, J=33.8 Hz), 122.6 (q, J=271.1 Hz), 126.2, 129.0, 129.3, 129.3, 129.4, 131.4, 151.7 (q, J=5.8 Hz); IR (neat) ν 3066, 2960, 2933, 2864, 1672, 1593 cm^{-1}; HRMS (CI) calcd for $C_{13}H_{14}{}^{35}ClF_3$ (M^+) 262.0736, found 262.0744. Anal. Calcd: C, 59.44; H, 5.17. Found: C, 59.79; H, 5.01.

4.7.9. (*Z*)-1,1,1-Trifluoro-3-[(4-methoxyphenyl)methyl]-2-heptene (3s). ^{1}H NMR ($CDCl_3$) δ 0.86 (3H, t, J=7.4 Hz), 1.24 (2H, tq, J=7.4, 7.5 Hz), 1.38 (2H, tt, J=7.5, 7.6 Hz), 3.54 (2H, s), 3.79 (3H, s), 5.54 (1H, q, J=8.5 Hz), 6.83 (2H, d, J=8.4 Hz), 7.09 (2H, d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −56.01 (3F, d, J=8.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.2, 29.4, 35.2, 36.4, 55.2, 113.9, 114.8 (q, J=32.9 Hz), 123.5 (q, J=274.9 Hz), 129.7, 129.8, 129.9, 154.2 (q, J=5.2 Hz), 158.3; IR (neat) ν 2933, 2861, 2837, 1668, 1612 cm^{-1}; HRMS (FAB) calcd for $C_{15}H_{19}{}^{35}ClF_3$ (M^+) 272.1388, found 272.1387.

4.7.10. (5*Z*,7*Z*)-5,8-Bis(4-chlorophenyl)-6,7-bis(trifluoromethyl)-5,7-dodecadiene (8). ^{1}H NMR ($CDCl_3$) δ 0.85 (6H, t, J=7.3 Hz), 1.15–1.25 (4H, m), 1.26–1.33 (4H, m), 2.34–2.42 (2H, m), 2.48–2.60 (2H, m), 7.12 (4H, d, J=8.5 Hz), 7.37 (4H, d, J=8.5 Hz); ^{19}F NMR ($CDCl_3$) δ −55.58 (6F, s); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.8, 28.6, 37.2, 122.1 (q, J=31.8 Hz), 122.5 (q, J=275.9 Hz), 128.3, 128.7, 133.9, 136.7, 154.4; IR (neat) ν 2962, 2873, 1631, 1488 cm^{-1}; HRMS (FAB) calcd for $C_{26}H_{26}{}^{35}Cl_2F_6$ (M^+) 522.1316, found 522.1309.

4.8. Typical procedure for the carbocupration of the fluorine-containing acetylene derivatives and the following coupling reaction of various carbon electrophiles

To a solution of CuBr (96 mg, 0.669 mmol) in THF (4 mL) was added a THF solution of *n*-butylmagnesium chloride (1.34 mmol, purchased from Aldrich) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (114 mg, 0.56 mmol) in THF (2 mL). After stirring at that temperature for 2 h, allyl bromide (324 mg, 2.68 mmol) was added slowly to the reaction mixture. After stirring of the solution for 1 h, the reaction was quenched with NH_3 aq./MeOH, and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (4*Z*)-5-(4-chlorophenyl)-4,4,4-trifluoro-1,3-nonadiene (110 mg, 0.364 mmol, 77% yield).

4.9. Preparation of fluorine-containing vinyl iodide

To a solution of CuBr (91 mg, 0.634 mmol) in THF (4 mL) was added a THF solution of *n*-butylmagnesium chloride (1.260 mmol, purchased from Aldrich) at −78 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −15 °C, then stirred for 5 min. The reaction mixture was again cooled to −78 °C, and to this mixture was added a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (94 mg, 0.459 mmol) in THF (2 mL). After stirring at that temperature for 2 h, iodine (644 mg, 2.54 mmol) in THF (2 mL) was added to the reaction mixture slowly. After 1 h, the reaction was quenched with NH_3 aq./MeOH, and a few drops of Na_2SO_3 were added until the color of the reaction mixture changed. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (152 mg, 0.392 mmol, 85% yield).

4.10. Typical procedure for the carbocupration of fluorine-containing acetylene derivatives with organozinc reagents

To a suspension of CuBr (50 mg, 0.349 mmol) in THF (4 mL) was added a THF solution of *n*-BuZnI (0.73 M, 0.95 mL, 0.697 mmol) at −78 °C for 20 min. To this solution was added dropwise a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (57 mg, 0.279 mmol) in THF (2 mL). After stirring at that temperature for 2 h, DMF (6 mL) was added as a co-solvent. The whole was allowed to warm to room temperature, and then to this solution was added a solution of iodine (355 mg, 1.40 mmol) in THF (2 mL). After stirring of the reaction mixture for 1 h, the reaction was quenched with NH_3 aq./MeOH, and a few drops of Na_2SO_3 were added until the color of the reaction mixture changed. The whole was extracted with Et_2O three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-heptene (98 mg, 0.252 mmol, 90% yield).

4.10.1. (*Z*)-3-(4-Chlorophenyl)-1,1,1-trifluoro-2-pentene (3t). ^{1}H NMR ($CDCl_3$) δ 1.03 (3H, t, J=7.4 Hz), 2.40 (2H, q, J=7.4 Hz), 5.66 (1H, q, J=8.0 Hz), 7.11 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −56.50 (3F, d, J=8.0 Hz); ^{13}C NMR ($CDCl_3$) δ 11.8, 32.9, 114.9 (q, J=33.6 Hz), 122.8 (q, J=270.9 Hz), 128.3, 128.5, 133.9, 136.9, 154.4 (q, J=5.5 Hz); IR (neat) ν 2976, 2943, 1492, 1465 cm^{-1}; HRMS (FAB) calcd for $C_{11}H_{10}{}^{35}ClF_3$ (M^+) 234.0423, found 234.0421.

4.10.2. Methyl (*Z*)-4-(4-chlorophenyl)-6,6,6-trifluoro-4-hexenoate (3u). ^{1}H NMR ($CDCl_3$) δ 2.36 (2H, t, J=7.5 Hz), 2.71 (2H, t, J=7.5 Hz), 3.65 (3H, s), 5.72 (1H, q, J=7.9 Hz), 7.11 (2H, d, J=8.4 Hz), 7.33 (2H, d, J=8.4 Hz); ^{19}F NMR ($CDCl_3$) δ −56.87 (3F, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 31.6, 34.8, 51.8, 116.8 (q, J=33.7 Hz), 122.4 (q, J=271.1 Hz), 128.5, 128.7, 134.3, 135.6, 151.0 (q, J=5.5 Hz), 172.3; IR (neat) ν 2955, 1740, 1668 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{13}{}^{35}ClF_3O_2$ (M^+) 293.0556, found 293.0563.

4.10.3. (*Z*)-4-(4-Chlorophenyl)-6,6,6-trifluoro-4-hexenenitrile (3v). ^{1}H NMR ($CDCl_3$) δ 1.70 (2H, tt, J=7.0, 7.6 Hz), 2.34 (2H, t, J=7.0 Hz), 2.57 (2H, t, J=7.6 Hz), 5.76 (1H, q, J=7.9 Hz), 7.11 (2H, d, J=8.3 Hz), 7.36 (2H, d, J=8.3 Hz); ^{19}F NMR ($CDCl_3$) δ −56.82 (3F, d, J=7.9 Hz); ^{13}C NMR ($CDCl_3$) δ 16.4, 22.8, 38.3, 117.4 (q, J=34.0 Hz), 118.7, 122.2 (q, J=271.3 Hz), 128.5, 128.7, 134.6, 135.3, 150.5 (q, J=5.4 Hz); IR (neat) ν 2943, 2248, 1668 cm^{-1}; HRMS (FAB) calcd for $C_{13}H_{11}{}^{35}ClF_3N$ (M^+) 273.0532, found 273.0528.

4.11. Typical procedure for the carbocupration of the fluorine-containing acetylene derivatives with organozinc reagents and the following coupling reaction of various electrophiles

To a suspension of CuBr (50 mg, 0.349 mmol) in THF (4 mL) was added Et_2Zn (0.70 ml, 0.700 mmol) at −45 °C for 20 min. To this solution was added dropwise a solution of 1-(4-chlorophenyl)-3,3,3-trifluoropropyne (63 mg, 0.308 mmol) in THF (2 mL). After stirring at that temperature for 2 h, DMF (6 mL) was added as additive. The whole was stirred for 10 min, then to this solution was added a solution of iodine (355 mg, 1.40 mmol) in THF (2 mL). After 1 h later, the reaction was quenched with NH_3 aq./MeOH, and a few drops of Na_2SO_3 were added until color of the reaction mixture was changed. And the whole was extracted with Et_2O three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-3-(4-chlorophenyl)-1,1,1-trifluoro-2-iodo-2-pentene (81 mg, 0.225 mmol, 73%).

4.12. Total synthesis of panomifene

To a solution of CuCN (56 mg, 0.625 mmol) and 3,3,3-trifluoro-1-phenylpropyne (81 mg, 0.476 mmol) in THF (4 mL) was added *p*-methoxyphenylmagnesium bromide (1.25 mmol, purchased from Aldrich) at −45 °C. After stirring for 10 min, the reaction mixture was allowed to warm to −5 °C, then stirred for 30 min. The reaction mixture was again cooled to −45 °C. After stirring at that temperature for 2 h, iodine (635 mg, 2.50 mmol) in THF (2 mL) was added slowly. After 1 h, the reaction was quenched with NH_3 aq./MeOH, and a few drops of Na_2SO_4 were added until the color of the reaction mixture changed. The whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over anhydrous Na_2SO_4, then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-3,3,3-trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (99 mg, 0.245 mmol, 51% yield).

4.12.1. (*Z*)-3,3,3-Trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (5x). ^{1}H NMR ($CDCl_3$) δ 3.81 (3H, s), 6.87 (2H, d, J=8.2 Hz), 7.13–7.17 (4H, m), 7.30–7.31 (3H, m); ^{19}F NMR ($CDCl_3$) δ −54.21 (3F, s); ^{13}C NMR ($CDCl_3$) δ 55.2, 85.2 (q, J=34.2 Hz), 113.7, 121.4 (q, J=270.5 Hz), 128.1, 128.1, 129.8, 137.7, 139.7, 158.6 (q, J=3.2 Hz), 160.8; IR (neat) ν 1604, 1508, 1461 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{12}F_3IO$ (M^+) 403.9885, found 403.9889. Anal. Calcd: C, 47.55; H, 2.99. Found: C, 47.54; H, 2.71.

To a solution of (*Z*)-3,3,3-trifluoro-2-iodo-1-(4-methoxyphenyl)-1-phenylpropene (100 mg, 0.247 mmol) in CH_2Cl_2 (5 mL) was added a CH_2Cl_2 solution of boron tribromide (0.5 mmol, purchased from Aldrich) at room temperature. After stirring at that temperature for 1 h, the reaction was quenched with saturated NH_4Cl aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over Na_2SO_4, and then concentrated in vacuo. Without purification, the reaction mixture was used for next reaction.

To a solution of NaH (12 mg, 0.494 mmol) in DMF (4 mL) was added a solution of the above-obtained crude product in DMF (2 mL) at 0 °C, and the resulting mixture was stirred at this temperature for 30 min. Then 2-chloroethyl tosylate (116 mg, 0.494 mmol) was added to this mixture. The reaction mixture was allowed to 80 °C. After 2 h, the reaction was quenched with saturated NH_4Cl aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*Z*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-2-iodo-1-phenylpropene (74 mg, 0.163 mmol, 67% yield).

4.12.2. (*Z*)-3,3,3-Trifluoro-2-iodo-1-[4-(2-chloroethoxy)phenyl]-1-phenylpropene (14x). ^{1}H NMR ($CDCl_3$) δ 3.82 (2H, t, J=5.8 Hz), 4.23 (2H, t, J=5.8 Hz), 6.89 (2H, d, J=8.7 Hz), 7.15–7.32 (7H, m); ^{19}F NMR ($CDCl_3$) δ −54.26 (3F, s); ^{13}C NMR ($CDCl_3$) δ 44.7, 67.9, 85.8 (q, J=34.3 Hz), 114.3, 121.3 (q, J=274.0 Hz), 128.1, 128.4, 129.9, 138.4, 139.5, 158.3 (q, J=6.4 Hz); IR (KBr) ν 1606, 1510, 1454, 1296, 1249 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{13}{}^{35}ClF_3IO$ (M^+) 451.9652, found 451.9656. Anal. Calcd: C, 45.11; H, 2.89. Found: C, 45.18; H, 2.80.

A solution of (*Z*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-2-iodo-1-phenylpropene (59 mg, 0.130 mmol) and $Pd(PPh_3)_4$ (16 mg, 0.013 mmol) in benzene (5 mL) was added Na_2CO_3 (34 mg, 0.325 mmol), $PhB(OH)_2$ (63 mg, 0.517 mmol), H_2O (0.15 mL) and EtOH (0.15 mL). The whole was refluxed for 12 h, then the reaction was quenched with saturated NH_4Cl aq., and the whole was extracted with EtOAc three times. The combined organic layers were washed with NaCl aq., dried over Na_2SO_4, and then concentrated in vacuo. The residue was purified by silica gel column chromatography to give the corresponding (*E*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-1,2-diphenylpropene (52 mg, 0.130 mmol, 100% yield).

4.12.3. (*E*)-3,3,3-Trifluoro-1-[4-(2-chloroethoxy)phenyl]-1,2-diphenylpropene (15x). Mp 108–109 °C; ^{1}H NMR ($CDCl_3$) δ 3.63 (3H, t, J=5.8 Hz), 3.99 (3H, t, J=5.8 Hz), 6.48 (2H, d, J=8.8 Hz), 6.48 (2H, d, J=8.8 Hz), 6.74 (2H, d, J=8.8 Hz), 7.14–7.31 (10H, m); ^{19}F NMR ($CDCl_3$) δ −57.05 (3F, s); ^{13}C NMR ($CDCl_3$) δ 41.7, 67.7, 113.7, 123.7 (q, J=275.5 Hz), 127.8, 127.8, 127.9, 128.0, 128.6, 128.6 (q, J=28.8 Hz), 131.4, 131.5, 134.0, 135.3, 140.2, 149.6 (q, J=3.4 Hz), 157.3; IR (KBr) ν 1606, 1510, 1326 cm^{-1}; HRMS (FAB) calcd for $C_{23}H_{18}{}^{35}ClF_3O$ (M^+) 402.0998, found 402.0995. Anal. Calcd: C, 68.58; H, 4.50. Found: C, 68.23; H, 4.18.

A mixture of (*E*)-1-[4-(2-chloroethoxy)phenyl]-3,3,3-trifluoro-1,2-diphenylpropene (84 mg, 0.201 mmol) and 2-methoxyethanol (3 mL) was refluxed for 10 h. It was diluted with dichloromethane and washed with 4% aqueous NaOH solution and water, dried (Na_2SO_4) and evaporated. The residue was purified by silica gel column

chromatography to give the target compound, panomifene (71 mg, 0.167 mmol, 83% yield).

4.12.4. (*E*)-3,3,3-Trifluoro-1-{4-[2-(2-hydroxyethylamino)ethoxy]phenyl}-1,2-diphenylpropene (Panomifene, 10). Mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 2.02 (2H, br s), 2.73 (2H, t, J=5.1 Hz), 2.86 (2H, t, J=5.1 Hz), 3.55 (2H, t, J=5.1 Hz), 3.85 (2H, t, J=5.1 Hz), 6.48 (2H, d, J=8.7 Hz), 6.74 (2H, d, J=8.7 Hz), 7.14–7.31 (10H, m); ^{19}F NMR ($CDCl_3$) δ −55.94 (3F, s); ^{13}C NMR ($CDCl_3$) δ 48.1, 50.7, 60.8, 67.1, 113.5, 123.7 (q, J=274.9 Hz), 127.7, 129.8, 127.9, 128.0, 128.3 (q, J=28.4 Hz), 128.6, 131.40, 131.50, 133.50, 135.34, 140.79, 149.70 (q, J=2.8 Hz), 157.87; IR (KBr) ν 3348, 3032, 2925, 1735, 1606, 1573, 1510, 1445, 1415, 1363, 1249, 1074, 981, 952, 918, 821, 762, 707, 630, 588 cm^{-1}; HRMS (FAB) calcd for $C_{25}H_{25}F_3NO_2$ (M+H) 428.1837, found 428.1839. Anal. Calcd: for $C_{25}H_{25}F_3NO_2$: C, 70.24; H, 5.66; N, 3.28. Found: C, 69.44; H, 5.84; N, 3.18.

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Efficient synthesis of new 11-thiasteroids and their oxides and dioxides

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Abstract—We show that our strategy, involving the use of an intramolecular Diels–Alder cycloaddition of *o*-xylylenes as the key step, can be applied efficiently to sulphur molecules. The synthesis of sulfoxide and sulfone derivatives is described and the vinyl group of those latters is oxidized, using the Wacker process, in good yields. Moreover, X-ray crystal structures of thiasteroids **11a** and **12a** matching the trans-*anti*-trans ring configuration of natural products are reported.

1. Introduction

We have recently reported a synthetic route to steroids possessing an aromatic A-ring, which is present in a lot of hormonal steroids as estrogens. It has been well established that estrogens act as important endocrine growth factors for at least a third of breast cancers.[1]

If carefully selected substituents are added to the basic skeleton of steroids, there can be considerable changes in the properties of the new compounds. The 3- and the 11-positions are well known to be particularly amenable to such changes.[2]

Such heterosteroids, in which the heteroatom takes the place of a carbon atom in a position of marked biological significance have a potential interest.[3] For example, Wolff and Zanati have reported that some A-ring hetero-androstanes have androgenic activity on the order of that of testosterone.[4]

Several types of thiasteroids have been also synthesized but so far these have been largely limited to compounds with the heteroatom in rings A and B. This prompted us to synthesize novel thiasteroids possessing the heteroatom in the C-ring. In an earlier publication,[5] we reported the first total synthesis of 11-thiasteroids. The strategy developed in our laboratory to prepare such thiasteroids involved an intramolecular Diels–Alder cycloaddition of *o*-quinodimethanes, which are generated by thermal ring opening of a benzocyclobutene.[6] This methodology has a remarkable advantage for the formation of the B/C cycle. These findings have led us to prepare new thiasteroid derivatives, which might present an interesting biological potential.

So, as a continuation of our synthetic and stereochemical studies on thiasteroids, our present aim was firstly the extension of our strategy to 11-thiasteroids having a bromine atom at 2-position or a methoxy group at 2 and/or 3-positions. And otherwise, the functionalisation of those latters and particularly the obtention of sulfoxide and sulfone derivatives, interesting from a biological point of view, have been envisaged.

It is therefore hoped that intramolecular cycloaddition of *o*-xylylene occurs with good stereoselectivity to provide the carbocyclic framework of the naturally occuring A-ring aromatic steroids.

2. Results and discussion

We therefore used the same synthetic approach to prepare the precursor **4**. The synthetic pathway is depicted in the following scheme. Condensation of 1,8-bis(trimethylsilyl)-2,6-octadiene (BISTRO) **1** with chloroacetic anhydride led to (±)-2,5-divinylcyclopentan-1-ol **2**, which was treated by *t*-BuOK in ethanol to give epoxide **3** in good yield.[5] Treatment of epoxide **3** with potassium thioacetate led to compound **4** in 51% overall yield (Scheme 1).

Keywords: Intramolecular Diels–Alder; Orthoquinodimethane; Thia steroid; Sulfoxide; Sulfone; Wacker oxidation.
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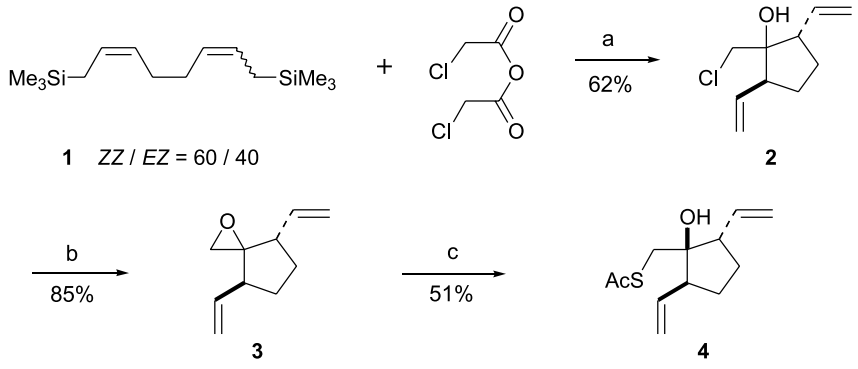
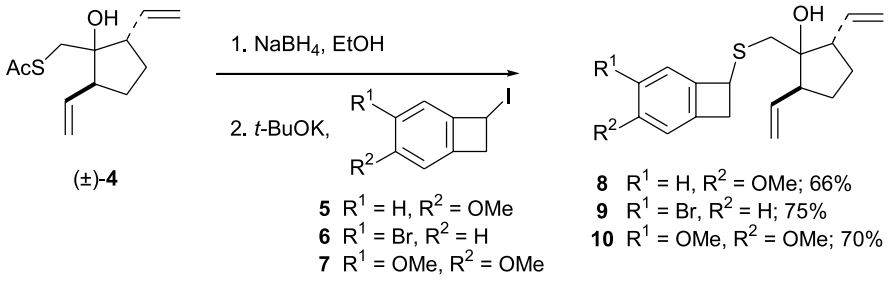


Scheme 1. Synthesis of the precursor **4**. Reaction conditions: (a) $TiCl_4$, CH_3NO_2, CH_2Cl_2, 12 h, −60 °C; (b) *t*-BuOK, EtOH, 0 °C, 2 h; (c) CH_3COSK, CH_3COSH, CH_2Cl_2, −78 °C to rt, 48 h.



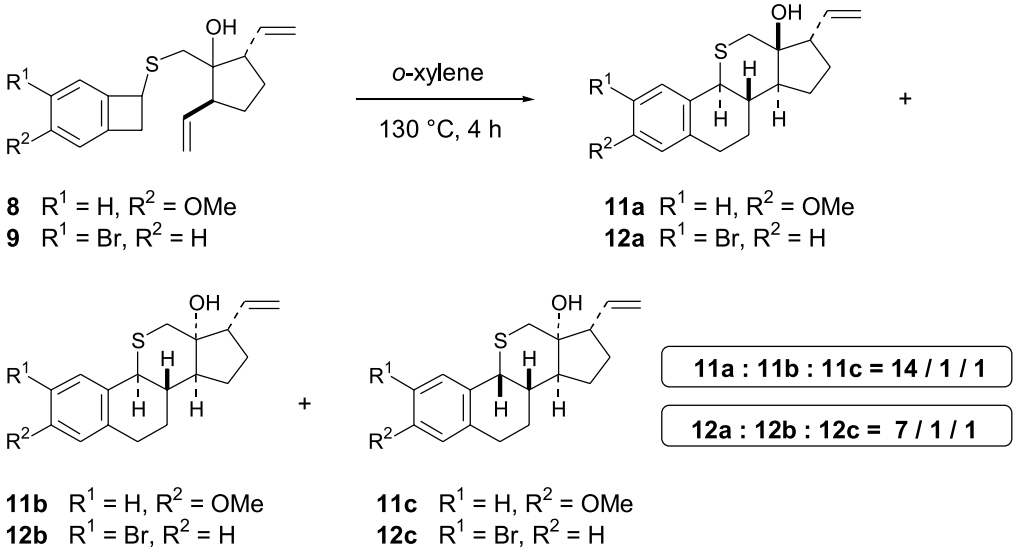
Scheme 2. Synthesis of the steroid precursors **8**–**10**.

In the next step of the synthesis, the potassium thiolate resulting from the reduction of **4** with sodium borohydride and treatment with a base, was cross-coupled with 1-iodobenzocyclobutenes **5**–**7**, affording the corresponding 1-alkylthio-benzocyclobutenes **8**–**10** in good yields (Scheme 2).

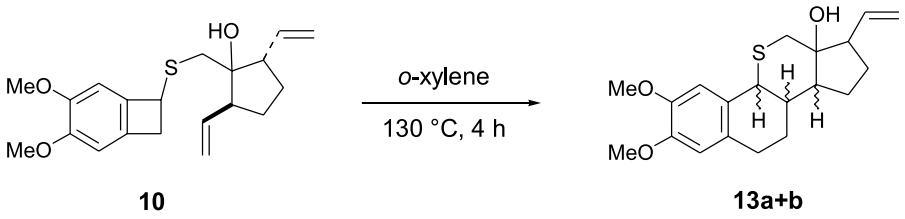
Thermolysis of the precursors **8** and **9** at 130 °C in *o*-xylene afforded a mixture of racemic trans-*anti*-trans steroid **11a/12a**, trans-*anti*-cis and cis-*anti*-cis steroids **11b/12b** and **11c/12c** in, respectively, 14/1/1 and 7/1/1 ratios and in good overall yields. These thiasteroids were easily separated by flash chromatography on silica gel. Interestingly, in the two cases, the major isomer **11a/12a** matched the ring-fusion configuration found in the natural products (Scheme 3).

In the case of **10**, upon thermolysis at 130 °C in *o*-xylene, the cycloadducts **13a**+**b** were produced in a 70:30 ratio and a 85% overall yield. Unfortunately, at this step of the synthesis, they were unseparable and for this reason the determination of their relative stereochemistries was not possible (Scheme 4).

The structures of steroid **11a**–**c** and **12a**–**c** were characterized on the basis of their spectroscopic properties including



Scheme 3. Synthesis of steroids **11a**–**c** and **12a**–**c**.



Scheme 4. Thermolysis of **10**.

a series of NMR experiments (COSY and phase NOESY, 400 MHz) while that of the major **11a** or **12a** was also confirmed unambiguously by single crystal X-ray analysis[7] (Figs. 1 and 2).

It is worth pointing out similar results with the work, we described recently.[5] Indeed, the isomer's ratio observed for **11** and **12** is exactly or quite the same as that reported for steroids with the methoxy substituent in 2-position of the A-ring. Interesting is also to note the high yield (92% for **11** and 90% for **12**), the good stereoselectivity of this step and on top of that in favour of the isomer matching the trans-*anti*-trans ring fusion of natural products. To the best of our knowledge, there is no total synthesis of such compounds reported in the literature.

The synthetic utility of organic sulfur compounds has been reviewed.[8] Otherwise, compounds containing a sulfide, sulfoxide or sulfone moiety present not only a synthetic interest but also for some of them a medicinal relevance.[9] Indeed, during metabolism organic sulfides can undergo oxidation to sulfoxides and then to sulfones.[10] Thus, for example, tazofelone an inflammatory bowel disease agent, undergoes oxidative metabolism forming stereoisomeric sulfoxides.[11] So, we envisaged to oxidize our thiasteroids by using a chemical method.[12] And (Scheme 5), oxidation of sulfides **11a** and **12a** with 1 equiv of 3-chloroperbenzoic acid in dichloromethane led to a mixture of the corresponding sulfoxide **14α/15α** and **14β/15β** in good yields. The equatorial sulfoxide is the major isomer in accord with the known behaviour of peroxy acids with cyclic sulfides.[13]

Then, we were interested to prepare sulfone derivatives (Scheme 6). And in this case, in order to obtain the sulfone as the sole product, oxidation on compounds **11a**, **12a** and **16** (this thiasteroid and its sulfoxide were previously reported[5]) was conducted with 2 equiv of *m*-CPBA in dichloromethane at room temperature. The corresponding

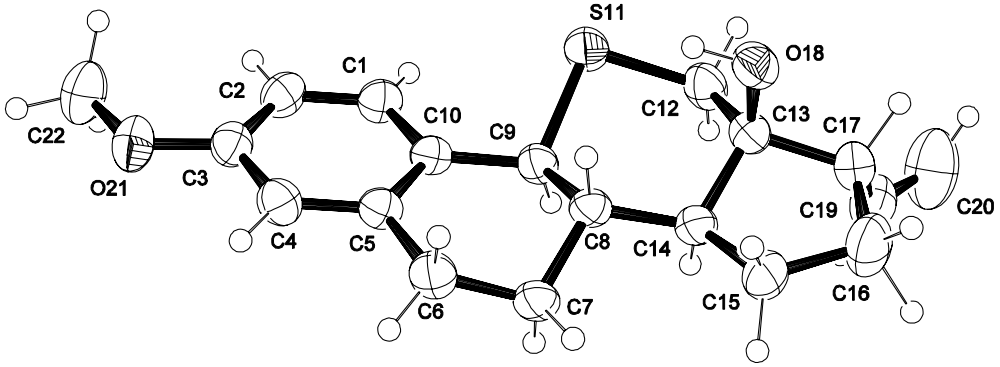


Figure 1. ORTEP drawing of the crystal structure of thiasteroid **11a**.

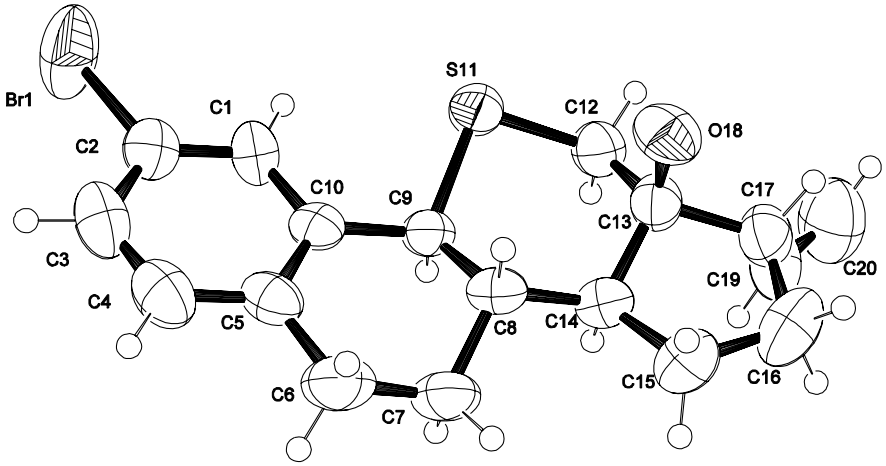
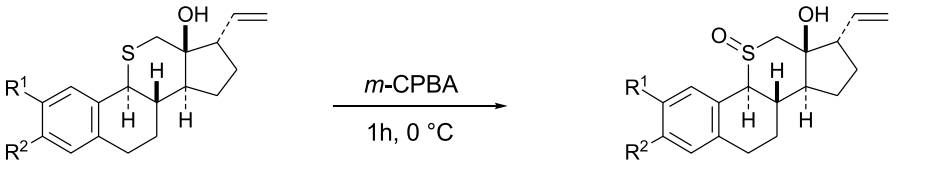


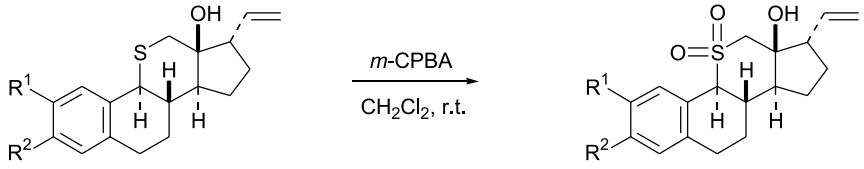
Figure 2. ORTEP drawing of the crystal structure of thiasteroid **12a**.



11a R^1 = H, R^2 = OMe
12a R^1 = Br, R^2 = H

14α-14β R^1 = H, R^2 = OMe; 86%
15α-15β R^1 = Br, R^2 = H; 100%

Scheme 5. Synthesis of sulfoxides **14** and **15**.



11a R^1 = H, R^2 = OMe
12a R^1 = Br, R^2 = H
16 R^1 = OMe, R^2 = H

17 R^1 = H, R^2 = OMe; 85%
18 R^1 = Br, R^2 = H; 70%
19 R^1 = OMe, R^2 = H; 81%

Scheme 6. Synthesis of sulfones **17**–**19**.

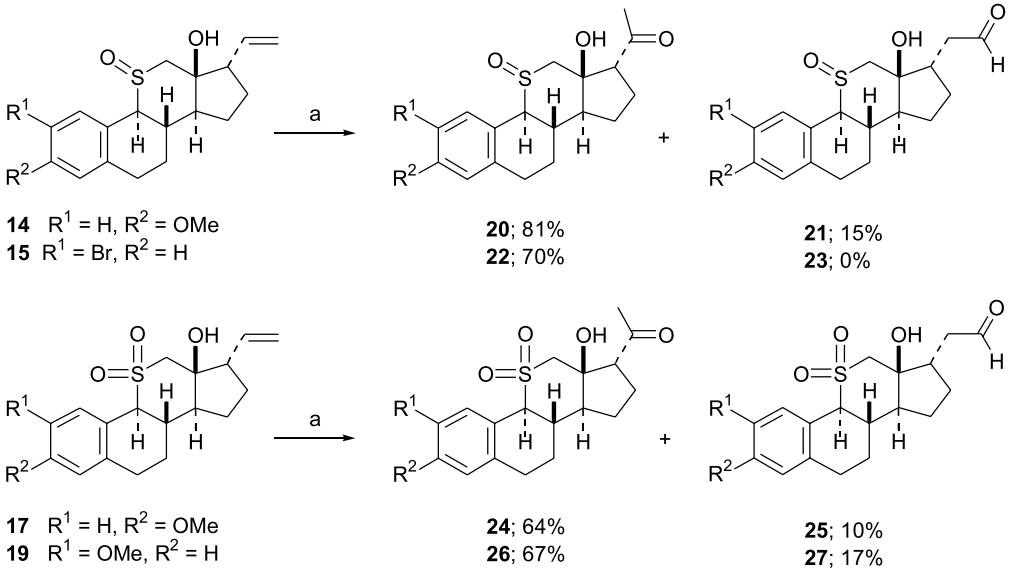
steroids **17**–**19**, matching the trans-*anti*-trans ring fusion of natural products and a sulfone moiety, were isolated in good yields.

Having transformed our thiasteroids either into sulfoxides or into sulfones, we turned then our attention to the introduction of an acetyl group present in numerous steroids at the C-17 position. The Wacker-type oxidation, well established synthetic organic reaction,[14] using palladium acetate–benzoquinone in the presence of perchloric acid, was first applied to sulfoxides **14** and **15**, and then to sulfones **17** and **19** (Scheme 7). Thus, in the two cases oxidation of the 17α-vinyl groups according to the Miller and Wayner procedure,[15] afforded the expected 17α-acetyl derivatives in good yields. Minor amounts of the unexpected terminal aldehydes resulting from an *anti*-Markovnikov hydroxypalladation were obtained besides ketones.[16]

Finally, in order to develop novel steroids matching various functionalities, and particularly to introduce different substituents at C-13 via conjugate additions, we decided to create an unsaturation between C-13 and C-17 (Scheme 8). Thus, reaction of steroids **24** and **26** with $BF_3 \cdot Et_2O$[17] in dichloromethane led to the corresponding α,β-unsaturated ketones **28** and **29**, respectively, in good yields.

3. Conclusion

In conclusion, we succeeded in introducing a sulfoxide and



14 R^1 = H, R^2 = OMe
15 R^1 = Br, R^2 = H

20; 81%
22; 70%

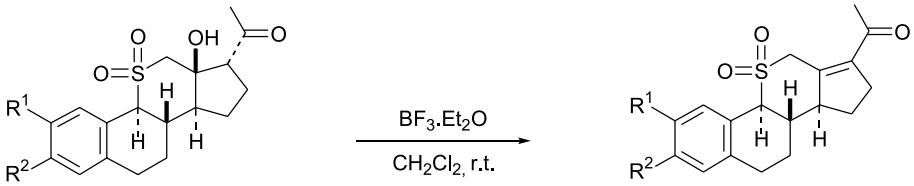
21; 15%
23; 0%

17 R^1 = H, R^2 = OMe
19 R^1 = OMe, R^2 = H

24; 64%
26; 67%

25; 10%
27; 17%

Scheme 7. Wacker type-oxidation of sulfoxides and sulfones. (a) Pd $(OAc)_2$, benzoquinone, 0.3 M $HClO_4$, CH_3CN, H_2O, 12 h, rt.



24 R^1 = H, R^2 = OMe
26 R^1 = OMe, R^2 = H

28 R^1 = H, R^2 = OMe; 84%
29 R^1 = OMe, R^2 = H; 75%

Scheme 8. Synthesis of α,β-unsaturated ketones **28** and **29**.

a sulfone moiety onto the steroid skeleton by using our simple strategy based on an intramolecular cycloaddition of *o*-xylylene. Otherwise, the functionalisation realized on our steroids allows us to envisage the introduction of a methyl group at C-13. Moreover, an enzymatic approach in order to obtain pure epoxide **3** and ultimately extend our process to optically active relatives is under progress and will be reported in due course.

4. Experimental

4.1. General

All reactions were run under argon in oven-dried glassware. ^{1}H and ^{13}C NMR spectra are recorded at 200 or 300, 50, 75 MHz, respectively, in $CDCl_3$ solutions. Chemical shift (δ) are reported in ppm with tetramethylsilane as internal standard. IR spectra were recorded on a Perkin-Elmer 1600 spectrophotometer. Flash chromatography was performed on silica gel (Merk 60 F_{254}) and TLC on silica gel. All solvents used were anhydrous. Dichloromethane was distilled from P_2O_5 and tetrahydrofuran (THF) over sodium/benzophenone.

4.1.1. (±)-1-(Thioacetylmethyl)-2,5-divinylcyclopentol 4. The title compound is prepared according to the previously described procedure.[18]

4.1.2. 1-Iodo-4-methoxybenzocyclobutene 5 and 1-iodo-4,5-dimethoxybenzocyclobutene 7. The title compounds are prepared according to the previously described procedure.[19]

4.1.3. 1-Iodo-5-bromobenzocyclobutene 6. The title compound is prepared according to the previously described procedure.[20]

4.2. General procedure for the alkylation of 4

Compound **4** (0.3 g, 1.32 mmol) were dissolved in anhydrous EtOH (5 mL), under argon. The solution was cooled at 0 °C and $NaBH_4$ (0.06 g, 1.59 mmol) was added. After stirring at this temperature for 4 h, 0.18 g (1.59 mmol) of *t*-BuOK and 1.72 mmol of 1-iodobenzocyclobutene **5**, **6** or **7** were added. After stirring at room temperature for 12 h, the resulting mixture was hydrolysed with a saturated solution of NH_4Cl. The aqueous layer was extracted with Et_2O (3×25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ether, 9.5:0.5).

4.2.1. 1-(4-Methoxybenzocyclobuten-1-yl-1-sulfanyl-methyl)-2,5-divinylcyclopentanol (8). Yield, 0.28 g (66%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.80 (m, 4H), 2.66 (m, 4H), 3.10 (m, 1H), 3.53 (m, 1H), 3.73 (s, 3H), 4.45 (m, 1H), 5.05 (m, 4H), 5.80 (m, 2H), 6.64 (d, J=3.0 Hz, 1H), 6.75 (d, J=8.1 Hz, 1H), 7.03 (dd, J=8.1, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=27.6, 28.8, 38.6, 39.2, 44.3, 51.3, 54.4, 55.3, 82.7, 108.6, 114.2, 115.7, 116.8, 123.3, 137.4, 137.7, 138.9, 143.5, 160.6. HRMS (EI): Calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1500.

4.2.2. 1-(5-Bromobenzocyclobuten-1-yl-1-sulfanyl-methyl)-2,5-divinylcyclopentanol (9). Yield, 0.366 g (75%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=2.00 (m, 4H), 2.82 (m, 4H), 5.10 (m, 4H), 5.75 (m, 2H), 6.85 (d, J=7.8 Hz, 1H), 7.28 (s, 1H), 7.35 (d, J=7.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=27.8, 28.7, 38.7, 39.2, 44.7, 51.3, 54.4, 82.8, 116.0, 117.0, 121.1, 124.9, 125.7, 131.9, 137.6, 138.8, 141.2, 147.4. HRMS (EI): Calcd for $C_{18}H_{21}BrOS$ 364.0497, found 364.0499.

4.2.3. 1-(4,5-Dimethoxybenzocyclobuten-1-yl-1-sulfanyl-methyl)-2,5-divinylcyclo-pentanol (10). Yield, 0.32 g (70%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.40 (m, 1H), 1.75 (m, 2H), 2.30 (m, 1H), 2.62 (m, 4H), 2.90 (m, 1H), 3.47 (m, 1H), 3.77 (s, 6H), 4.38 (m, 1H), 5.01 (m, 4H), 5.69 (m, 2H), 6.58 (s, 1H), 6.66 (s, 1H), 7.03 (dd, J=8.1, 3.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=27.6, 28.6, 37.8, 39.0, 44.3, 51.1, 54.1, 55.9, 82.5, 106.0, 106.8, 115.6, 116.4, 133.7, 136.1, 137.5, 138.7, 149.7, 150.7. HRMS (EI): Calcd for $C_{20}H_{26}O_3S$ 346.1598, found 346.1602.

4.3. Experimental procedure for the preparation of 11 and 12

A solution of **8** or **9** (3 mmol) in *o*-xylene (40 mL) was stirred under argon at 130 °C. The progress of the reaction is followed by TLC analysis. After cooling at room temperature, the solvent is removed under reduced pressure (1 mmHg). The resulting oil is purified by flash chromatography on silica gel (petroleum ether/diethyl ether, 95:5–7:3).

4.3.1. (±)-(8β,9α,14α)-3-Methoxy-17α-vinyl-11-thia-gona-1,3,5(10)-trien-13β-ol (11a). Yield, 0.765 g (80%). White crystals, mp 133 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.35 (m, 3H), 1.60 (m, 1H), 1.85 (m, 2H), 1.95 (m, 1H), 2.20 (m, 1H), 2.66 (½AB, d, J=13.3 Hz, 1H), 2.88

(m, 3H), 2.96 (½AB, d, J=13.3 Hz, 1H), 3.66 (d, J=10.2 Hz, 1H), 3.75 (s, 3H), 5.02 (m, 2H), 5.65 (m, 1H), 6.60 (d, J=2.4 Hz, 1H), 6.71 (dd, J=8.7, 2.6 Hz, 1H), 7.49 (d, J=8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=26.1, 27.5, 27.9, 29.9, 39.9, 43.5, 48.3, 50.8, 53.2, 55.2, 76.5, 112.1, 113.8, 115.4, 127.1, 128.8, 138.1, 139.6, 158.4. HRMS (EI): Calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1494.

4.3.2. (±)-(8β,9α,14α)-3-Methoxy-17α-vinyl-11-thiagona-1,3,5(10)-trien-13α-ol (11b). Yield, 0.06 g (6%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.25 (m, 1H), 1.55 (m, 1H), 1.60 (m, 2H), 1.75 (m, 1H), 1.95 (m, 1H), 2.05 (m, 1H), 2.09 (m, 1H), 2.76 (½AB, d, J=13.5 Hz, 1H), 2.78 (m, 3H), 2.94 (½AB, d, J=13.5 Hz, 1H), 3.75 (s, 3H), 3.80 (d, J=9.6 Hz, 1H), 5.16 (m, 2H), 5.80 (m, 1H), 6.58 (d, J=2.6 Hz, 1H), 6.71 (dd, J=8.7, 2.6 Hz, 1H), 7.47 (d, J=8.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=27.1, 27.2, 28.3, 29.8, 35.4, 45.9, 46.9, 47.3, 53.7, 55.3, 80.6, 112.2, 112.7, 113.6, 118.3, 124.8, 129.2, 136.7, 158.3. HRMS (EI): Calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1500.

4.3.3. (±)-(8β,9β,14α)-3-Methoxy-17α-vinyl-11-thiagona-1,3,5(10)-trien-13α-ol (11c). Yield, 0.057 g (6%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.32 (m, 1H), 1.70 (m, 3H), 1.95 (m, 2H), 2.10 (m, 1H), 2.19 (m, 1H), 2.43 (d, J=13.8 Hz, 1H), 3.75 (m, 3H), 4.18 (d, J=3.8 Hz, 1H), 5.10 (m, 2H), 5.92 (m, 1H), 6.57 (d, J=2.5 Hz, 1H), 6.71 (dd, J=8.5, 2.7 Hz, 1H), 7.38 (d, J=8.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=25.8, 26.6, 26.8, 28.7, 36.2, 37.5, 41.5, 47.5, 50.8, 55.3, 76.6, 112.5, 113.5, 116.1, 127.8, 130.9, 138.4, 138.7, 158.5. HRMS (EI): Calcd for $C_{19}H_{24}O_2S$ 316.1497, found 316.1496.

4.3.4. (±)-(8β,9α,14α)-2-Bromo-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol (12a). Yield, 0.78 g (70%). White crystals, mp 108 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.45 (m, 3H), 1.60 (m, 1H), 1.85 (m, 2H), 1.95 (m, 1H), 2.20 (m, 1H), 2.68 (½AB, d, J=13.2 Hz, 1H), 2.82 (m, 3H), 2.95 (½AB, d, J=13.2 Hz, 1H), 3.66 (d, J=10.2 Hz, 1H), 5.04 (m, 2H), 5.65 (m, 1H), 6.95 (d, J=8.1 Hz, 1H), 7.25 (dd, J=8.1, 2.1 Hz, 1H), 7.73 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=25.9, 27.0, 27.8, 29.0, 39.8, 42.8, 48.0, 50.8, 53.0, 76.3, 115.5, 119.6, 129.9, 130.5, 130.7, 137.0, 139.3. HRMS (EI): Calcd for $C_{18}H_{21}BrOS$ 364.0497, found 364.0498.

4.3.5. (±)-(8β,9α,14α)-2-Bromo-17α-vinyl-11-thiagona-1,3,5(10)-trien-13α-ol (12b). Yield, 0.11 g (10%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.20–2.70 (m, 11H), 2.50 (m, 3H), 2.90 (½AB, d, J=14.2 Hz, 1H), 3.80 (d, J=10.8 Hz, 1H), 5.30 (m, 2H), 5.70 (m, 1H), 6.90 (d, J=8.1 Hz, 1H), 7.22 (m, 1H), 7.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=26.9, 27.0, 27.9, 29.3, 29.6, 35.3, 45.0, 46.9, 47.0, 53.5, 63.4, 80.3, 118.3, 119.7, 126.0, 129.8, 130.5, 130.9, 136.5. HRMS (EI): Calcd for $C_{18}H_{21}BrOS$ 364.0497, found 364.0502.

4.3.6. (±)-(8β,9β,14α)-2-Bromo-17α-vinyl-11-thiagona-1,3,5(10)-trien-13α-ol (12c). Yield, 0.11 g (10%). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.20–2.70 (m, 11H), 2.55 (m, 3H), 2.95 (d, J=14.2 Hz, 1H), 3.95 (d, J=5.1 Hz, 1H), 5.25 (m, 2H), 5.75 (m, 1H), 6.95 (d, J=8.2 Hz, 1H), 7.24 (m, 1H), 7.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=23.9, 28.0, 29.4, 33.4, 39.7, 41.3, 51.0, 51.7, 75.7, 116.9, 119.6, 129.9, 130.7, 135.8, 136.4, 137.5. HRMS (EI): Calcd for $C_{18}H_{21}BrOS$ 364.0497, found 364.0499.

4.4. Experimental procedure for the preparation of sulfoxides 14 and 15

Compound **11a** or **12a** (0.95 mmol) were dissolved in CH_2Cl_2 (15 mL), under argon. The solution was cooled at 0 °C and *m*-CPBA (0.235 g, 0.95 mmol) was added. After stirring at this temperature for 1 h, the mixture was hydrolysed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (typically eluting with petroleum ether/ethyl acetate, 9:1–5:5) to give an inseparable 3/1 mixture of two diastereoisomers **14α/14**β or **15α/15**β.

4.4.1. (±)-(8β,9α,14α)-3-Methoxy-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol-11-oxide 14α. (Major isomer): yield, 0.271 g (86%). White crystals, mp 165 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.80 (m, 8H), 2.44 (½AB, d, J=14.2 Hz, 1H), 2.70 (m, 3H), 3.40 (½AB, d, J=14.2 Hz, 1H), 3.50 (d, J=10.8 Hz, 1H), 3.73 (s, 3H), 5.03 (m, 2H), 5.51 (m, 1H), 6.64 (d, J=2.2 Hz, 1H), 6.75 (dd, J=8.5, 2.2 Hz, 1H), 7.41 (d, J=8.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=25.7, 26.3, 27.1, 29.6, 30.7, 49.2, 51.3, 55.2, 55.3, 63.9, 81.9, 112.9, 114.5, 116.2, 121.8, 128.3, 138.9, 140.3, 158.8. HRMS (EI): Calcd for $C_{19}H_{24}O_3S$ 332.1446, found 332.1424.

4.4.2. (±)-(8β,9α,14α)-2-Bromo-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol-11-oxide 15α. (Major isomer): yield, 0.362 g (100%). White crystals, mp 158 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ=1.80 (m, 8H), 2.46 (½AB, d, J=14.4 Hz, 1H); 2.70 (m, 3H), 3.41 (½AB, d, J=14.4 Hz, 1H), 3.50 (d, J=10.6 Hz, 1H), 5.05 (m, 2H), 5.56 (m, 1H), 5.66 (s, 1H), 6.75 (dd, J=8.2, 2.5 Hz, 1H), 7.04 (d, J=8.2 Hz, 1H), 7.05 (d, J=2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=25.7, 26.6, 27.2, 28.5, 30.5, 49.5, 51.5, 55.2, 64.5, 81.9, 112.2, 113.9, 116.4, 130.7, 131.0, 138.8, 138.9, 158.2.

4.5. Experimental procedure for the preparation of sulfones 17, 18 and 19

Compound **11a** or **12a** or **16** (0.79 mmol) were dissolved in CH_2Cl_2 (15 mL), under argon. The solution was cooled at 0 °C and *m*-CPBA (0.39 g, 1.58 mmol) was added. After stirring at room temperature for 24 h, the mixture was hydrolysed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (typically eluting with CH_2Cl_2/MeOH, 10:0–9.5:0.5).

4.5.1. (±)-(8β,9α,14α)-3-Methoxy-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 17. Yield, 0.234 g (85%). White crystals, mp 198 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 2.00 (m, 8H), 2.85 (m, 3H), 3.20 (½AB, d, J=14.1 Hz, 1H), 3.27 (½AB, d, J=14.1 Hz, 1H), 3.76 (s, 3H), 4.03 (d, J=10.4 Hz, 1H), 5.08

(m, 2H), 5.57 (m, 1H), 6.64 (d, $J=2.4$ Hz, 1H), 6.74 (dd, $J=8.9$, 2.4 Hz, 1H), 8.75 (d, $J=8.9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) 25.3, 26.6, 27.7, 30.1, 37.2, 49.2, 50.4, 55.2, 53.7, 55.3, 59.5, 66.6, 79.6, 112.5, 114.7, 117.3, 117.9, 129.7, 138.3, 140.0, 159.4. HRMS (EI): Calcd for $C_{19}H_{24}O_4S$ 348.1395, found 348.1398.

4.5.2. (±)-(8β,9α,14α)-2-Bromo-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 18. Yield 0.22 g (70%). White crystals, mp 196 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 1.70 (m, 8H), 2.75 (m, 3H), 3.20 (½AB, d, $J=14.3$ Hz, 1H), 3.25 (½AB, d, $J=14.3$ Hz, 1H), 4.00 (d, $J=11.2$ Hz, 1H), 5.10 (m, 2H), 5.55 (m, 1H), 7.00 (d, $J=8.3$ Hz, 1H), 7.40 (d, $J=8.2$, 1.9 Hz, 1H), 8.33 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) 25.1, 26.2, 27.5, 29.2, 36.6, 50.2, 53.7, 59.6, 66.0, 79.3, 112.2, 117.2, 119.8, 127.9, 131.1, 131.3, 133.2, 137.2, 138.1. HRMS (EI): Calcd for $C_{18}H_{21}BrO_3S$ 396.0412, found 396.0415.

4.5.3. (±)-(8β,9α,14α)-2-Methoxy-17α-vinyl-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 19. Yield, 0.223 g (81%). White crystals, mp 185 °C (hexane). IR (film, cm^{-1}) 3504, 2973, 1609, 1502, 1264, 743. ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm) 1.90 (m, 8H), 2.78 (m, 3H), 3.21 (½AB, d, $J=14.4$ Hz, 1H), 3.31 (½AB, d, $J=14.4$ Hz, 1H), 3.77 (s, 3H), 4.05 (d, $J=10.6$ Hz, 1H), 4.06 (s, 1H), 5.10 (m, 2H), 5.59 (m, 1H), 6.81 (dd, $J=8.6$, 2.4 Hz, 1H), 7.04 (d, $J=8.6$ Hz, 1H), 7.77 (d, $J=8.6$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm) 25.4, 26.8, 27.7, 29.0, 37.1, 50.5, 53.7, 55.4, 59.7, 66.9, 79.6, 112.8, 115.4, 117.4, 126.7, 130.3, 131.8, 138.3, 157.8. HRMS (EI): Calcd for $C_{19}H_{24}O_4S$ 348.1395, found 348.1397.

4.6. General procedure for the Wacker-type oxidation

A 25 mL three-necked flash equipped with an argon inlet, a magnetic stirring bar and a septum cap was charged with $Pd(OAc)_2$ (0.01 g, 0.045 mmol) and benzoquinone (0.044 g, 0.41 mmol). A solution of CH_3CN–H_2O (7/1) (5.1 mL) and $HClO_4$ (0.3 M) is added. The resulting solution was stirred at room temperature for 1 h and steroid **14**, **15**, **17** or **19** (0.45 mmol) is then added. The reaction mixture is stirred at this temperature for 2 h and hydrolysed with a NaOH solution (30%). The aqueous phase is extracted with ether, and the organic layers are dried ($MgSO_4$), filtered and evaporated. After purification by flash chromatography, the corresponding ketones **20** (CH_2Cl_2/MeOH, 99:1–95:5), **22** (petroleum ether/ethyl acetate, 9:1–3:7), **24** (CH_2Cl_2/MeOH, 99:1) or **26** (CH_2Cl_2/MeOH, 99:1) and aldehydes **21**, **25** or **27** are obtained.

4.6.1. (±)-(8β,9α,14α)-3-Methoxy-17α-acetyl-11-thiagona-1,3,5(10)-trien-13β-ol-11-oxide (20) from 14. Yield, 0.127 g (81%). ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=$ 1.97 (m, 8H), 2.19 (s, 3H), 2.75 (m, 2H), 2.93 (½AB, d, $J=$ 13.8 Hz, 1H), 3.17 (dd, $J=9.8$, 3.8 Hz, 1H), 3.46 (½AB, d, $J=13.8$ Hz, 1H), 3.64 (d, $J=10.9$ Hz, 1H), 3.76 (s, 3H), 6.64 (d, $J=2.4$ Hz, 1H), 6.77 (dd, $J=8.7$, 2.6 Hz, 1H), 7.43 (d, $J=8.5$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=26.1$, 26.5, 26.7, 30.0, 30.9, 32.2, 48.5, 52.1, 55.7, 62.5, 64.1, 81.8, 113.3, 115.0, 122.1, 128.8, 140.7, 159.3, 210.9. HRMS (EI): Calcd for $C_{19}H_{24}O_4S$ 348.1395, found 348.1398.

4.6.2. (±)-(8β,9α,14α)-3-Methoxy-17α-(2-oxoethyl)-11-thiagona-1,3,5(10)-trien-13β-ol-11-oxide (21) from 14. Yield, 0.024 g (15%). ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.99$ (m, 8H), 2.17 (m, 2H), 2.40 (½AB, d, $J=13.6$ Hz, 1H), 2.78 (m, 2H), 3.48 (½AB, d, $J=13.6$ Hz, 1H), 3.60 (d, $J=$ 10.6 Hz, 1H), 3.75 (s, 3H), 5.66 (s, 1H), 6.65 (d, $J=2.5$ Hz, 1H), 6.77 (dd, $J=8.6$, 2.5 Hz, 1H), 7.42 (d, $J=8.7$ Hz, 1H), 9.71 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=25.7$, 26.4, 27.9, 29.5, 30.7, 44.2, 47.5, 48.6, 51.4, 55.2, 64.6, 81.9, 112.0, 113.4, 130.3, 131.5, 139.1, 159.4, 202.3. HRMS (EI): Calcd for $C_{19}H_{24}O_4S$ 348.1395, found 348.1404.

4.6.3. (±)-(8β,9α,14α)-2-Bromo-17α-acetyl-11-thiagona-1,3,5(10)-trien-13β-ol-11-oxide (22) from 15. Yield, 0.125 g (70%). White crystals, mp 139 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.80$ (m, 8H), 2.18 (s, 3H), 2.80 (m, 2H), 2.95 (½AB, d, $J=13.7$ Hz, 1H), 3.45 (½AB, d, $J=13.7$ Hz, 1H), 3.60 (d, $J=10.4$ Hz, 1H), 6.75 (d, $J=$ 8.1 Hz, 1H), 7.28 (dd, $J=8.1$, 1.9 Hz, 1H), 7.65 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=25.6$, 27.1, 28.8, 29.9, 30.4, 31.6, 48.3, 51.6, 61.9, 63.4, 81.2, 120.1, 130.1, 130.8, 131.5, 131.9, 172.8, 210.4. HRMS (EI): Calcd for $C_{18}H_{21}BrO_3S$ 396.0412, found 396.0417.

4.6.4. (±)-(8β,9α,14α)-3-Methoxy-17α-acetyl-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 24 from 17. Yield, 0.105 g (64%). White crystals, mp 168 °C (hexane). ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.95$ (m, 8H), 2.85 (m, 2H), 3.19 (m, 1H), 3.77 (s, 3H), 3.81 (s, 1H), 4.14 (d, $J=$ 10.8 Hz, 1H), 6.65 (d, $J=2.7$ Hz, 1H), 6.75 (dd, $J=8.9$, 2.8 Hz, 1H), 8.07 (d, $J=8.9$ Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=25.5$, 26.1, 26.4, 30.0, 31.6, 37.0, 50.6, 55.2, 57.8, 60.0, 66.3, 78.8, 112.4, 114.7, 117.6, 126.7, 129.7, 139.9, 159.3, 210.0. HRMS (EI): Calcd for $C_{19}H_{24}O_5S$ 364.1295, found 364.1298.

4.6.5. (±)-(8β,9α,14α)-3-Methoxy-17α-(2-oxoethyl)-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 25 from 17. Yield, 0.016 g (10%). ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.80$ (m, 8H), 2.25 (m, 3H), 2.47 (m, 1H), 2.65 (m, 2H), 3.18 (½AB, d, $J=13.7$ Hz, 1H), 3.30 (½AB, d, $J=13.7$ Hz, 1H), 3.77 (s, 3H), 3.79 (s, 1H), 6.66 (d, $J=2.6$ Hz, 1H), 6.76 (dd, $J=8.8$, 3.0 Hz, 1H), 8.08 (d, $J=8.7$ Hz, 1H), 9.72 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=25.3$, 26.5, 28.5, 29.9, 37.0, 42.8, 47.3, 50.5, 55.2, 58.7, 66.7, 79.2, 112.4, 114.7, 117.5, 129.6, 139.9, 159.4, 200.0. HRMS (EI): Calcd for $C_{19}H_{24}O_5S$ 364.1295, found 364.1297.

4.6.6. (±)-(8β,9α,14α)-2-Methoxy-17α-acetyl-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 26 from 19. Yield, 0.11 g (67%). White crystals, mp 184 °C (hexane). IR (film, cm^{-1}) 3434, 1636, 1264, 743. ^{1}H NMR (300 MHz, $CDCl_3$), $\delta=1.80$ (m, 8H), 2.19 (s, 3H), 2.75 (m, 2H), 2.94 (½AB, d, $J=14.1$ Hz, 1H), 3.15 (dd, $J=$ 9.6, 3.1 Hz, 1H), 3.47 (½AB, d, $J=14.1$ Hz, 1H), 3.64 (d, $J=10.9$ Hz, 1H), 3.75 (s, 3H), 5.80 (s, 1H), 6.75 (dd, $J=$ 8.6, 2.4 Hz, 1H), 7.02 (d, $J=8.6$ Hz, 1H), 7.03 (d, $J=$ 2.4 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), $\delta=25.7$, 26.1, 26.5, 28.5, 30.4, 31.9, 48.4, 51.9, 55.4, 62.1, 64.2, 81.4, 112.0, 114.0, 117.4, 129.7, 130.5, 131.0, 158.2, 210.6. HRMS (EI): Calcd for $C_{19}H_{24}O_5S$ 364.1295, found 364.1302.

4.6.7. (±)-(8β,9α,14α)-2-Methoxy-17α-(2-oxoethyl)-11-thiagona-1,3,5(10)-trien-13β-ol-11,11-dioxide 27 from 19. Yield, 0.028 g (17%). IR (film, cm^{-1}) 3486, 1721, 1611, 1502, 1264, 745. ^1H NMR (300 MHz, $CDCl_3$), δ= 1.80 (m, 8H), 2.15 (m, 2H), 2.41 (½AB, d, J=13.7 Hz, 1H), 2.49 (m, 2H), 2.80 (m, 2H), 3.49 (½AB, d, J=13.7 Hz, 1H), 3.56 (d, J=11.3 Hz, 1H), 3.76 (s, 3H), 5.69 (s, 1H), 6.76 (dd, J=8.2, 2.3 Hz, 1H), 7.02 (d, J=8.2 Hz, 1H), 7.03 (d, J=2.3 Hz, 1H), 9.70 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=25.8, 26.6, 27.9, 28.5, 30.6, 44.3, 47.5, 48.7, 51.6, 55.5, 64.6, 81.9, 112.3, 114.1, 130.4, 131.0, 131.1, 158.3, 201.2. HRMS (EI): Calcd for $C_{19}H_{24}O_5S$ 364.1295, found 364.1301.

4.7. Experimental procedure for the preparation of 28 and 29

A solution of **24** or **26** (1 mmol) and $BF_3 \cdot Et_2O$ (3 mmol, 0.38 mL) in CH_2Cl_2 (4 mL) was stirred under argon at room temperature during 24 h. The mixture was hydrolysed with a saturated solution of $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The organic phase was dried with $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/ethyl acetate, 7:3) to give **28** or **29**.

4.7.1. (±)-(8β,9α,14α)-3-Methoxy-17-acetyl-11-thiagona-1,3,5(10),13(17)-tetraene-11,11-dioxide 28. Yield, 0.29 g (84%). White crystals, mp 181 °C (hexane). ^1H NMR (300 MHz, $CDCl_3$), δ=1.42 (m, 1H), 1.72 (m, 1H), 2.14 (m, 3H), 2.24 (s, 3H), 2.78 (m, 5H), 3.76 (s, 3H), 3.83 (½AB, dd, J=15.3, 1.7 Hz, 1H), 4.29 (d, J=11.1 Hz, 1H), 5.27 (½AB, d, J=15.5 Hz, 1H), 6.64 (d, J=2.8 Hz, 1H), 6.75 (dd, J=8.9, 2.8 Hz, 1H), 8.10 (d, J=8.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=26.2, 27.2, 29.9, 30.3, 33.0, 44.1, 52.1, 54.5, 55.2, 65.0, 112.3, 114.5, 117.6, 130.3, 138.9, 140.0, 142.4, 159.2, 197.9. HRMS (EI): Calcd for $C_{19}H_{22}O_4S$ 346.1204, found 346.1208.

4.7.2. (±)-(8β,9α,14α)-2-Methoxy-17-acetyl-11-thiagona-1,3,5(10),13(17)-tetraene-11,11-dioxide 29. Yield, 0.26 g (75%). White crystals, mp 178 °C (hexane). ^1H NMR (300 MHz, $CDCl_3$), δ=1.41 (m, 1H), 1.72 (m, 1H), 2.15 (m, 3H), 2.22 (s, 3H), 2.74 (m, 5H), 3.75 (s, 3H), 3.82 (½AB, dd, J=15.5, 2.2 Hz, 1H), 4.28 (d, J=11.1 Hz, 1H), 5.26 (½AB, d, J=15.5 Hz, 1H), 6.78 (dd, J=8.5, 2.6 Hz, 1H), 7.05 (d, J=8.5 Hz, 1H), 7.76 (d, J=2.6 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ=26.6, 27.3, 28.8, 28.5, 30.3, 33.0, 44.1, 52.1, 54.8, 55.3, 65.4, 113.2, 115.4, 126.5, 130.4, 130.6, 139.0, 142.4, 157.8, 198.1. HRMS (EI): Calcd for $C_{19}H_{22}O_4S$ 346.1204, found 346.1210.

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References and notes

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